Thrombocytopenia in Pregnancy: Fetal and Neonatal Alloimmune Thrombocytopenia

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Abstract

Fetal/neonatal alloimmune thrombocytopenia (FNAIT) results from the formation of antibodies by the mother which are directed against a fetal platelet alloantigen inherited from the 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 in 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 stratified. Some centers continue to offer serial intrauterine platelet transfusions as first-line therapy, but the multiple cordocenteses that would be required to administer the platelets carry substantial risk of fetal demise. Possibilities for antenatal screening of first pregnancies are being developed. Postnatal screening does not prevent neonatal morbidity and mortality.

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Abbreviations

FBS	Fetal blood sampling
FNAIT	Fetal neonatal alloimmune thrombocytopenia
HPA	Human platelet antigen
ICH	Intracranial hemorrhage
ITP	Idiopathic thrombocytopenia
IUPT	Intrauterine platelet transfusion
IVIg	Intravenous immunoglobulin
NIPD	Noninvasive prenatal diagnosis
NOICH	Study: no intracranial hemorrhage study

12.1 Introduction

Fetal and neonatal alloimmune thrombocytopenia (FNAIT) occurs when the mother produces antibodies against a platelet alloantigen that the fetus has inherited from the father [68, 99]. The maternal alloantibodies against fetal platelet-specific antigens cross the placenta and destroy the baby's platelets, and this may result in internal bleeding, particular into the brain [13, 49]. 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 an fetal intracranial hemorrhage (ICH).

12.2 Nature and Incidence of Fetal and 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 the father that is incompatible with the HPA type of the mother, antibodies against that specific HPA type may be produced by the mother [48, 75, 85, 95]. These IgG antibodies can easily cross the placenta as early as the 14th week of gestation and cause fetal thrombocytopenia by prompting the fetal reticuloendothelial system to remove antibody-coated platelets from the fetal circulation [48, 51, 74]. The severity of thrombocytopenia 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 [13]. Transfer of antibodies increases as gestation progresses, until a maximum level is attained in the late third trimester [102]. 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* 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 [12, 41, 61, 69, 75]. The incidence of severe thrombocytopenia ($<50\times10^9$/L) is 1 in 1,695 live births [107]. However, the true incidence is likely to be higher. In the study by Turner et al., only 37 % of cases with severe FNAIT were detected [107].

In the Caucasian population, 98 % of people are HPA-1a positive; consequently, 2 % of pregnant women are HPA-1a negative (HPA1bb) and 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-HPA1a antibodies [61]. This is because the mother's immunogenetic background plays a major role [25, 71, 75]. 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 [25, 27, 40, 107, 109].

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 12.1). The diagnosis of FNAIT is made by identifying maternal HPA antibodies and documenting parental incompatibility for the HPA allele in question.

Table 12.1 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) [94]	90							
Mueller-Eckhardt et al. (1989) [70]	90				8			2
Kornfeld et al. (1996) [57]	90				10			
Letsky and Greaves (1996) [63]	80–90				5–15			
Khouzami et al. (1996) [52]	75							
Kanhai et al. (1996) [42]	79		5	11				
Uhrynowska et al. (1997) [108]	91	4			4			
Spencer and Burrows (2001) [102]	78		4		4			
Davoren et al. (2002) [23]	94		3		3			
Davoren et al. (2004) [24]	79	4	2	1	9		2	
Rayment et al. (2003) [92]	85				10	5		
Mandelbaum et al. (2005) [66]						2		
Ertel et al. (2005) [29]						1		
Kroll et al. (2005) [59]	75		2		18		2	
Porcelijn et al. (2006) [84]	73	1	5	1	15			

Table 12.2 Differences between Rh disease 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	ICH
Management of next pregnancy	Red cell transfusions *in utero*	IVI ± prednisolone ± platelet transfusions

12.3 Differences Between NAIT and Rhesus D Hemolytic Disease of the Newborn

Unlike in hemolytic disease of the newborn caused by maternal sensitization to fetal Rhesus D (RhD) inherited from the father, its red cell equivalent, 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 early in gestation that could be affected by FNAIT (discussed in Sect 12.11 below). Active antenatal management of this disease is confined to those women who have had a previously affected fetus [75]. There are important differences between RhD isoimmunization and FNAIT (Table 12.2).

12.4 Diagnosis

The diagnosis of FNAIT is based on clinical and serologic findings. The typical picture is that 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 [1, 11, 46, 104]. 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) [46, 74]. The platelet count is low at birth and tends to decrease 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 [53],

the platelet immunofluorescence test, or a novel antigen-specific particle assay [8, 35, 50, 54, 63, 67, 74]. The diagnosis of FNAIT is unequivocal when a parental incompatibility with corresponding maternal alloantibody is present [13, 19, 46, 51].

Recognition of FNAIT and appropriate therapy are important both for the affected neonate and for the management of subsequent pregnancies [96]. 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 [6, 16, 60, 103]. A number of FNAIT cases (10 %) have been reported in which no HPA antibody could be detected [18, 44, 76, 112]. The diagnosis is then based on maternal-fetal or maternal-paternal HPA incompatibility and exclusion of other causes of thrombocytopenia [15, 44, 79]. In some cases, antibodies may become detectable in the weeks or months after delivery or during/after a subsequent pregnancy [46, 55, 104, 114]. 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 [114]. Some studies have demonstrated significant correlation between high anti-HPA-1a antibody titers (>1:32) and fetal platelet counts below 50×10^9/L [40, 55, 114], whereas others have not [10, 84, 107]. 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 [10].

HPA typing of mother, father and fetus/neonate is important, not only for (a) the diagnosis of FNAIT but also (b) providing HPA-matched blood components to neonates with FNAIT and (c) genetic counseling and (d) estimation of the recurrence risk [65]. Conventional serologic immunophenotyping for HPA is limited by the unavailability of certain rare but well-characterized typing antisera, such as anti-HPA-1b and anti-HPA-4b [65]. Even when nonpaternity 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 [83]. 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.

12.5 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 about 10–30 % of severe cases. ICH is associated with death in 10 % and neurologic sequelae in 10–20 % of cases [16, 46, 69, 74]. Chaoying et al. [21] found that FNAIT is the most important cause of ICH and poor outcome in neonates. About 25–50 % of cases of FNAIT-related ICH occur *in utero*. The majority occur between 30 and 35 weeks gestation [16, 75], but have been reported to occur in earlier gestation. Without treatment, the risk of ICH exists as long as severe thrombocytopenia persists [94]. Thrombocytopenia is most severe in the presence of HPA-1a incompatibility, which accounts for most cases of *in utero* ICH. Because no circulating antibodies can be detected in about 10 % of FNAIT-affected women, the maternal antibody level has limited use in predicting the severity of fetal/neonatal thrombocytopenia [40, 114]. Furthermore, neonatal thrombocytopenia as the result of FNAIT usually becomes progressively more severe and occurs earlier in subsequent pregnancies [11, 50, 51]. Following severe neonatal thrombocytopenia (i.e., $<50 \times 10^9$/L), a cerebral ultrasound or nuclear magnetic resonance scan is advised to detect clinically silent ICH [74, 75]. A few cases of ICH resulting from incompatibility for HPA-3a, HPA-4b, HPA-5b, or HPA-9b alloantigens have been reported [39, 86].

12.6 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) [44, 72], (b) weekly intravenous immunoglobulins (IVIg), and (c) immunosuppression with corticosteroids [15, 49, 73]. Over the last 15 years, there has been a gradual change from an invasive management protocol to a less invasive management protocol to a completely noninvasive approach. However, controversy still exists over the optimal antenatal management strategy.

12.6.1 Diagnostic Fetal Blood Sampling (FBS) and Intrauterine Platelet Transfusions (IUPT)

Fetal blood sampling involves the insertion of a needle into the umbilical or intrahepatic vein to sample fetal blood in order to ascertain the 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 [72, 81, 101]. With reports of a fetal loss rate of around 6 % per pregnancy [80], serial (weekly) intrauterine platelet transfusions are considered 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 fetal blood sampling [7, 89]. FBS, with its associated risks of bleeding, boosting of antibody levels, fetal bradycardia requiring emergency (preterm) Caesarean 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 [78, 90, 91, 112].

12.6.2 Intravenous Immunoglobulin

After empirical observation by Bussel et al. [16] 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 [116]. IVIg is often given to the mother on a weekly basis, using various regimens, until delivery. After birth, the neonatal platelet count and the presence of ICH provide measures for IVIg efficacy.

The mechanism of action of IVIg in FNAIT is still unclear. Four possible explanations are cited in the literature. Firstly, in the maternal circulation, the IVIg will dilute the anti-HPA antibodies, resulting in a lower proportion of anti-HPA antibodies within the IgG transferred via the Fc-receptors in the placenta. Secondly, in the placenta, IVIg may block the placenta receptor (Fc-R) and decrease 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 [89]. Another possible mechanism could be that IVIg may also enhance the expression of inhibitory receptors on splenic macrophages [98] and, as a result, suppress maternal antibody production and reduce placental transfer of the antibodies [22]. So far, evidence for only the first mechanism exists.

Short-term mild side-effects that have been associated with IVIg therapy include headaches, 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, reactions including severe headaches and febrile reactions, 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 [89]. Since IVIg is known for its immunomodulating characteristics, there is always a possibility of long-time side-effects for the mother and child. Further more, weekly IVIg administration is expensive.

Weekly maternal IVIg is the most commonly used therapy today. The IgG level after IVIg infusion decreases by 30 % after 24 h and by 50 % after 72 h [21]. Maternal administration of IVIg has been reported to increase the fetal platelet count and/or prevent ICH in 55–85 % of FNAIT [11, 17, 31, 64]; IVIg treatment seems to reduce the risk of ICH even if the fetal platelet count is not altered [7, 87]. The mechanism of the latter effect is unclear. There is conflicting evidence on the efficacy of IVIg in preventing ICH, with most reports documenting favorable results [17, 18, 64] while others report failure of IVIg in prevent ICH [58, 73, 96]. However, in the latter reports, only IVIg 1.0 g/kg/week was utilized.

Results from the study reported by Bussel at al. [17] suggested 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 [17] 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 of Bussel et al. [15]. 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 as a result from IVIg treatment. This suggests a limitation of the placental Fc receptor [89].

Significant correlation between the antibody level detected by different methods in the mother and the severity of thrombocytopenia in the newborn has been observed [40, 89]. 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. (2006) 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). Survival was 100 %; none of the neonates had an ICH; however, unfortunately, this trial ended prematurely because of a lack of patient recruitment [111]. 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. The NOICH (no intracranial hemorrhage) 2 study is aimed at providing evidence for the effectiveness of 0.5 g/kg/week IVI in the prevention of fetal ICH in pregnancies complicated by FNAIT (www.medscinet.com/noich). Van den Akker et al. (2007) also recommend noninvasive treatment without recourse to invasive strategies, which is both safe and effective in the antenatal management of FNAIT [112].

12.6.3 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 [15]. Corticosteroids have been administered in a selection of studies alongside IVIg 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 %) [6, 7]. Both IVIg alone and IVIg combined with any corticosteroids resulted in an improved clinical outcome in treated FNAIT fetuses compared to their untreated siblings [113]. At present, prednisone seems to be the corticosteroid of choice for treatment of FNAIT [6, 7].

Dexamethasone is now avoided as it may cross the fetal blood–brain barrier. In addition, it has been associated with oligohydramnios at higher doses [15] and a lack of efficacy at lower doses [17]. 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 antenatal management of FNAIT. It is recommended that treatment be 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 from 30 weeks onward [86, 87].

The role of concomitant steroids alongside IVIg needs more clarity. Bussel et al. (2010) [20] 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 on only if the fetal platelet counts were $<30\times10^9$/L in non-responders to IVIg therapy alone. Clinical outcomes in this study were favorable. Similarly, Berkowitz et al. (2007) 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 than IVIg and prednisone and a low response rate [6, 7]. Furthermore, they also 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 pretreatment fetal platelet count of $<20\times10^9$/L) [7].

Since there are substantial risks associated with FBS [78, 90, 91] and noninvasive treatment is effective, therapy for FNAIT can be instituted without invasive procedures [11, 82, 87].

A Cochrane review in 2010 [93] 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 nonresponders, and long-term follow-up of children.

12.6.4 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 pretreatment 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 has been suggested to be more effective in raising the fetal platelet count than IVIg alone in high-risk pregnancies, where the pretreatment 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 is unclear, but studies demonstrating efficacy initiated treatment at 20–26 weeks.

12.7 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 gestation via PCR amplification of DNA obtained from amniocytes. If the fetus is found to be negative for the HPA allele, no further testing is indicated [3, 97, 102]. Preimplantation diagnosis can be considered [2]. Noninvasive prenatal diagnosis using free fetal nucleic acids 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. Although an increasing antibody titer may correlate with the severity of thrombocytopenia, occasionally the antibody may be undetectable or of low titer in severely affected cases [9, 33, 92]. Therefore, the antibody titer measurements are not useful in the clinical management of FNAIT. The clinical history of an affected sibling is currently the best indicator of risk in a current pregnancy [1, 11, 88]. The recurrence rate of ICH in the subsequent pregnancies of women with FNAIT was 72 % (of previous pregnancies without fetal deaths) and 79 % (of previous pregnancies including fetal death) [88]. Conversely, the risk of ICH in those with a history of FNAIT but without ICH was estimated to be 7 %.

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 2007 [19], 50 % of 98 affected fetuses already had platelet counts of $<20\times10^9$/L by 25 weeks, indicating early severity. Forty percent had lower fetal platelet counts at that time than their previously affected siblings had at birth, indicating increasing severity in subsequent pregnancies. They concluded that FNAIT when it occurs early in gestation is severe and is more severe in fetuses with an older affected sibling who had had an antenatal ICH. This suggests that fetuses may require different management strategies depending upon the history of their previous sibling. There has been a trend and a strong recommendation to utilize noninvasive strategies (IVIg) in the management of FNAIT at high risk of *in utero* or postnatal ICH [26, 43].

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-1 [34], while incompatibilities of HPA-5b and HPA-9b are less severe [45]. HPA-4 incompatibility seems also to be severe [30], and most rare antigens are identified because of a severe case of neonatal FNAIT.

12.8 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 [36]. 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 fetal platelet counts exceed 50×10^9/L [17]. With platelet counts below 50×10^9/L, IUPT have been performed before vaginal delivery for protection against bleeding at the time of delivery, with associated risks. There is no evidence that vaginal delivery of a fetus with a platelet count $<50\times10^9$/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 $<50\times10^9$/L in four neonates [110]. Caesarean delivery alone is not considered to be effective in preventing antenatal or perinatal hemorrhage [74, 100]. Instrumental vaginal delivery, ventouse, fetal scalp electrodes, and fetal scalp blood samples should be avoided. The neonatologist on duty during delivery should be informed in advance, as should a consultant in haematology/transfusion medicine and the blood transfusion laboratory should also be asked in advance to obtain HPA compatible platelets.

12.9 Treatment of the Neonate

Treatment of the neonate is dictated by the condition of the newborn. 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 $<30\times10^9$/L, therapy is needed and must be rapid and effective. First-line therapy is prompt transfusion of ideally HPA-compatible platelets which will not

be destroyed by maternal antibodies in the neonate's circulation. Blood centres should be able to supply platelets, which should be HPA-1a and 5b negative. 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 [114]. 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 [114]. The effectiveness of IVIg in the neonate has not been shown in some studies [106]. The therapeutic effect on the platelet count, however, is delayed for 24–48 h, when the neonate remains at risk of ICH.

12.10 Preconception Counseling

Pregnant women are at risk for FNAIT if they have a history of a previous neonate with FNAIT or are known to have circulating alloantibodies [13]. Before a subsequent pregnancy, these women should be referred to a tertiary center which 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 % [5, 11, 88]. 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.

12.11 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 [11, 32, 56, 62, 76], although this was not a universal view [28]. 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 [75].

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 in 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 lifelong severe neurological morbidity.

Three large studies of antenatal screening for HPA-1a incompatibility have been performed [61, 107, 115]. Two, from East Anglia [115] and Scotland [107] in the UK, were performed in approximately 25,000 cases each. The largest study in Norway encompassed more than 100,000 pregnancies [61]. Another study from Norway concluded that without a screening programme, the detection rate of NAIT in Norway is only 14% of expected [105]. 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 screening for HPA-1a alloimmunization detects about two cases in 1,000 pregnancies and that severe FNAIT occurs in about 40 per 1,000,000 pregnancies. Despite several antenatal interventions, severe ICH occurred in three to four 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 [41, 47, 90, 91]. These data indeed indicate that large-scale screening studies including comparison of intervention strategies are warranted [37, 38].

Conclusions

The most serious complication of FNAIT is ICH, which occurs in 10–30 % of severe cases, causing death (10 %) and neurologic sequelae (10–20 %). In the majority of cases, fetal thrombocytopenia is more severe and occurs successively earlier in subsequent pregnancies [16]. There is a 70–80 % risk of antenatal ICH in a subsequent pregnancy complicated by FNAIT if a previous child had ICH [11, 87]. 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 is 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 [4–6, 20]. 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 [86, 87].

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 [112]. Spontaneous vaginal delivery is preferred in FNAIT cases while avoiding procedures that might increase the risk of fetal hemorrhage (no scalp electrodes, no fetal scalp blood samples, and no instrumental vaginal delivery or ventouse) [110]. Caesarean section may be performed in high-risk fetuses selectively.

At present, there is no approved method of antenatal screening to detect the first affected pregnancy [55, 77, 115]. Postnatal screening, although simple, cannot prevent neonatal morbidity and mortality [76].

The aim of current research must be to develop reliable predictors of disease severity in affected infants and increase the effectiveness of noninvasive treatment strategies for FNAIT. Prospective trials (such as NOICH 2, www.medscinet.com/noich) are necessary to evaluate different treatment strategies and to acquire additional data on optimal prevention programs.

Learning Points

1. All cases of FNAIT should be managed by maternal-fetal medicine specialists in tertiary referral centers, with appropriate liaison with specialists in neonatology and haematology/transfusion medicine.
2. 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.
3. Effective noninvasive antenatal treatment (IVIg) exists for cases recognized as a result of a previously affected sibling.
4. Invasive treatment (intrauterine platelet transfusions) appears to be required only in nonresponders.

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