Thrombocytopenia in Pregnancy: Fetal and Neonatal Alloimmune Thrombocytopenia

16

Sukrutha Veerareddy and Pranav P. Pandya

Abstract

Fetal/neonatal alloimmune thrombocytopenia (FNAIT) results from the formation by the mother of antibodies that are directed against a fetal platelet alloantigen inherited from its father. The maternal alloantibodies cross the placenta and destroy the baby's platelets, and the resulting fetal thrombocytopenia may cause bleeding, particularly into the brain, before or shortly after birth. Approximately 10–20 % of affected fetuses have intracranial hemorrhages, one quarter to one half of which occur in utero. There are considerable controversies regarding the optimal management of FNAIT-affected pregnancies. There is no clear approach to the antenatal management of first affected pregnancies, and several questions remain around the approaches to the management of second and subsequent affected pregnancies. Currently, antenatal management of FNAIT consists of weekly maternal intravenous immunoglobulin (IVIg) infusions, with or without oral steroid therapy – the optimal steroid dosages and protocols remain to be defined. Some centers continue to offer serial intrauterine platelet transfusions as first-line therapy, but the multiple cordocenteses required to administer the platelets carry substantial risk of fetal demise. Potential techniques for antenatal screening of first pregnancies are being developed. Postnatal screening does not prevent neonatal morbidity and mortality.

Keywords

Fetal/neonatal alloimmune thrombocytopenia • FNAIT • Platelets • Maternal intravenous immunoglobulin infusions • Serial intrauterine platelet transfusions

S. Veerareddy, BSc, MBBS, MRCOG, PhD
Women's Health Services,
Queen Elizabeth Hospital, Lewisham
and Greenwich NHS Trust, Stadium Road,
London SE18 4QH, UK
e-mail: sukrutha.veerareddy@nhs.net

P.P. Pandya, BSc, MBBS, MD, FRCOG (✉)
Fetal Medicine Unit, University College
London Hospitals NHS Foundation Trust,
1 Elizabeth Garrett Anderson Wing,
25 Grafton Way, London WC1E 6DB, UK
e-mail: pranav.pandya@uclh.nhs.uk

H. Cohen, P. O'Brien (eds.), *Disorders of Thrombosis and Hemostasis in Pregnancy: A Guide to Management*, DOI 10.1007/978-3-319-15120-5_16, © Springer-Verlag London 2015

16.1 Introduction

Fetal and neonatal alloimmune thrombocytopenia (FNAIT) occurs when the mother produces antibodies against a platelet alloantigen that the fetus has inherited from its father [1, 2] These maternal alloantibodies cross the placenta and destroy the baby's platelets, which may result in internal bleeding, in particular into the fetal brain [3–5]. As a result, babies may die in utero or have long-lasting disability. FNAIT is usually diagnosed following the birth of a thrombocytopenic baby, or less commonly, it may be suspected following the antenatal detection of a fetal intracranial hemorrhage (ICH).

16.2 Nature and Incidence of Fetal Neonatal Autoimmune Thrombocytopenia (FNAIT)

Platelet-specific alloantigens or human platelet alloantigens (HPAs) are expressed predominantly on platelets. If the fetus has inherited a HPA type from its father that is incompatible with the HPA type of its mother, antibodies against that specific HPA type may be produced by the mother [6–9]. These IgG antibodies can easily cross the placenta as early as the 14th week of gestation, prompting the fetal reticuloendothelial system to remove antibody-coated platelets from the fetal circulation [6, 10, 11]. This can cause fetal thrombocytopenia, the severity of which depends on several variables, such as (a) the concentration and subclass of maternal IgG alloantibodies; (b) the density of the target antigens on the fetal platelets; (c) the activity of phagocytes in the fetal reticuloendothelial system; and (d) the ability of the fetal bone marrow to compensate for the accelerated destruction of antibody-sensitized platelets [4]. Transfer of antibodies increases as gestation progresses, until a maximum level is attained in the late third trimester [12]. The first case of FNAIT within a family is usually detected at or shortly after birth. The newborn usually presents with skin bleeding or, in a small percentage of cases, is found to have a low platelet count. However, in severe cases, ICH may occur in utero during the antenatal period or during labor, or shortly after birth.

The incidence of FNAIT in Caucasian populations is between 1 in 1,000 and 1 in 1,500 live births [7, 13–16]. The incidence of severe thrombocytopenia ($<50\times10^9$/L) is 1 in 1,695 live births [17]. However, the true incidence is likely to be higher; in one study [17] only 37 % of cases with severe FNAIT were detected.

In the Caucasian population, 98 % of people are HPA-1a positive; consequently, 2 % of pregnant women are HPA-1a negative (HPA1bb). These women are most likely to carry a HPA-1a-positive fetus and are therefore at risk of being immunized. Interestingly, only 6–12 % of HPA1bb pregnant women develop anti-HPA-1a antibodies [15]. This is because the mother's immunogenetic background plays a major role [7, 18, 19]. Several studies have shown that anti-HPA-1a sensitization occurs only if the mother is HLA type DR52a, and anti-HPA-5b sensitization occurs only with HLA type DRw6 [17, 18, 20–22].

In Caucasians, antibodies to HPA-1a are the major cause of FNAIT (75 %), followed by HPA-5b (15 %) and HPA-3a (5 %), whereas in the Japanese population most cases involve antibodies to HPA-4b (Table 16.1) [12, 23–36]. The diagnosis of FNAIT is made by identifying maternal HPA antibodies and documenting parental incompatibility for the HPA allele in question.

16.3 Differences Between NAIT and Rhesus D Hemolytic Disease of the Fetus and Newborn

Unlike in hemolytic disease of the fetus and newborn (HDFN) caused by maternal sensitization to fetal Rhesus D (RhD) inherited from the father (the red cell equivalent of FNAIT), FNAIT often occurs in the first pregnancy. However, there is currently no consensus regarding the utility of screening in previously unaffected women for antiplatelet antibodies and thus identifying women whose babies could be affected by FNAIT early in gestation (discussed in Sect. 16.11). Active antenatal manage-

Table 16.1 HPA antibodies involved in FNAIT in Caucasians and their prevalences: literature review

Author and year	HPA-1a (%)	HPA-1b (%)	HPA-3a (%)	HPA-5a (%)	HPA-5b (%)	HPA-15 (%)	HPA-1a & HPA-5b (%)	Other (%)
Reznikoff-Etievant (1988) [23]	90							
Mueller-Eckhardt et al. (1989) [24]	90				8			2
Kornfeld et al. (1996) [25]	90				10			
Letsky and Greaves (1996) [26]	80–90				5–15			
Khouzami et al. (1996) [27]	75							
Kanhai et al. (1996) [28]	79		5	11				
Uhrynowska et al. (1997) [29]	91	4			4			
Spencer and Burrows (2001) [12]	78		4		4			
Davoren et al. (2002) [30]	94		3		3			
Davoren et al. (2004) [31]	79	4	2	1	9		2	
Rayment et al. (2003) [32]	85				10	5		
Mandelbaum et al. (2005) [33]						2		
Ertel et al. (2005) [34]						1		
Kroll et al. (2005) [35]	75		2		18		2	
Porcelijn et al. (2006) [36]	73	1	5	1	15			

Table 16.2 Differences between RhD HDFN and FNAIT

	Rh	FNAIT
Incidence	1/100	1/1,000
First child affected	No	Yes
Routine screening in place	Yes	No
Testing readily available	Yes	No
Prophylaxis available	Yes	No
Severe clinical phenotype	Hydrops	Intracranial hemorrhage
Management of next pregnancy	Red cell transfusions in utero	IVIg ± prednisolone ± platelet transfusions

ment of this disease is confined to those women who have had a previously affected fetus [7]. There are important differences between RhD isoimmunization and FNAIT (Table 16.2).

16.4 Diagnosis

The diagnosis of FNAIT is based on clinical and serological findings. The typical picture is of a neonate presenting with purpura within minutes to hours after birth, born to a healthy mother with no history of a bleeding disorder, after an uneventful pregnancy with a normal maternal platelet count [37–40]. The first step in the diagnosis of FNAIT is confirmation of neonatal thrombocytopenia, followed by exclusion of the most frequent causes of neonatal thrombocytopenia such as infection, disseminated intravascular coagulation, and maternal immune thrombocytopenia (ITP) [11, 39]. The platelet count is low at birth and tends to fall further during the first 24–48 h of life. Laboratory diagnosis involves the detection of maternal circulating alloantibodies against a HPA type shared by neonatal and paternal platelets. This is accomplished using the monoclonal antibody-specific immobilization of platelet antigen (MAIPA) test [41], the platelet immunofluorescence test, or a novel antigen-specific particle assay [11, 26, 42–46]. The diagnosis of FNAIT is unequivocal when a parental incompatibility with corresponding maternal alloantibody is present [4, 10, 39, 47].

Recognition of FNAIT and appropriate therapy are important both for the affected neonate and for the management of subsequent pregnancies [48]. Indications for testing for FNAIT prenatally include any fetus with ICH, selected cases of ventriculomegaly (e.g., moderate to

severe unilateral), neonates with thrombocytopenia of unclear etiology, neonatal ICH with significant thrombocytopenia, and familial transient neonatal thrombocytopenia [49–52]. A number of FNAIT cases (10 %) have been reported in which no HPA antibody could be detected [53–56]. The diagnosis is then based on maternal-fetal or maternal-paternal HPA incompatibility and exclusion of other causes of thrombocytopenia [54, 57, 58]. In some cases, antibodies may become detectable in the weeks or months after delivery or during/after a subsequent pregnancy [39, 40, 59, 60]. In unconfirmed FNAIT cases, antibodies detected before 20 weeks in a subsequent pregnancy require confirmation by a later specimen, because early transient antibodies may exist and do not seem to be of clinical significance [60]. Some studies have demonstrated significant correlation between high anti-HPA-1a antibody titers (>1:32) and a fetal platelet count below 50×10^9/L [21, 59, 60], whereas others have not [17, 36, 61]. This discrepancy may be due to differences in the size of the series, parity of the women, timing of blood sampling, or the method of antibody titration [61].

HPA typing of mother, father and fetus/neonate is important, not only for the diagnosis of FNAIT but also for provision of HPA-matched blood components to neonates with FNAIT, for genetic counseling and for estimation of the recurrence risk [62]. Conventional serological immuno-phenotyping for HPA is limited by the lack of certain rare but well-characterized typing antisera, such as anti-HPA-1b and anti-HPA-4b [62]. Even when non-paternity has been ruled out, it is not always possible to demonstrate parental incompatibility of platelet-specific alloantigens in the presence of corresponding maternal alloantibodies, especially if the mother is sensitized to a rare paternal antigen, making the diagnosis more difficult [63]. If there is a strong suspicion of FNAIT, testing the maternal serum against the paternal platelets (using a blood sample from the father or the fetus/neonate) may confirm incompatibility.

16.5 Fetal/Neonatal Risks

FNAIT may affect the fetus as early as the beginning of the second trimester and usually remits spontaneously within 1–3 weeks after delivery, depending on the rate of removal of maternal platelet antibodies from the neonatal circulation. Thrombocytopenia can be severe and can cause antenatal ICH in around 10–30 % of severe cases. ICH is associated with death in 10 % and neurological sequelae in a further 10–20 % [6, 11, 39, 50]. Chaoying et al. [64] found that FNAIT is the most important cause of ICH and poor outcome in neonates.

Around 25–50 % of cases of FNAIT-related ICH occur in utero. The majority occur between 30 and 35 weeks of gestation [7, 50], but ICH have also been reported at earlier gestations. The international No IntraCranial Haemorrhage (NOICH) registry, an observational cohort study, characterised pregnancies between 2001 and 2010 where the fetus or neonate was diagnosed with fetal and neonatal alloimmune thrombocytopenia (FNAIT) and suffered from intracranial haemorrhage (ICH), with special focus on time of bleeding onset. Of 592 FNAIT cases in the registry, 43 confirmed cases of ICH due to FNAIT were included in the study. The majority of bleeding episodes (23/43; 54 %) occurred before 28 weeks of gestation and often affected the first born child (27/43; 63 %). One-third (35 %) of the children died within 4 days after delivery. Twenty-three (53 %) children survived with severe neurological disabilities and only 5 (12 %) were alive and well at time of discharge. Antenatal treatment was not given in most (91 %) cases of fetal/neonatal ICH. The authors concluded that ICH caused by FNAIT often occurs during second trimester and the clinical outcome is poor. In order to prevent ICH caused by FNAIT, at-risk pregnancies must be identified and prevention and/ or interventions should start early in the second trimester [65]. Without treatment, there is a risk of ICH as long as severe thrombocytopenia persists [23]. Thrombocytopenia is most severe in the presence of HPA-1a incompatibility, which accounts for most cases of in utero ICH.

Although high levels of maternal anti-HPA-1a may correlate with the severity of thrombocytopenia [21, 66], in up to 30 % of cases no antibody is found [67]. In some cases, antibody detection can be improved by varying assay conditions [68, 69]. Severe thrombocytopenia or ICH in HPA-1a-alloimmunized pregnancies cannot be predicted with sufficient sensitivity and specificity for clinical application from maternal anti-HPA-1a potency, bioactivity or isotype [32, 70, 71]. The maternal antibody level therefore has limited use in prediction of the severity of fetal/neonatal thrombocytopenia.

Neonatal thrombocytopenia due to FNAIT usually becomes progressively more severe and occurs earlier in subsequent pregnancies [10, 38, 44]. Following severe neonatal thrombocytopenia ($<50 \times 10^9$/L), a cerebral ultrasound or nuclear magnetic resonance (MRI) scan is advised to detect clinically silent ICH [7, 11]. A few cases of ICH resulting from incompatibility for HPA-3a, HPA-4b, HPA-5b, or HPA-9b alloantigens have been reported [72, 73].

16.6 Antenatal Management and Outcomes

The goal of antenatal management is to prevent severe thrombocytopenia and thus ICH which may result in death, either in utero or after birth, or long-lasting disability. A balance must be found between the inherent risks of the condition itself and the risks of diagnostic testing and therapy. The antenatal treatment of FNAIT has evolved over the past 25 years, largely based on published case series, detailing outcomes with differing regimens. They include: (a) fetal blood sampling (FBS) and serial intrauterine platelet transfusions (IUT) [54, 74]; (b) weekly intravenous immunoglobulin (IVIg) infusions; and (c) immunosuppression with corticosteroids [5, 57, 75]. Over the last 15 years, there has been a gradual change from invasive management to a less invasive management protocol to a completely non-invasive approach. However, controversy still exists over the optimal antenatal management strategy.

16.6.1 Diagnostic Fetal Blood Sampling and Intrauterine Platelet Transfusions

Fetal blood sampling (FBS) involves the insertion of a needle into the umbilical or intrahepatic vein to sample fetal blood in order to ascertain the fetal platelet count. The procedure is usually complemented by the transfusion of a specially selected, very concentrated platelet suspension that is both HPA and ABO and RhD blood group compatible, to reduce the risk of bleeding associated with individual procedures [74, 76, 77]. With reports of a fetal loss rate of around 6 % per pregnancy [78], serial (weekly) intrauterine platelet transfusions (IUPT) are reserved for the management of affected fetuses that do not respond to medical management alone. An important unresolved issue in the management of at-risk pregnancies is how to safely minimize or eliminate FBS [66, 79]. FBS, with its associated risks of bleeding, boosting antibody levels, fetal bradycardia requiring emergency (preterm) Cesarean section, and fetal loss, may not be necessary before medical therapy for FNAIT is instituted, but may be required subsequently to determine the fetal response to treatment and IUPT in selected cases [56, 80–82].

16.6.2 Intravenous Immunoglobulin

After anecdotal observation by Bussel et al. [50] that antenatal maternal treatment with high-dose IVIg seemed to prevent ICH in high-risk pregnancies, IVIg became increasingly popular in the treatment of FNAIT [83]. It is often given to the mother on a weekly basis, using various regimens, until delivery. After birth, the neonatal platelet count and the absence of ICH provide measures of IVIg efficacy.

The mechanism of action of IVIg in FNAIT is still unclear. Four possible explanations are cited in the literature. First, in the maternal circulation IVIg will dilute the anti-HPA antibodies, resulting in a lower proportion of anti-HPA antibodies

within the IgG transferred to the fetus via the Fc-receptors in the placenta. Secondly, in the placenta, IVIg may block the placenta receptor (Fc-R) and reduce the placental transmission of maternal antibodies, including anti-HPA antibodies. Thirdly, in the fetus, IVIg can block the Fc-receptors on the macrophages and thereby prevent the destruction of antibody-covered cells [66]. A fourth possible mechanism could be that IVIg may enhance the expression of inhibitory receptors on splenic macrophages [84] and, as a result, suppress maternal antibody production and reduce placental transfer of the antibodies [85]. So far, evidence for only the first mechanism exists.

Short-term mild side effects that have been associated with IVIg therapy include headache, febrile reactions, nausea, malaise and myalgia, but these are more common with rapid infusion and can be minimized by slowing the infusion rate. Several rare but serious side-effects such as aseptic meningitis, acute renal failure, thrombosis, transmission of blood-borne diseases, and reactions including severe headache and fever, and anaphylaxis, have also been reported.

The long-term side effects of IVIg for mother and child are still unclear, but it is generally considered safe. A possible increase of IgE in children after maternal IVIg administration compared to the normal population has been suggested. However, no clinically apparent adverse effects in early childhood could be demonstrated [66]. Since IVIg is known for its immunomodulating characteristics, there is always a possibility of long-time side-effects for the mother and child. Furthermore, weekly IVIg administration is expensive.

Weekly maternal IVIg is the most commonly used therapy today. Following IVIg infusion, the IgG level falls by 30 % after 24 h and by 50 % after 72 h [64]. Maternal administration of IVIg has been reported to increase the fetal platelet count and/or prevent ICH in 55–85 % of FNAIT cases [38, 86–88]. IVIg treatment seems to reduce the risk of ICH even if the fetal platelet count is not altered [79, 89]; the mechanism of this latter effect is unclear. There is conflicting evidence on the efficacy of IVIg in preventing ICH, with most reports documenting favorable results [53, 86, 88] while others report failure of IVIg to prevent ICH [48, 75, 90]. However, in the latter reports, the IVIg dose used was only 1.0 g/kg/week.

The study by Bussel et al. [86] suggested a substantial elevation in fetal platelet count following treatment with IVIg 1.0 g/kg/week; the reported response rate in the literature varies from 30 to 85 %. Results from a randomized placebo-controlled trial [86] suggest no beneficial effect of adding dexamethasone to the administered IVIg. The dose of IVIg of 1.0 g/kg/week has been commonly used ever since the first publication by Bussel et al. in 1988 [57]. However, the optimal treatment dose regimen of IVIg has not been formally evaluated. In treating chronic ITP, the standard dose is 400 mg/kg daily for 5 days, although 1 g/kg/day for 2 days may be more effective. Placental antibody transfer does not appear to be further increased despite high IgG concentrations in the mother resulting from IVIg treatment. This suggests a limitation of the placental Fc receptor [66].

High levels of maternal anti-HPA 1a have been reported to be strongly associated with severe thrombocytopenia in the neonate [21, 66]. This has prompted the suggestion that in cases of low maternal titers of anti-HPA antibodies, a lower dose of IVIg may be sufficient to reduce transmission of pathogenic HPA antibodies leading to thrombocytopenia. Van den Akker et al. conducted a randomized international multicenter trial to compare the effectiveness of a low dose of IVIg (0.5 g/kg/week) with the commonly used dose (1.0 g/kg/week). Survival was 100 % and none of the neonates had an ICH. However, unfortunately this trial ended prematurely because of inadequate patient recruitment [91]. This study might be regarded as a successful pilot study, and the use of 0.5 g/kg/week IVIg in pregnant women with FNAIT and a previous child without ICH is still an option. However, this should be restricted to patients that participate in a formal prospective study. Van den Akker et al. also recommend non-invasive treatment without recourse to invasive strategies, which is both safe and effective in the antenatal management of FNAIT [56].

16.6.3 Corticosteroids

The administration of steroids as the sole treatment for FNAIT is controversial, as their efficacy is variable and chronic steroid therapy has been associated with adverse effects [57]. In a selection of studies corticosteroids have been administered as a means of supporting the action of IVIg. A study in which very high-risk patients (initial fetal platelet count $<20\times10^9$/L or a sibling with perinatal ICH) received weekly IVIg infusions along with daily corticosteroid therapy showed that the combination was more effective than IVIg alone in eliciting a satisfactory fetal platelet response (82 % vs. 18 %) [49, 79]. Both IVIg alone and IVIg combined with any corticosteroids resulted in an improved clinical outcome in treated FNAIT fetuses compared to their untreated siblings [92]. At present, prednisone seems to be the corticosteroid of choice for treatment of FNAIT [49, 79].

Dexamethasone is now avoided as it may cross the fetal blood-brain barrier. In addition, at higher doses it has been associated with oligohydramnios [57] and, at lower doses, a lack of efficacy [86]. Although mothers may experience side-effects of systemic corticosteroids, clinical experience suggests no abnormalities in children of mothers treated with usual doses of prednisone throughout pregnancy.

In summary, IVIg is the mainstay of the antenatal management of FNAIT. It is recommended that treatment is started 4–6 weeks before the estimated gestational age at which the ICH occurred or severe thrombocytopenia was detected in the previous affected fetus. If this information about the previous pregnancy is unavailable or if the previous sibling did not suffer ICH, IVIg therapy can be instituted at 26–28 weeks' gestation because intrauterine ICH has generally been reported after 30 weeks [73, 89].

The role of concomitant steroids alongside IVIg needs further clarification. Bussel et al. [93] treated women with a history of previous early ICH at various gestations. Treatment comprised initial IVIg 1 or 2 g/kg/week infusion at 12 weeks, with the addition of prednisone later only if the fetal platelet count fell below 30×10^9/L in non-responders to IVIg therapy alone. Clinical outcomes in this study were favorable. Similarly, Berkowitz et al. [79] have proposed that 1 g/kg/week of IVI alone is clearly insufficient in siblings of fetuses with a previous ICH in utero. If the initial fetal platelet count is $<20\times10^9$/L at 20 weeks of gestation, IVIg alone 1 g/kg/week has a substantially lesser effect, and a lower response rate, than IVIg and prednisone combined [49, 79]. Furthermore, they claim that prednisone in low doses is almost as good as 1 g/kg/week of IVIg in the least affected fetuses (those with a sibling without an ICH and with a pre-treatment fetal platelet count of $<20\times10^9$/L) [79].

Since there are substantial risks associated with FBS [80–82] and non-invasive treatment is effective, therapy for FNAIT can be instituted without invasive procedures [38, 89, 94].

A Cochrane review in 2010 [95] concluded that there are insufficient data from randomized controlled trials to determine the optimal antenatal management of FNAIT and that future trials should consider the dose of IVIg, the timing of initial treatment, monitoring of response to treatment, laboratory measures to define pregnancies with a high risk of ICH, management of non-responders, and long-term follow-up of children.

16.6.4 Implications for Practice

1. IVIg can be used as first-line treatment for standard-risk FNAIT, where there was no peripartum ICH in an affected sibling and the pre-treatment fetal platelet count (if performed) is $>20\times10^9$/L. However, the optimal dose of IVIg has not been established and further guidance based on the results of the NOICH 2 study is awaited.
2. IVIg in combination with prednisone may be more effective in raising the fetal platelet count than IVIg alone in high-risk pregnancies, where the pre-treatment fetal platelet count $<20\times10^9$/L or the affected sibling sustained a peripartum ICH. The optimal timing of administration and the dose of prednisone and IVIg are unclear, but studies have demonstrated efficacy when treatment was initiated at 20–26 weeks.

16.7 Suggested Antenatal Management of a Subsequent Affected Fetus

Following the affected pregnancy, the father should be tested for the presence of the relevant HPA. The risk of recurrence in subsequent pregnancies is virtually 100 % if the father is homozygous for the responsible HPA and 50 % if he is heterozygous. In the latter case, it is possible to determine the fetal platelet type by 16 weeks of gestation via PCR amplification of DNA obtained from amniocytes (obtained at amniocentesis). If the fetus is found to be negative for the HPA allele, no further testing is indicated [12, 96, 97]. Pre-implantation diagnosis (PGD) can be considered [98]. Non-invasive prenatal diagnosis (NIPD) using cell-free fetal DNA obtained from maternal plasma and serum is now a clinical reality, particularly in the management of RhD hemolytic disease, and many investigators are evaluating NIPD in FNAIT that may in the future form part of national antenatal screening programs.

The severity of FNAIT usually increases with each pregnancy. Attempts have been made to predict a fetus at risk from severe thrombocytopenia by the use of serial antibody titers in order to determine which fetus needs treatment. As stated above (Sect. 16.5), the antibody titer measurements are not a reliable predictor of the severity of FNAIT and are thus of limited use in the clinical management of FNAIT. The clinical history of an affected sibling is currently the best indicator of risk in a current pregnancy [37, 38, 99]. The recurrence rate of ICH in the subsequent pregnancies of women with FNAIT was 72 % (when the previous pregnancy was without fetal death) and 79 % (when the previous pregnancy included a fetal death). Conversely, the risk of ICH in those with a history of FNAIT but without ICH was estimated at 7 % [99].

It is presumed that, in fetuses with early severe fetal thrombocytopenia, ICH will be seen in a second pregnancy even though this did not occur in the first sibling. In a study by Bussel and Kaplan [47], 50 % of 98 affected fetuses already had a platelet count of $<20\times10^9$/L by 25 weeks' gestation, indicating early severity. Forty percent had a lower fetal platelet count at that time than their previously affected siblings had at birth, indicating increasing severity in subsequent pregnancies. These authors concluded that when FNAIT occurs at an early gestation, it is severe; and it is more severe in fetuses with an older affected sibling that had an antenatal ICH. This suggests that fetuses may require different management strategies depending on the history of their previous sibling. There has been a trend and a strong recommendation to utilize non-invasive strategies (IVIg) in the management of FNAIT at high risk of in utero or postnatal ICH [100, 101].

For platelet antigen incompatibilities other than HPA-1a, much less data exist regarding antenatal management and clinical course. Incompatibility of HPA-3a, while infrequent, is as severe as that of HPA-1a [102], while incompatibilities of HPA-5b and HPA-9b are less severe [103]. HPA-4 incompatibility also seems to be severe [104], and most rare antigens are identified because of a severe case of neonatal FNAIT.

16.8 Timing and Mode of Birth

The delivery plan should be based on the patient's risk category, the response to treatment, and the most recent fetal platelet count, if pertinent [105]. The appropriate gestational age for delivery has not been established. The risk of prematurity and the costs of neonatal intensive care unit admission should be weighed against the risk of continued exposure of the fetus to the harmful antibodies and the cost of IVIg therapy. Different units recommend delivery between 35 weeks and term. Vaginal delivery is reasonable if the fetal platelet count exceeds 50×10^9/L [87]. With platelet counts below 50×10^9/L, IUPT has been performed before vaginal delivery for protection against bleeding at the time of delivery, with its associated risks. There is no evidence that vaginal delivery of a fetus with a platelet count below 50×10^9/L increases the risk of ICH. In a Dutch study of 32 pregnancies complicated by FNAIT in which the thrombocytopenic sibling did not have an ICH, vaginal delivery was not associated

with neonatal intracranial bleeding, even though the platelet count was $<50 \times 10^9$/L in 4 neonates [106]. Cesarean delivery alone is not considered effective in preventing antenatal or perinatal hemorrhage [11, 107]. Instrumental vaginal delivery, ventouse, fetal scalp electrode and fetal scalp blood sampling should be avoided. The neonatologist on duty during delivery should be informed in advance, as should a consultant in hematology/transfusion medicine, and the blood transfusion laboratory should also be asked in advance to obtain HPA compatible platelets.

16.9 Treatment of the Neonate

Treatment of the neonate is dictated by its condition. If there are no signs of bleeding and the thrombocytopenia is mild or moderate, no therapy is necessary. In cases of neonatal bleeding or a platelet count below 30×10^9/L, therapy is needed and must be rapid and effective. First-line therapy is prompt transfusion of (ideally) HPA-compatible platelets that will not be destroyed by maternal antibodies in the neonate's circulation. Blood centers should be able to supply HPA-1a and 5b negative platelets. If these are not available, an amendment to the British Committee in Standards for Haematology (BCSH) guidelines recommends using platelets that are not selected for HPA status [60]. Treatment of neonatal FNAIT with IVIg and/or steroids is advised when severe thrombocytopenia and/or hemorrhage persist despite transfusion of HPA-compatible platelets. Platelet transfusion thresholds of $20–30 \times 10^9$/L and 50×10^9/L are recommended for neonates, depending on the clinical situation [60]. The effectiveness of IVIg in the neonate has not been shown in some studies [108]. The therapeutic effect on the platelet count, however, is delayed for 24–48 h, during which time the neonate remains at risk of ICH.

16.10 Preconception Counseling

Pregnant women are at risk of FNAIT if they have a history of a previous neonate with FNAIT or are known to have circulating alloantibodies [4]. Before a subsequent pregnancy, these women should be referred to a tertiary center that specializes in the treatment of FNAIT. The risks of ICH in a subsequent pregnancy and the diagnosis and treatment strategies that might be of benefit should be discussed, as addressed above. If the previously affected child had an ICH, there is a 70–80 % chance that the next affected child will have an ICH. However, if the pregnancy complicated by FNAIT did not involve ICH, the risk of ICH in a subsequent pregnancy is less than 10 % [38, 99, 109]. Counseling is most effective after HPA typing of the father. If the father is homozygous for the HPA allele, the risk of recurrence of FNAIT is 100 %, whereas the risk of recurrence is 50 % if the father is heterozygous.

16.11 Screening for FNAIT in the First Pregnancy

The implementation of an antenatal screening program for FNAIT depends on cost-effectiveness and is currently under debate. Several studies provided calculations and reached the conclusion that screening is likely to be cost-effective [38, 55, 110–112], although this was not a universal view [113]. Antenatal screening for FNAIT might identify alloimmunized women during their first pregnancy, allowing antenatal intervention to prevent ICH. Even if no antenatal intervention was undertaken, delivery could be planned so that compatible platelets would be available [7].

The major determinants of the costs are the initial HPA typing, antibody detection in those at risk, and costs of interventions. Although these costs are considerable, even for the most expensive strategy (e.g. offering IVIg to all immunized women), they are easily outweighed by the savings made in preventing most cases of life-long severe neurological morbidity.

Three large studies of antenatal screening for HPA-1a incompatibility have been performed [15, 17, 114]. Two, from East Anglia [114] and Scotland [17] in the UK, were performed in approximately 25,000 cases each. The largest study in Norway included more than 100,000

pregnancies [15]. Another study from Norway concluded that, without a screening programme, the detection rate of NAIT in Norway is only 14 % of expected [115]. Key findings from these studies suggest that the incidence of FNAIT in the neonate was approximately 1:5,000 but, on antenatal screening, a higher incidence of 1:1,000 using HPA-1a incompatibility only was noted. A systematic review suggests that screening for HPA-1a alloimmunization detects around 2 cases in 1,000 pregnancies and that severe FNAIT occurs in around 40 per 1,000,000 pregnancies. Despite several antenatal interventions, severe ICH occurred in 3–4 children per 1,000,000 pregnancies screened. Furthermore, the review highlighted that the incidence of ICH in non-screened populations is likely to be higher. Screening of all pregnancies together with effective antenatal treatment such as IVIg may reduce the mortality and morbidity associated with FNAIT without known risks for the mother or child [14, 82, 83, 116]. These data indicate that large-scale screening studies including comparison of intervention strategies are warranted [117, 118].

Conclusions

The most serious complication of FNAIT is ICH, which occurs in 10–30 % of severe cases, causing death (10 %) and neurological sequelae (10–20 %). In the majority of cases, fetal thrombocytopenia is more severe and occurs successively earlier in subsequent pregnancies [50]. There is a 70–80 % risk of antenatal ICH in a subsequent pregnancy complicated by FNAIT if a previous child had ICH [38, 90]. Most cases of in utero ICH involve HPA-1a incompatibility with severe thrombocytopenia, although a few cases have resulted from incompatibility for HPA-3a, HPA-4b, HPA-5b, or HPA-9b alloantigens.

Antenatal management of FNAIT includes weekly maternal IVIg infusions which are very effective. Concomitant usage of steroids alongside IVIg has been suggested to show favorable results in high-risk fetuses that have not responded to IVIg alone [49, 94, 109, 119]. Treatment should start 4–6 weeks before the estimated gestational age at which ICH or severe thrombocytopenia occurred in the previous pregnancy, or at approximately 28 weeks' gestation [73, 89].

FBS with its significant associated risks may not be necessary before therapy for FNAIT is instituted, but may become necessary to determine the fetal response to treatment [56]. Spontaneous vaginal delivery is preferred in FNAIT cases, while avoiding procedures that might increase the risk of fetal hemorrhage (such as fetal scalp electrode, fetal scalp blood sampling, forceps or ventouse assistance) [106]. Cesarean section may be performed in selected high-risk fetuses.

At present, there is no approved method of antenatal screening to detect the first affected pregnancy [59, 114, 120]. Postnatal screening, although simple, cannot prevent neonatal morbidity and mortality [55].

The aim of current research must be to develop reliable predictors of disease severity in affected infants and to increase the effectiveness of non-invasive treatment strategies for FNAIT. Prospective trials are necessary to evaluate different treatment strategies and to acquire additional data on optimal prevention programs.

16.12 Case Studies

Case Study 1

A 36 year old primigravida delivered a baby girl vaginally at 41 weeks' gestation. The Apgar scores were 8 at 1 min and 9 at 5 min. The 1-h assessment was normal except for bruising on the scalp. By 6 h of age, however, the infant was feeding poorly and was hypothermic, with decreased tone, irritability, and hyper-responsiveness to stimulation; her anterior and posterior fontanelles were full. Bruising was noted over the entire scalp, with petechiae covering the entire chest, abdomen, and upper and lower limbs.

A full blood count showed severe thrombocytopenia (platelets 16×10^9/L). A coagulation screen (prothrombin time (PT), activated partial thromboplastin time (APTT) and fibrinogen) was normal. The CT scan showed a very large acute subdural hematoma on the right side of the cerebellum, with midline shift to the left. The compressed cerebellum

caused obstruction of the cisterns and increased the size of the temporal horns of the lateral ventricles, resulting in increased intracranial pressure (ICP). A repeat platelet count was 6×10^9/L. The infant was transferred to a neonatal intensive care unit and emergency surgery was undertaken to evacuate the subdural hematoma. After surgery, the ICP dropped, and the ventricular size was normal on repeat CT scan.

In the meantime, the mother, who had a normal platelet count, was tested for antibodies. Her platelet count was normal, but her screen was positive for anti-HPA-1 antibodies, consistent with a diagnosis of neonatal alloimmune thrombocytopenia (NAIT) (confirmation of the diagnosis would require maternal-fetal or maternal-paternal HPA incompatibility and exclusion of other causes of thrombocytopenia). During the first 36 h of life, the infant was transfused with random donor platelets, red blood cells, FFP, and cryoprecipitate. The platelet count improved and by day 5 was 228×10^9/L, increasing to 346×10^9/L by discharge on Day 7 of life. The infant was eating well and gaining weight by discharge. The platelet count remained stable at 2 weeks and 1 month of age. At 1-year follow-up, the infant was thriving and developmentally appropriate [121].

Case Studies 2 & 3

Maternal immunization against low-frequency, platelet (PLT)-specific antigens is being recognized with increasing frequency as a cause of NAIT. These two cases of severe NAIT were caused by maternal immunization against previously unrecognized, low-frequency antigens created by amino acid substitutions in GPIIb/IIIa (αIIb/β3 integrin). They highlight that a search should be conducted for novel paternal antigens in cases of apparent NAIT not explained on the basis of maternal-fetal incompatibility for known human platelet antigens.

Case Study 2 (HPA-22bw, Sey)

A 31 year old mother had a spontaneous vaginal birth of a female infant. The baby had scattered petechial hemorrhages at birth associated with severe thrombocytopenia (platelets 13×10^9/L), with the remainder of the blood count normal. A random-donor platelet transfusion and intravenous immunoglobulin (IVIg) 1.0 g/kg body weight were administered, after which the platelet count increased to 80×10^9/L. During the next 11 days, the baby received two additional platelet transfusions and two IVIg infusions. After each transfusion, the platelet count increased to the range of 50×10^9/L to 80×10^9/L, but subsequently declined. On Day 9, the platelet count had fallen to 22×10^9/L and bloody stools were observed. A platelet transfusion and IVIg were again administered. The platelets rose to 65×10^9/L and increased steadily thereafter. The child was discharged on Day 15 with a normal platelet count.

Case Study 3 (HPA-23bw, Hug)

The second child, a boy, was born to a 22-year-old woman by spontaneous vaginal delivery.

He developed widespread petechial and subconjunctival hemorrhages soon after birth and was found to have a platelet count of 13×10^9/L. Other hematological findings were unremarkable except for a weakly positive direct antiglobulin test thought to be a consequence of maternal-fetal incompatibility for blood group B. At 1 day of age, the baby's petechial hemorrhages were resolving and its platelet count was 27×10^9/L. IVIg, 1 g/kg body weight, was administered. The platelet counts were 38×10^9/L the next day and 102×10^9/L 2 days later. The baby was discharged on day 5 [122].

Key Learning Points

- All cases of FNAIT should be managed by maternal-fetal medicine specialists in tertiary referral centers, with appropriate liaison with specialists in neonatology and hematology/transfusion medicine.
- If the previously affected sibling had an ICH, the next affected fetus is highly likely to have early, severe thrombocytopenia and in utero ICH, in the absence of effective treatment.
- Effective non-invasive antenatal treatment (IVIg) exists for cases recognized as a result of a previously affected sibling.
- Invasive treatment (intrauterine platelet transfusions) appears to be required only in non-responders.

References

1. Moulinier J. Alloimmunisation maternelle antiplaquettaire duzo. In: Proceedings of the 6th congress of the European society of haematology. Paris: European Society of Hematology; 1953. p. 817–20.
2. Shulman NR, Marder VJ, et al. Platelet and leukocyte isoantigens and their antibodies: serologic physiologic and clinical studies. Prog Hematol. 1964;4:222–304.
3. Burrows RF, Kelton JG. Fetal thrombocytopenia and its relation to maternal thrombocytopenia. N Engl J Med. 1993;329:1463–6.
4. Blanchette VS, Johnson J, Rand M. The management of alloimmune neonatal thrombocytopenia. Baillieres Best Pract Res Clin Haematol. 2000;13: 365–90.
5. Kaplan C, Murphy MF. Feto-maternal alloimmune thrombocytopenia: antenatal therapy with IvIgG and steroids – more questions than answers. European Working Group on FMAIT. Br J Haematol. 1998; 100(1):62–5.
6. Kaplan C, Forestier F, Daffos F. Management of fetal and neonatal alloimmune thrombocytopenia. Transfus Med Rev. 1996;10:233–40.
7. Murphy MF, Williamson LM. Antenatal screening for fetomaternal alloimmune thrombocytopenia: an evaluation using the criteria of the UK National Screening Committee. Br J Haematol. 2000;111:726–32.
8. Proulx C, Filion M, Goldman M. Analysis of immunoglobulin class, IgG subclass and titre of HPA-1a antibodies in alloimmunized mothers giving birth to babies with or without neonatal alloimmune thrombocytopenia. Br J Haematol. 1994;87:813–7.
9. Rothenberger S. Neonatal alloimmune thrombocytopenia. Ther Apher. 2002;6:32–5.
10. Kaplan C. Platelet alloimmunity: the fetal/neonatal alloimmune thrombocytopenia. Vox Sang. 2002;83 Suppl 1:289–91.
11. Murphy MF, Manley R, Roberts D. Neonatal alloimmune thrombocytopenia. Haematologica. 1999;84: 110–4.
12. Spencer JA, Burrows RF. Feto-maternal alloimmune thrombocytopenia: a literature review and statistical analysis. Aust N Z J Obstet Gynaecol. 2001;41:45–55.
13. Blanchette VS, Chen L, de Friedberg ZS. Alloimmunisation to the PlA1 platelet antigen: results of a prospective study. Br J Haematol. 1990;74:209–15.
14. Kamphuis MM, Paridaans N, Porcelijn L, De Haas M, van der Schoot CE, Brand A, Bonsel GJ, Oepkes D. Screening in pregnancy for fetal or neonatal alloimmune thrombocytopenia: systematic review. BJOG. 2010;117(11):1335–43.
15. Kjeldsen-Kragh J, Killie MK, Tomter G, Golebiowska E, Randen I, Hauge R. A screening and intervention program aimed to reduce mortality and serious morbidity associated with severe neo-natal alloimmune thrombocytopenia. Blood. 2007;110:833.
16. Mueller-Eckhardt C, Mueller-Eckhardt G, Willen-Ohff H, Horz A, Kuenzlen E, O'Neill GJ. Immunogenicity of and immune response to the human platelet antigen Zwa is strongly associated with HLAB8 and DR3. Tissue Antigens. 1985;26:71–6.
17. Turner ML, Bessos H, Fagge T. Prospective epidemiologic study of the outcome and cost-effectiveness of antenatal screening to detect neonatal alloimmune thrombocytopenia due to anti-HPA-1a. Transfusion. 2005;45:1945–56.
18. Decary F, L'Abbe D, Tremblay L. The immune response to the HPA-1a antigen: association with HLA-DRw52a. Transfus Med. 1991;1:55–62.
19. Mueller-Eckhardt C, Santoso S, Kiefel V. Platelet alloantigens molecular, genetic, and clinical aspects. Vox Sang. 1994;67S3:89–93.
20. Doughty HA, Murphy MF, Metcalfe P. Antenatal screening for fetal alloimmune thrombocytopenia: the results of a pilot study. Br J Haematol. 1995;90:321–5.
21. Jaegtvik S, Husebekk A, Aune B. Neonatal alloimmune thrombocytopenia due to anti-HPA-1a antibodies; the level of maternal antibodies predicts the severity of thrombocytopenia in the newborn. Br J Obstet Gynaecol. 2000;107:691–4.
22. Valentin N, Vergracht A, Bignon JD. HLA-DRw52a is involved in alloimmunization against PL-A1 antigen. Hum Immunol. 1990;27:73–9.
23. Reznikoff-Etievant MF. Management of alloimmune neonatal and antenatal thrombocytopenia. Vox Sang. 1988;55:193–201.
24. Mueller-Eckhardt C, Grubert A, Weisheit M. 348 cases of suspected neonatal alloimmune thrombocytopenia. Lancet. 1989;1:363–6.
25. Kornfeld I, Wilson RD, Ballem P. Antenatal invasive and noninvasive management of alloimmune thrombocytopenia. Fetal Diagn Ther. 1996;11:210–7.
26. Letsky EA, Greaves M. Guidelines on the investigation and management of thrombocytopenia in pregnancy and neonatal alloimmune thrombocytopenia. Br J Haematol. 1996;95:21–6.
27. Khouzami AN, Kickler TS, Callan NA. Devastating sequelae of alloimmune thrombocytopenia: an entity that deserves more attention. J Matern Fetal Med. 1996;5:137–41.
28. Kanhai HHH, Porcelijn L, van Zoeren D. Antenatal care in pregnancies at risk of alloimmune thrombocytopenia: report of 19 cases in 16 families. Eur J Obstet Gynecol Reprod Biol. 1996;68:67–73.
29. Uhrynowska M, Maslanka K, Zupanska B. Neonatal thrombocytopenia: incidence, serological and clinical observations. Am J Perinatol. 1997;14:415–8.
30. Davoren A, McParland P, Barnes CA. Neonatal alloimmune thrombocytopenia in the Irish population: a discrepancy between observed and expected cases. J Clin Pathol. 2002;55:289–92.
31. Davoren A, Curtis BR, Aster RH. Human platelet antigen-specific alloantibodies implicated in 1162 cases of neonatal alloimmune thrombocytopenia. Immunohematology. 2004;44:1220–5.

32. Rayment R, Birchall J, Yarranton H, Hewertson J, Allen D, Murphy MF. Neonatal alloimmune thrombocytopenia. BMJ. 2003;327:331–2.
33. Mandelbaum M, Koren D, Eichelberger B. Frequencies of maternal platelet alloantibodies and autoantibodies in suspected fetal/neonatal alloimmune thrombocytopenia, with emphasis on human platelet antigen-15 alloimmunization. Vox Sang. 2005;89:39–43.
34. Ertel K, Al-Tawil M, Santoso S. Relevance of the HPA-15 (Gov) polymorphism on CD109 in alloimmune thrombocytopenic syndromes. Transfusion. 2005;45:366–73.
35. Kroll H, Yates J, Santoso S. Immunization against a low-frequency human platelet alloantigen in fetal alloimmune thrombocytopenia is not a single event: characterization by the combined use of reference DNA and novel allele-specific cell lines expressing recombinant antigens. Transfusion. 2005;45:353–8.
36. Porcelijn L, Huiskes E, Overbeeke M. Rare anti HPA-5a NAIT cases. Vox Sang. 2006;91S2:Abstract 55.
37. Ahya R, Turner ML, Urbaniak SJ. Fetomaternal alloimmune thrombocytopenia. Transfus Apher Sci. 2001;25:139–45.
38. Birchall J, Murphy MF, Kaplan C. European collaborative study of the antenatal management of feto-maternal alloimmune thrombocytopenia. Br J Haematol. 2003;122:275–88.
39. Kaplan C, Morel-Kopp MC, Clemenceau S. Fetal and neonatal alloimmune thrombocytopenia: current trends in diagnosis and therapy. Transfus Med. 1992; 2:265–71.
40. Taaning E. HLA antibodies and fetomaternal alloimmune thrombocytopenia: myth or meaningful? Transfus Med Rev. 2000;14:275–80.
41. Kiefel V. The MAIPA assay and its applications in immunohaematology. Transfus Med. 1992;2:181–8.
42. Bertrand G, Jallu V, Gouet M. Quantification of human platelet antigen-1a antibodies with monoclonal antibody immobilization of platelet antigens procedure. Transfusion. 2005;45:1319–23.
43. Goldman M, Trudel E, Richard L. Report on the eleventh international society of blood transfusion platelet genotyping and serology workshop. Vox Sang. 2003;85:149–55.
44. Kaplan C. Alloimmune thrombocytopenia of the fetus and the newborn. Blood Rev. 2002;16:69–72.
45. Killie MK, Kjeldsen-Kragh J, Skogen B. Maternal anti-HPA1a antibody level as predictive value in neo-natal alloimmune thrombocytopenic purpura (NAITP). Blood. 2004;104:Abstract 2072.
46. Meyer O, Agaylan A, Borchert H. A simple and practical assay for the antigen-specific detection of platelet antibodies. Transfusion. 2006;46:1226–31.
47. Bussel JB, Kaplan C. The fetal and neonatal consequences of maternal alloimmune thrombocytopenia. Baillieres Clin Haematol. 2007;11:391–408.
48. Sainio S, Teramo K, Kekomaki R. Prenatal treatment of severe fetomaternal alloimmune thrombocytopenia. Transfus Med. 1999;9:321–30.
49. Berkowitz RL, Kolb A, Mcfarland JG. Parallel randomized trials of risk-based therapy for fetal alloimmune thrombocytopenia. Obstet Gynecol. 2006;107:91–6.
50. Bussel JB, Skupski DW, Mcfarland JG. Fetal alloimmune thrombocytopenia: consensus and controversy. J Matern Fetal Med. 1996;5:281–92.
51. Kuhn MJ, Couch SM, Binstadt DH. Prenatal recognition of central nervous system complications of alloimmune thrombocytopenia. Comput Med Imaging Graph. 1992;16:137–42.
52. Stanworth SJ, Hackett G, Williamson LM. Fetomaternal alloimmune thrombocytopenia presenting antenatally as hydrops fetalis. Prenat Diagn. 2001; 21:418–24.
53. Bussel JB. Immune thrombocytopenia in pregnancy: autoimmune and allo-immune. J Reprod Immunol. 1997;37:35–61.
54. Kaplan C, Daffos F, Forestier F. Management of alloimmune thrombocytopenia: antenatal diagnosis and in utero transfusion of maternal platelets. Blood. 1988;72:340–3.
55. Murphy MF, Williamson LM, Urbaniak SJ. Antenatal screening for fetomaternal alloimmune thrombocytopenia: should we be doing it? Vox Sang. 2002;83 Suppl 1:409–16.
56. Van den Akker ES, Oepkes D, Lopriore E, Brand A, Kanhai HH. Noninvasive antenatal management of fetal and neonatal alloimmune thrombocytopenia: safe and effective. BJOG. 2007;114(4):469–73.
57. Bussel JB, Berkowitz RL, McFarland JG. Antenatal treatment of neonatal alloimmune thrombocytopenia. N Engl J Med. 1988;319:1374–8.
58. Ohto H, Yamaguchi T, Takeuchi C. Anti-HPA-5b-induced neonatal alloimmune thrombocytopenia: antibody titre as predictor. Br J Haematol. 2000;110:223–7.
59. Killie MK, Husebekk A, Kjeldsen-Kragh J. Significance of antibody quantification. Vox Sang. 2006;91:15. Abstract 51.
60. BCSH guidelines, Gibson BES, Bolton-Maggs PHB, Pamphilon D, et al. Transfusion guidelines for neonates and older children. Br J Haematol. 2004;124:433–53;2005 amendment to these guidelines: www.bcshguidelines.com.
61. Bessos H, Turner M, Urbaniak SJ. Is there a relationship between anti-HPA-1a concentration and severity of neonatal alloimmune thrombocytopenia? Immunohematology. 2005;21:102–8.
62. Lyou JY, Chen YJ, Hu HY. PCR with sequence-specific primer-based simultaneous genotyping of human platelet antigen-1 to -13w. Transfusion. 2002; 42:1089–95.
63. Peterson JA, Balthazor SM, Curtis BR. Maternal alloimmunization against the rare platelet-specific antigen HPA-9b (Max-a) is an important cause of neonatal alloimmune thrombocytopenia. Transfusion. 2005;45:1487–95.
64. Chaoying M, Junwu G, Chituwo BM. Intraventricular haemorrhage and its prognosis, prevention and treatment in term infants. J Trop Pediatr. 1999;45: 237–9.

65. Tiller H, Kamphuis MM, Flodmark O, Papadogiannakis N, David AL, Sainio S, Koskinen S, Javela K, Wikman AT, Kekomaki R, Kanhai HH, Oepkes D, Husebekk A, Westgren M. Fetal intracranial haemorrhages caused by fetal and neonatal alloimmune thrombocytopenia: an observational cohort study of 43 cases from an international multicentre registry. BMJ Open. 2013;3(3). pii:e002490. doi:10.1136/bmjopen-2012-002490.
66. Radder CM, Kanhai HH, Brand A. On the mechanism of high dose maternal intravenous immunoglobulin (IVIG) in alloimmune thrombocytopenia. In: Management of fetal alloimmune thrombocytopenia. Amsterdam: Print Partners Ipskamp; 2004. p. 69–81.
67. Kaplan C, Daffos F, Forestier F, Morel MC, Chesnel N, Tchernia G. Cur- rent trends in neonatal alloimmune thrombocytopenia: diagnosis and therapy. In: Kaplan-Gouet C, Schlegel N, Salmon C, McGregor J, editors. Platelet immunology: fundamental and clinical aspects. Paris: Colloque INSERM/John Libbey Eurotext; 1991. p. 267–78.
68. Prouix C, Filion M, Goldman M, Bradley A, Devine D, Decary F, Chartrand P. Analysis of immunoglobulin class, IgG subclass and titre of HPA-1a antibodies in alloimmunised mothers giving birth to babies with or without neonatal alloimmune thrombocytopenia. Br J Haematol. 1994;87:813–7.
69. Marzusch K, Fischer Dietl J, Wiest E, Volklein K, Schnaid M. Difficulties in the antenatal assessment of neonatal alloimmune thrombocytopenia. Acta Obstet Gynecol Scand. 1993;72:583–5.
70. Bertrand G, Martageix C, Jallu V. Predictive value of sequential maternal anti-HPA-1a antibody concentrations for the severity of fetal alloimmune thrombocytopenia. J Thromb Haemost. 2006;4:628–37.
71. Ghevaert C, Campbell K, Stafford P, Metcalfe P, Casbard A, Smith GA, Allen D, Ranasinghe E, Williamson LM, Ouwehand WH. HPA-1a antibody potency and bioactivity do not predict severity of feto-maternal alloimmune thrombocytopenia. Transfusion. 2007;7:1296–305.
72. Ino H, Torigoe K, Numata O. A case of neonatal alloimmune thrombocytopenic purpura by anti-HPA-4b with intracranial hemorrhage. J Jpn Pediatr Soc. 2000;104:682–5.
73. Radder CM, Kanhai HH, de Beaufort AJ. Evaluation of gradual conversion to a less invasive therapeutic strategy for pregnant women with alloimmune thrombocytopenia in the fetus for prevention of intracranial hemorrhage. Ned Tijdschr Geneeskd. 2000;144:2015–8.
74. Murphy MF, Pullon HWH, Metcalfe P, Chapman JF, Jenkins E, Waters AH. Management of fetal alloimmune thrombocytopenia by weekly in utero platelet transfusions. Vox Sang. 1990;58:45–9.
75. Murphy MF, Waters AH, Doughty HA, Hambley H, Mibashan RS, Nicolaides K. Antenatal management of fetal alloimmune thrombocytopenia. Transfus Med. 1994;4:281–92.
76. Paidas MJ, Berkowitz RL, Lynch L, Lockwood CJ, Lapinski R, McFarland JG. Alloimmune thrombocytopenia: fetal and neonatal losses related to cordocentesis. Am J Obstet Gynecol. 1995;172:475–9.
77. Simsek S, Christiaens GCLM, Kanhai HHH. Human platelet antigen-1 (Zw) typing of fetuses by analysis of polymerase chain reaction-amplified genomic DNA from amniocytes. Transfus Med. 1994;4: 15–9.
78. Overton TG, Duncan KR, Jolly M, Letsky E, Fisk NM. Serial aggressive platelet transfusion for fetal alloimmune thrombocytopenia: platelet dynamics and peri-natal outcome. Am J Obstet Gynecol. 2002;186(4):826–31.
79. Berkowitz RL, Lesser ML, McFarland JG, Wissert M, Primiani A, Hung C. Antepartum treatment without early cordocentesis for standard-risk alloimmune thrombocytopenia: a randomised controlled trial. Obstet Gynecol. 2007;110(2 Pt 1):249–55.
80. Nicolini U, Kochenour NK, Greco P, Letsky EA, Johnson RD, Contreras M. Consequences of fetomaternal haemorrhage after intrauterine transfusion. BMJ. 1988;297:1379–81.
81. Radder CM, Roelen DL, Van de Meer-Prins EM, Claas FHJ, Kanhai HHH, Brand A. The immunologic profile of infants born after maternal immunoglobulin treatment and intrauterine platelet transfusions for fetal/neonatal alloimmune thrombocytopenia. Am J Obstet Gynecol. 2004;191:815–20.
82. Radder CM, de Haan MJJ, Brand A, Stoelhorst GMSJ, Veen S, Kanhai HHH. Follow up of children after antenatal treatment for alloimmune thrombocytopenia. Early Hum Dev. 2004;80:65–76.
83. Zimmermann R, Huch A. In utero therapy with immunoglobulin for alloimmune thrombocytopenia. Lancet. 1992;340:1034–5.
84. Samuelsson A, Towers TL, Ravetch JV. Anti-inflammatory activity of IVIG mediated through the inhibitory Fc receptor. Science. 2001;291:484–6.
85. Clark AL, Gall SA. Clinical uses of intravenous immunoglobulin in pregnancy. Am J Obstet Gynecol. 1998;176:241–53.
86. Bussel JB, Berkowitz RL, Lynch L, Lesser ML, Paidas MJ, Huang CL. Antenatal management of alloimmune thrombocytopenia with intravenous gamma-globulin: a randomized trial of the addition of low dose steroid to intravenous gamma-globulin. Am J Obstet Gynecol. 1996;174(5):1414–23.
87. Gaddipati S, Berkowitz RL, Lembet AA. Initial fetal platelet counts predict the response to intravenous gammaglobulin therapy in fetuses that are affected by PLA1 incompatibility. Am J Obstet Gynecol. 2001;185:976–80.
88. Lynch L, Bussel JB, McFarland JG, Chitkara U, Berkowitz RL. Antenatal treatment of alloimmune thrombocytopenia. Obstet Gynecol. 1992;80:67–71.
89. Radder CM, Brand A, Kanhai HH. A less invasive treatment strategy to prevent intracranial hemorrhage in fetal and neonatal alloimmune thrombocytopenia. Am J Obstet Gynecol. 2001;185:683–8.

90. Kroll H, Kiefel V, Giers G, Bald R, Hoch J, Hanfland P. Maternal intravenous immunoglobulin treatment does not prevent intracranial haemorrhage in fetal alloimmune thrombocytopenia. Transfus Med. 1994;4(4):293–6.
91. Van den Akker ESA, Westgren M, Husbekk A, Kanhai HHH, Oepkes D. Fetal or neonatal alloimmune thrombocytopenia: a new randomized con-trolled trial and international multicenter data collection [abstract]. J Obstet Gynaecol. 2006;26 Suppl 1:S63.
92. Ward MJ, Pauliny J, Lipper EG, Bussel JB. Long-term effects of fetal and neonatal alloimmune thrombocytopenia and its antenatal treatment on the medical and developmental outcomes of affected children. Am J Perinatol. 2006;23(8):487–92.
93. Bussel JB, Berkowitz RL, Hung C, Kolb EA, Wissert M, Primiani A, Tsaur FW, Macfarland JG. Intracranial hemorrhage in alloimmune thrombocytopenia: stratified management to prevent recurrence in the subsequent affected fetus. Am J Obstet Gynecol. 2010;203(2):135.e1–14.
94. Paternoster DM, Cester M, Memmo A. The management of feto-maternal alloimmune thrombocytopenia: report of three cases. J Matern Fetal Neonatal Med. 2006;19:517–20.
95. Rayment R, Brunskill SJ, Soothill PW, Roberts DJ, Bussel JB, Murphy MF. Antenatal interventions for fetomaternal alloimmune thrombocytopenia. Cochrane Database Syst Rev. 2011;(5):CD004226. doi:10.1002/14651858.CD004226.pub3.
96. Bennett PR, Warwick R, Vaughan J. Prenatal determination of human platelet antigen type using DNA amplification following amniocentesis. Br J Obstet Gynaecol. 1994;101:246–9.
97. Sainio S, Jarvenpaa AL, Renlund M. Thrombocytopenia in term infants: a population-based study. Obstet Gynecol. 2000;95:441–6.
98. Bennett PR, Vaughan J, Handyside A. Potential for pre-implantation determination of human platelet antigen type using DNA amplification: a strategy for prevention of allo-immune thrombocytopenia. Fetal Diagn Ther. 1994;9:229–32.
99. Radder CM, Brand A, Kanhai HHH. Will it ever be possible to balance the risk of intracranial haemorrhage in fetal or neonatal alloimmune thrombocytopenia against the risk of treatment strategies to prevent it? Vox Sang. 2003;84:318–25.
100. Deruelle P, Wibaut B, Manessier L, Subtil D, Vaast P, Puech F, Valat AS. Is a non-invasive management allowed for maternofetal alloimmune thrombocytopenia? Experience over a 10-year period. Gynecol Obstet Fertil. 2007;35(3):199–204.
101. Kanhai HH, van den Akker ES, Walther FJ, Brand A. Intravenous immunoglobulins without initial and follow-up cordocentesis in alloimmune fetal and neonatal thrombocytopenia at high risk for intracranial hemorrhage. Fetal Diagn Ther. 2006;21(1):55–60.
102. Glade-Bender J, McFarland JG, Kaplan C, Porcelijn L, Bussel JB. Anti-HPA-3A induces severe neonatal alloimmune thrombocytopenia. J Pediatr. 2001;138:862–7.
103. Kaplan C, Morel-Kopp MC, Kroll H, Kiefel V, Sohlege N, Chesnel N, Mueller-Eckhardt C. HPA-5b (Br(a)) neonatal alloimmune thrombocytopenia: clinical and immunological analysis of 39 cases. Br J Haematol. 1991;78:425–9.
104. Friedman JM, Aster RH. Neonatal alloimmune thrombocytopenic purpura and congenital porencephaly in two siblings associated with a "new" maternal antiplatelet antibody. Blood. 1985;65:1412–5.
105. Gyamfi C, Eddleman KA. Alloimmune thrombocytopenia. Clin Obstet Gynecol. 2005;48:897–909.
106. Van den Akker E, Oepkes D, Brand A, Kanhai HH. Vaginal delivery for fetuses at risk of alloimmune thrombocytopenia? BJOG. 2006;113(7):781–3.
107. Sia CG, Amigo NC, Harper RG. Failure of cesarean section to prevent intracranial hemorrhage in siblings with isoimmune neonatal thrombocytopenia. Am J Obstet Gynecol. 1985;153:79–81.
108. te Pas AB, Lopriore E, van den Akker ES, Oepkes D, Kanhai HH, Brand A, Walther FJ. Postnatal management of fetal and neonatal alloimmune thrombocytopenia: the role of matched platelet transfusion and IVIG. Eur J Pediatr. 2007;166(10):1057–63.
109. Berkowitz R, Bussel JB, Hung C, Wissert M. A randomised prospective treatment trial for patients with "standard risk" alloimmune thrombocytopenia (AIT). Am J Obstet Gynecol. 2006;195 Suppl 1:S23.
110. Gafni A, Blanchette VS. Screening for alloimmune thrombocytopenia: an economic perspective. Curr Stud Hematol Blood Transfus. 1988;54:140–7.
111. Killie MK, Kjeldsen-Kragh J, Husebekk A, Skogen B, Olsen JA, Kristiansen IS. Cost-effectiveness of ante-natal screening for neonatal alloimmune thrombocytopenia. BJOG. 2007;114:588–95.
112. Kjedsen-Kragh J, Husebekk A, Kjaer Killie M, Skogen B. Is it time to include screening for neonatal alloimmune thrombocytopenia in the general antenatal health program? Transfus Apher Sci. 2008;38:183–8.
113. Durand-Zaleski I, Schlegel N, Blum-Boisgard C, Uzan S, Dreyfus M, Kaplan C. Screening primiparous women and newborns for fetal/neonatal alloimmune thrombocytopenia: a prospective comparison of effectiveness and costs. Am J Perinatol. 1996;13:423–31.
114. Williamson LM, Hackett G, Rennie J. The natural history of fetomaternal alloimmunization to the platelet-specific antigen hpa-1a (pi-a1, zw-a) as determined by antenatal screening. Blood. 1998;92:2280–7.
115. Tiller H, Killie MK, Skogen B, Øian P, Husebekk A. Neonatal alloimmune thrombocytopenia in Norway: poor detection rate with nonscreening versus a general screening programme. BJOG. 2009; 116(4):594–8.
116. Kaplan C. Alloimmune thrombocytopenia of the fetus and neonate: prospective antenatal screening. Third European symposium on platelet and granulocyte immunobiology, Cambridge; 26–29 June 1994.
117. Husebekk A, Killie MK, Kjeldsen-Kragh J. General overview over screening programs. Vox Sang. 2006;91:15. Abstract 49.

118. Husebekk A, Killie MK, Kjeldsen-Kragh J, Skogen B. Is it time to implement HPA-1 screening in pregnancy? Curr Opin Hematol. 2009;16(6):497–502.
119. Berkowitz RL, Bussel JB, Mc Farland JG. Alloimmune thrombocytopenia: state of the art. Am J Obstet Gynecol. 2006;195:907–13.
120. Murphy MF, Bussel JB. Advances in the management of alloimmune thrombocytopenia. Br J Haematol. 2007;136:366–78.
121. Beachy J. Neonatal alloimmune thrombocytopenia: a case study (Lab Values). Neonatal Netw J Neonatal Nurs. 2011;30(6):407.
122. Peterson JA, Pechauer SM, Gitter ML, Kanack A, Curtis BR, Reese J, et al. New platelet glycoprotein polymorphisms causing maternal immunization and neonatal alloimmune thrombocytopenia. Transfusion. 2012;52(5):1117–24.