

REVIEW

Fetal and neonatal alloimmune thrombocytopenia: prenatal interventions

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Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is a potentially devastating condition, which may lead to intracranial haemorrhage (ICH) in the fetus or neonate, often with death or major neurological damage as consequence. In the absence of screening, preventive measures are only possible in the next pregnancy of women with an affected child. Controversy exists on the best intervention to minimise the risk of ICH. Most centres have abandoned treatment with serial fetal blood sampling (FBS) and platelet transfusions, because of a high rate of complications and the availability of quite effective non-invasive alternatives. In pregnancies with FNAIT and a previous affected child without ICH, weekly intravenous administration of immunoglobulins to the mother appears close to 100% effective to prevent fetal or neonatal ICH. Some centres add prednisone; this combination leads to slightly higher platelet counts at birth. In pregnant women with a previous child with ICH, the recurrence risk seems particularly high, and more aggressive maternal medical treatment is recommended, starting earlier with immunoglobulins. Whether a higher intravenous immunoglobulin dose or the addition of prednisone is really necessary is unclear. What does seem to be clear is that the use of FBS should be minimised, possibly even abandoned completely. Copyright © 2011 John Wiley & Sons, Ltd.

KEY WORDS: fetal and neonatal alloimmune thrombocytopenia; fetal therapy; intracranial haemorrhage; intravenous immunoglobulins

INTRODUCTION

Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is a potentially devastating condition, which may lead to intracranial haemorrhage (ICH) in the fetus or neonate, often with death or major neurological damage as consequence. The reported incidence of FNAIT ranges from 1 : 350 (Williamson *et al.*, 1998) to 1 : 1000 (Turner *et al.*, 2005). FNAIT is the most common cause of thrombocytopenia in neonates. Thrombocytopenia is defined as a platelet count (PC) $<150 \times 10^9/L$. However, the risk of clinically significant bleeding problems is minimal unless platelet counts drop below 30 or even $20 \times 10^9/L$. A generally accepted definition of severe FNAIT is a PC $<50 \times 10^9/L$. In this group, ICH occurs in around 10% of fetuses and neonates (Kamphuis *et al.*, 2010). Many cases, even of severe FNAIT, may therefore occur unnoticed.

The most severe complication is ICH, leading to perinatal mortality in 1–7% and surviving children with often severe neurological sequelae including mental retardation, cerebral palsy, cortical blindness and seizures in 7–26% of affected pregnancies (Kamphuis *et al.*, 2010; Knight *et al.*, 2011). Unlike in the pathophysiologically similar red cell alloimmunisation, fetuses in a first pregnancy can be severely

affected. In the absence of any screening programmes, the disease is virtually always only detected after birth of an affected child. Preventive measures can then only be taken in the next pregnancy. There is still controversy on type and timing of various interventions in pregnancies with FNAIT. In this review article, we critically evaluate the literature on these preventive interventions for pregnancies known to be complicated with FNAIT.

PATHOPHYSIOLOGY

FNAIT is caused by an immunological process in which the mother produces an antibody-mediated response against a platelet-specific antigen that she herself lacks but that is present on the fetal platelets, inherited from the father. The fetal platelet antigens are expressed as early as 16–18 weeks of gestation (Kaplan, 2002).

The mother's antibodies [of the immunoglobulin G (IgG) type] can cross the placenta and bind to fetal platelets. The antibody-coated platelets are subsequently removed from the fetal circulation by the reticuloendothelial system, which results in fetal thrombocytopenia. These same antibodies also may inhibit platelet production (Pearson *et al.*, 1964; Warwick *et al.*, 1994). The proportion of individuals belonging to a particular platelet antigen type varies according to race. Human Platelet Antigen (HPA)-1a is the immunodominant antigen in Caucasian individuals responsible for 85% of the FNAIT cases, followed by HPA-5b (Mueller-Eckhardt *et al.*, 1989; Spencer and Burrows, 2001).

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IDENTIFYING PREGNANCIES AT RISK

Only around 10% of HPA-1a-negative pregnant women actually produce HPA-antibodies despite carrying an HPA-1a-positive fetus (Kamphuis *et al.*, 2010). There appears to be an association between maternal Human Leucocyte Antigen (HLA) type and tendency to produce these antibodies. Most immunisations occur in women with HLA DRB3*0101, and in the absence of this phenotype, immunisation is rare. According to Bussel and Primiani (2008) the positive predictive value of this phenotype is only 35%, but negative predictive value would be 99.6%. However, in the largest prospective study thus far, by Kjeldsen-Kragh *et al.* (2007), 12 of 150 HPA-1a-negative women were HLA DRB3*0101 negative and 2 of 12 still gave birth to thrombocytopenic children. At this point, the use of HLA typing to direct clinical management in our view is therefore questionable but more data are needed.

Several investigators aimed to detect a certain threshold of HPA-antibody level in the maternal serum below which severe FNAIT would not occur or which level would predict the degree of thrombocytopenia. The largest prospective study evaluating possible predictive value of HPA-antibody levels came from Norway (Kil-lie *et al.*, 2008). Antibody quantitation was carried out in 160 pregnancies with FNAIT. In most multiparous women, the antibody levels decreased during pregnancy, whereas in first immunisation a rise was commonly seen. Although there was a correlation between area under the curve of antibody levels measured in the second half of pregnancy and the neonatal PC, clinical application would be difficult. Using antibody levels taken at 22 and 34 weeks of gestation, and a cut-off level of 3.0 IU/mL, 8–18% of severe FNAIT cases would be missed.

In a recent large retrospective study by Kaplan's group, the area under the curve of maternal antibody concentration had some predictive value for a neonatal PC $<50 \times 10^9/L$ in pregnancies treated with intravenous immunoglobulin (IVIG) and IVIG + steroids. With a not very impressive sensitivity of 64% and a specificity of 83%, and derivation of the cut-off level from the same population, it seems likely that in a prospective cohort the diagnostic accuracy of this test proves to be disappointing (Bertrand *et al.*, 2011).

Fetuses with FNAIT with PCs $<50 \times 10^9/L$, have a potential risk of bleeding. The most feared complication, and the true disease that needs to be prevented, is ICH. The best estimate of the incidence of ICH comes from a systematic review of all prospective screening studies in unselected populations, encompassing a total of 176 084 pregnancies (Kamphuis *et al.*, 2010). In 7 of 71 (10%) pregnancies with severe FNAIT (PCs $<50 \times 10^9/L$), severe adverse outcome occurred with ICH, leading to death ($n = 2$) or permanent neurological sequelae in most others. All except one of these bleedings occurred before birth. Even these prospectively derived data are an underestimation, as in all these studies, some form of preventive measure was taken in screen-positive pregnancies. Our best estimate is therefore that the incidence of clinically significant ICH due to FNAIT ranges between 3 and 10 per 100 000 pregnancies.

Given the often life-long handicaps in survivors, a screening and intervention programme would in most Western countries almost certainly be cost-effective (Turner *et al.*, 2005; Husebekk *et al.*, 2009; Kamphuis *et al.*, 2010).

PRENATAL MANAGEMENT OF PREGNANCIES WITH FNAIT

With the current lack of screening programmes, we only need to focus on how best to manage pregnancies with known FNAIT, thus those pregnant women with a previously affected child. This indicates the value of recognising this diagnosis in relation to the prenatal management of subsequent pregnancies.

Commonly used prenatal treatments include serial fetal platelet transfusions or transplacental medical treatment using immunoglobulins and/or corticosteroids. Other options which may be used in conjunction to fetal therapy are near-term induction of labour, near-term caesarean section, and delivery in a tertiary care centre. In case of a vaginal birth, it is commonly advised to refrain from using forceps, ventouse, scalp electrodes and fetal scalp blood sampling. In pregnancies with timely diagnosed severe fetal ICH, termination of pregnancy (TOP) could be offered.

These modalities will be discussed in more detail. A suggested flowchart for the management of pregnancies with FNAIT is given in Figure 1.

INVASIVE FETAL THERAPY FOR FNAIT: FETAL BLOOD SAMPLING AND INTRAUTERINE PLATELET TRANSFUSION

Until 1984, the traditional management of subsequent pregnancies in women with a previous history of FNAIT consisted of an early elective caesarean section and transfusion of platelets after birth. Since the publication of Daffos *et al.* (1984), one of the pioneers of fetal blood sampling (FBS), several centres throughout the world started treating fetal thrombocytopenia in a similar fashion to anaemia due to red cell alloimmunisation, by serial intrauterine platelet transfusions (IUPTs) (Kaplan *et al.*, 1988; Lynch *et al.*, 1988; Nicolini *et al.*, 1988). In red cell alloimmunisation, this therapy has no alternative, and has been shown to be relatively safe in experienced hands, with procedure-related loss rates below 2% (Van Kamp *et al.*, 2005). Two important differences with blood transfusion for fetal anaemia must be stressed.

First, puncturing the umbilical cord in fetuses with a low PC increases the risk of complications, particularly exsanguination. In our experience and that of others, immediate platelet transfusion does not always prevent such a disaster (Overton *et al.*, 2002). All large centres involved in the treatment of FNAIT have reported fetal losses because of FBS and/or IUPT, except for a group from Germany who reported no fetal loss in 470 IUPTs for FNAIT, all done by a single operator (Giers *et al.*, 2010). Combining data from three relatively large series

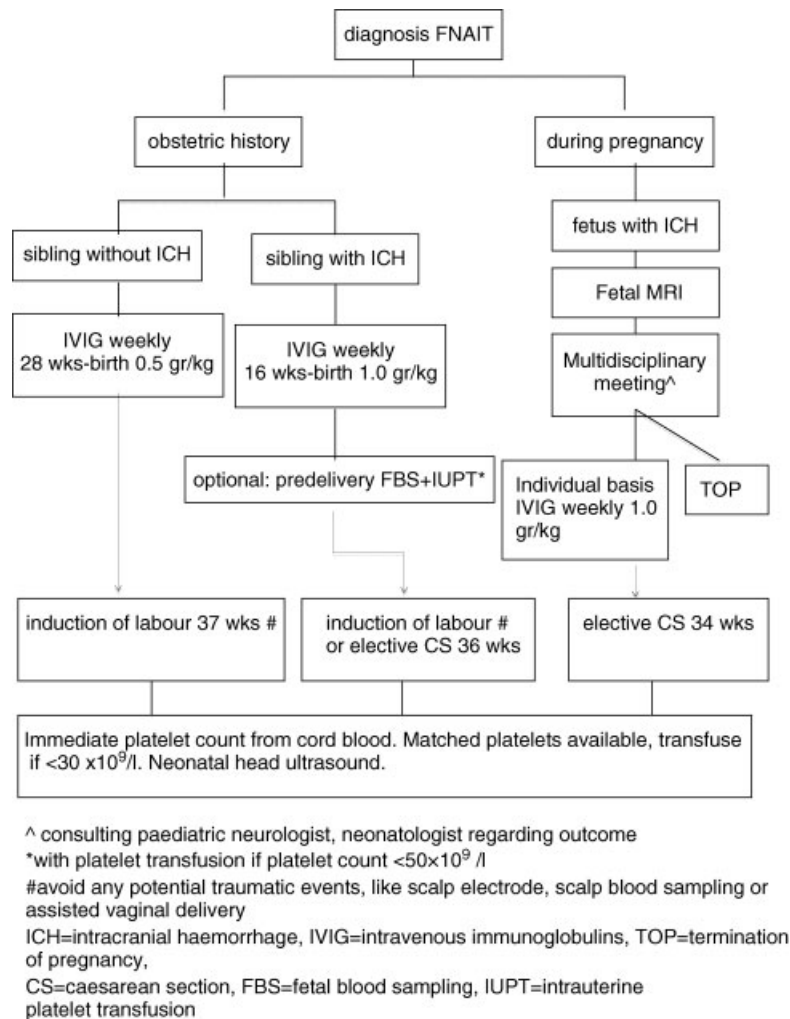


Figure 1—Flowchart for perinatal management of fetal and neonatal alloimmune thrombocytopenia

from experienced centres, the cumulative risk of fetal loss per pregnancy directly related to complications of FBS and IUPT was 6% (Paidas *et al.*, 1995; Overton *et al.*, 2002; Birchall *et al.*, 2003; Berkowitz *et al.*, 2006; Ghevaert *et al.*, 2007). Prolonged bradycardia is more often noted as compared to red cell transfusions, possibly related to a larger content of plasma (Sainio *et al.*, 1999).

Second, Bussel *et al.* (1988) already pointed out that the half life of transfused platelets is very short, a few days only, which means that platelet transfusions would be required at least weekly if not more often. This is clearly shown by the pretransfusion PCs in subsequent transfusions in patients treated with IUPTs. Commonly, these values are within a week again well below $50 \times 10^9/L$, indicating that even weekly transfusions are likely inadequate to maintain safe PCs (Nicolini *et al.*, 1990; Sainio *et al.*, 1999; Knight *et al.*, 2011).

With the mounting evidence that non-invasive treatment using immunoglobulins with or without steroids has high success rates, very few centres nowadays continue to use FBS and IUPT as the sole treatment of FNAIT. Some groups still use one or two diagnostic FBS to fine-tune and verify the medical therapy, or a predelivery fetal blood sample to enable vaginal birth.

In the group of patients with an affected previous sibling without an ICH, which is the majority of cases referred to our national fetal therapy centre, we have refrained from any invasive procedure for the past 10 years (Van den Akker *et al.*, 2007).

NON-INVASIVE MANAGEMENT OF FNAIT: IVIG AND STEROIDS

Concerns about the risks of invasive treatment have led to the exploration of maternal treatment. The first report on clinical efficacy of IVIG in FNAIT dates from 1988, where Bussel *et al.* described the successful use of a weekly dose of 1 g/kg maternal weight in seven pregnancies. The treatment regimen was based on experience with idiopathic thrombocytopenic purpura (ITP) patients. Several observational studies in women with a previous child affected by FNAIT suggested that this treatment is highly effective in this group (Table 1).

How does IVIG work? This is in fact still unknown, although a combination of mechanisms seems likely. First, in the maternal circulation the IVIG will dilute

Table 1—Maternal IVIG to prevent ICH in fetal and neonatal alloimmune thrombocytopenia: summary of the literature^a

	Number of fetuses	Dose (g/kg/week)	ICH (n)	Plt count at birth ($\times 10^9/L$)	Neonatal Plt $<50 \times 10^9/L$
Lynch <i>et al.</i> (1992)	4	1.0	0	184 (57–322)	0
Birchall <i>et al.</i> (2003)	12	1.0	0	83	4 (33%)
Berkowitz <i>et al.</i> (2007)	37	2.0	1 ^a	169 (14–312)	5 (14%)
Yinon <i>et al.</i> (2006)	24	1.0	0	118	<30: 2 (8%)
Van den Akker <i>et al.</i> (2007)	45	1.0	0	136	7 (16%)
Giers <i>et al.</i> (2010)	30	1.0	0	31 ^b (6–117)	26 (87%)
Bertrand <i>et al.</i> (2011)	27	1.0	0	89 (95% CI 55–123)	12 (44%)
Knight <i>et al.</i> (2011)	17	n.s.	0	n.s.	n.s.

Studies included only if IVIG was given alone, without steroids or intrauterine platelet transfusions, in women with an affected previous child without ICH.

GA, gestational age; ICH, intracranial haemorrhage; IVIG, intravenous immunoglobulin; n.s., not stated; Plt, platelet.

^a Neonatal grade 1 subependymal bleeding, with platelet count at birth $133 \times 10^9/L$, not considered treatment failure.

^b Value obtained by fetal blood sampling just before birth, followed by single platelet transfusion.

the anti-HPA antibodies, resulting in a lower proportion of anti-HPA antibodies among the IgG transferred via the Fc-receptors through the placenta. Second, IVIG can block the placental receptor and decrease the placental transmission of maternal antibodies including anti-HPA antibodies. Third, in the fetal circulation, IVIG may block the Fc-receptors on the macrophages and prohibit the destruction of antibody-covered cells (Radder *et al.*, 2004a, 2004b; Ni *et al.*, 2006). However, other effects of IVIG, such as anti-idiotypic neutralisation of anti-HPA antibodies or suppression of antibody-producing B-cells, cannot be excluded.

IVIG is regarded as an expensive but safe and well-tolerated drug, although due to its production from plasma from multiple (>1000) blood donors, concern remains on risks for viral and other infections. Main dose-related side effects include headache and fever, whereas rarely more serious adverse events including chest pain, laryngeal oedema, renal failure, aseptic meningitis and thrombotic complications have been reported.

The long-term side effects for mother and child are still unclear. As IVIG is known for its immunomodulating characteristics, there are some concerns. A study on short-term follow-up found a possible increase of IgE in children after maternal IVIG administration compared to the normal population. However, no clinically apparent adverse effects in early childhood could be demonstrated (Radder *et al.*, 2004a, 2004b).

Since Bussel's first report, the standard dose of IVIG in FNAIT has empirically been 1 g/kg given weekly, starting anywhere between 20 and 32 weeks of gestation. Only two studies on dose have been performed, with 0.5 or 2 g instead of 1 g, without showing clear evidence for a particular dose (Berkowitz *et al.*, 2007; Van den Akker *et al.*, 2008). There is theoretical and *in vitro* evidence that fetal IgG levels do not increase when the mother is given more than 0.5 g/kg/week, suggesting a saturation of the placental IgG transfer (Urbaniak *et al.*, 1999; Radder *et al.*, 2004a, 2004b).

EFFICACY OF IVIG

Several hundreds of women with FNAIT have now been treated with IVIG, with a close to 100% success, with success defined as the absence of ICH (Table 1). To our knowledge, only one often quoted well-documented case has been reported of fetal ICH despite 11 weeks of IVIG (1.0 g/kg) treatment (Kroll *et al.*, 1994). Interestingly, this fetus was also managed by serial FBS and a total of 13 IUPTs, of which six were given prior to the detection of the ICH at 32 weeks. A second case, with less details but with remarkable similarities, was incorporated in a recent cohort study by Knight *et al.* (2011). This pregnancy was managed with IVIG, steroids and IUPTs without improvement in PC, the infant had ICH. An outlier study is the one by Giers *et al.* (2010), describing a cohort of FNAIT pregnancies treated with IVIG, with a diagnostic FBS done before every weekly IVIG gift. The 30 fetuses showed remarkable little response to the IVIG (Table 1). Jim Bussel, in an accompanying editorial, suggested that the serial FBS might have increased sensitisation causing the low PCs in this cohort (Vinograd and Bussel, 2010). This may have played a role in the two above-mentioned cases of apparently failed IVIG treatment.

NON-RESPONDERS?

However, in all studies reporting on IVIG in the treatment of FNAIT, around 20% (range 8–87, Table 1) of fetuses do not seem to respond, with PCs remaining below $50 \times 10^9/L$. There is currently no explanation for this phenomenon. The 'non-responders' may thus still be at risk for ICH, although surprisingly, this seems extremely rare in IVIG-treated fetuses. An intriguing hypothesis is that IVIG apart from often causing a rise in platelets, may aid in protection against bleeding (Kanhai *et al.*, 2006; Van den Akker *et al.*, 2007). A proposed mechanism supporting this hypothesis was described by Van Gils *et al.* (2009), studying the effects of HPA-1a antibodies on Fc-receptors on endothelial cells. This area certainly deserves further research.

As many investigators consider the non-response to the commonly used IVIG dose of 1.0 g/kg maternal weight per week a failure of the treatment, other medication regimens have been studied. The two most common variants are increasing the dose of IVIG to 2 g/kg/week, and the addition of corticosteroids.

CORTICOSTEROIDS

In early studies by the group of Bussel, dexamethasone (3–5 mg/kg) was used in combination with IVIG 1.0 g/week, but soon abandoned, due to both a limited effect and significant side effects for both mother and fetus (oligohydramnios) (Lynch *et al.*, 1992). A lower dose of dexamethasone (1.5 mg) with IVIG was then studied, and shown not to be superior to IVIG alone (Bussel *et al.*, 1996). Since then, most investigators have used high dose prednisone to add to IVIG, or prednisone alone. The maximum tolerable dose of prednisone is 0.5 mg/kg per day (Bussel and Primiani, 2008). Oligohydramnios is uncommon with prednisone treatment.

COMPARISON OF DIFFERENT APPROACHES

Although the end-point in many studies on the efficacy of various treatments often was, and should be, the occurrence of ICH, all studies published thus far were seriously underpowered to find any significant difference in this outcome (Rayment *et al.*, 2011). Using the surrogate outcome of PC at birth, several randomised controlled trials by the group of Bussel, compared a variety of treatments in pregnancies with FNAIT, subdivided in groups perceived to have different risks of recurrence. In all pregnancies, one or more diagnostic FBS were done to monitor treatment. None of the treatment regimens proved to be significantly superior, although a trend towards higher PCs was observed for the use of 2.0 g/kg IVIG or the combined use of IVIG and prednisone in the cases with a previous prenatal ICH (Bussel and Primiani, 2008).

When we compared our results of empiric or 'blind' treatment (without the use of diagnostic FBS) with 1.0 g/kg IVIG (Van den Akker *et al.*, 2007) ($n = 49$) with two published comparable series by Birchall *et al.* (2003) ($n = 18$) and Berkowitz *et al.* (2006) ($n = 79$), both using IVIG or IVIG and steroids together with serial FBS for monitoring, we found that our non-invasive approach resulted in 100% survival without ICH, whereas in the other series ICH occurred twice, two cases of fetal loss due to FBS and 13–17% emergency caesarean sections during FBS, resulting in premature birth (Porcelijn *et al.*, 2008).

A recent retrospective cohort study from the UK, describing 45 pregnancies with known FNAIT, two children were born prematurely by emergency caesarean section following complications of FBS (Knight *et al.*, 2011). One-third of these cases were treated with IVIG alone, one third with combined IVIG, steroids and IUPT,

11% with IVIG and IUPT and 9% with IUPT alone, all in the years 2006–2008. This nicely illustrates the lack of consensus on the best treatment for FNAIT. The most important finding was that in pregnancies with known FNAIT and 1 year follow-up ($n = 28$), all children were alive and healthy, whereas in the group with unknown or unrecognised FNAIT ($n = 88$), disability or death occurred in 10%.

Similar results were reported recently from France and Switzerland (Bertrand *et al.*, 2011). Pregnancies with known FNAIT ($n = 92$) were most often treated with IVIG + steroids (59%), followed by IVIG alone (29%) and steroids alone (12%). Again, none of these pregnancies ended in birth of a child with ICH. Neonatal PCs were highest in the group receiving IVIG + steroids ($135 \times 10^9/L$), followed by the group with IVIG alone ($89 \times 10^9/L$) and steroids alone ($46 \times 10^9/L$). Severe thrombocytopenia defined as platelets $<50 \times 10^9/L$ occurred in these groups in 27, 44 and 73%, respectively.

The intriguing question remains whether the favourable outcomes in the treated groups are due to actual treatment effects, or that the natural history is less similar to Rhesus disease than we commonly think, with possibly reduced risk in subsequent pregnancies. Antibody-level studies from Norway suggest that this might be true (Killie *et al.*, 2008). Only a randomised controlled trial including a placebo arm would provide appropriate evidence.

An elegant decision analysis model study by Thung and Grobman (2005) suggested that considering all options, empiric or 'blind' treatment with IVIG (thus without any FBS) would be the most cost-effective approach.

MANAGEMENT OF PREGNANCY PRESENTING WITH FETAL ICH

Finally we would like to discuss the management of pregnancies presenting with ICH secondary to FNAIT. It is a rare but problematic condition, therefore multidisciplinary approach including paediatric neurologist and neonatologist is advised. After detection of ICH on ultrasound, fetal magnetic resonance imaging (MRI) may further determine the extent of cerebral damage and the prognosis. In the few cases we have managed in our centre, we opted for treatment with IVIG until birth (around 34 weeks, by caesarean section) with the aim to protect the fetus from further bleeding while allowing for further (lung) maturation (Figure 1). A separate article about these case series is in progress. For some couples TOP might be an option if cerebral damage is severe and seems incompatible with live. Finally, in cases with an expected poor prognosis, vaginal birth without fetal monitoring and refraining from neonatal interventions might be considered, meaning no intervention based on fetal condition. We do realise that some of these options may be restricted by law, varying by country.

PREVIOUS CHILD WITH ICH: VERY HIGH-RISK GROUP

Most reports support the assumption that pregnant women with a previous child with an intracranial bleeding comprise the highest risk group. Most clinicians caring for such pregnancies choose for a more aggressive approach as compared with the group in which the affected sib did not have an ICH. Over time, many centres have reduced their use of FBS and IUPT, as also or even more clearly, in this very high-risk group the invasive procedures do more harm than good. Kanhai *et al.* (2006) was the first to describe completely non-invasive management using IVIG only in this group. They treated seven pregnancies with IVIG 1.0 g/kg/week, no ICH occurred, although PCs at birth were low (mean $27 \times 10^9/L$, range 10–49). These findings again support a possible protective role against bleeding of IVIG in so-called 'non-responders'. Recently, Bussel *et al.* (2010) reported a relatively large series of FNAIT pregnancies with a previous child with ICH. The 37 cases were subdivided in three risk categories depending on the assumed timing of the ICH, and received IVIG 1.0 or 2.0 g/kg with or without prednisone in a complicated scheme. Only one pregnancy was treated with the use of IUPT. Three ICHs occurred, two in fetuses treated with IVIG 1.0 g/kg + prednisone 1 mg/kg/day, and one in a fetus treated with 1.0 g/kg IVIG alone. No clear advantage from one type of treatment over another could be observed.

Following one of our studies (Kanhai *et al.*, 2006) we continued our non-invasive protocol in this high-risk group. In order to allow a vaginal delivery we offer this small group of women predelivery FBS to determine the PC, in a set-up prepared for immediate caesarean section, if needed followed by platelet transfusion, in order to achieve a safe level for vaginal birth.

There is no consensus about the gestational age of starting prenatal treatment. Some groups start at 12 weeks (Bussel *et al.*, 2010), others at 16 weeks of gestation (Kanhai *et al.*, 2006). As fetal platelets antigens are fully expressed as early as 16–18 weeks (Kaplan, 2002) we believe starting with IVIG at 16 weeks should both be safe and effective in preventing bleeding complications due to FNAIT (Figure 1).

DELIVERY, MODE AND TIMING

Caesarean section is often routinely employed for delivery in pregnancies with FNAIT. Evidence for a protective effect of caesarean section reducing the risk of ICH is lacking. Our recent systematic review showed that none of the cases of ICH seemed to have occurred intrapartum, and such cases are extremely rare in the literature as well (Kamphuis *et al.*, 2010). The only study on this subject, by Van den Akker *et al.* (2006) obviously underpowered with 32 FNAIT pregnancies with a sibling with thrombocytopenia but without an ICH, suggested that vaginal delivery was not associated with neonatal intracranial bleeding. Most pregnant women with known

FNAIT are multiparous, and a non-traumatic delivery is usually expected. We routinely advise near-term induction in multiparous women with known FNAIT and a sibling without ICH. In the small group of women with a previous child with an ICH, we offer elective caesarean section after steroids or predelivery FBS with matched platelets for transfusion at 36–37 weeks, although again, no evidence for such a policy exists.

The Norwegian investigators defended their choice of caesarean section in all women with FNAIT with three arguments. The first was the ability to deliver the child 2–4 weeks prior to term. This is obviously also possible with the currently quite effective prostaglandin or balloon induction. Second, they refer to a radiologic study in which 26% of neonates born vaginally had signs of haemorrhage on MRI, compared with 0% in the group delivered by caesarean section (Looney *et al.*, 2007). However, most of these bleedings were small subdural haematomas; none were symptomatic and most disappeared within 5 weeks. A more recent larger study by Rooks *et al.* (2008) with a similar design showed presence of such haematomas also in neonates born after caesarean section. This type of bleeding is thought to originate from tearing of small veins by the (normal) movement of the skull bones during labour and delivery, and are quite different from intraventricular and intraparenchymal bleeding commonly seen in ICH due to FNAIT. The third argument was that planned caesarean section would provide time for the blood bank to prepare matched platelets. This is however a matter of logistics and would be equally true for planned induction of labour. In conclusion, although not proven to be safer, we cannot entirely exclude that elective caesarean section protects against ICH. The associated maternal morbidity and increased risks in subsequent pregnancies must be weighed against perceived although possibly non-existent benefits.

POSTNATAL MANAGEMENT OF NEONATES WITH FNAIT

FNAIT in neonates has a variable course, in most cases thrombocytopenia resolves spontaneously in 1 to 16 weeks after birth. The most feared complication, ICH, mainly occurs *in utero*, so at birth the damage is already done.

The primary goal of the management of a neonate with FNAIT is to prevent or stop thrombocytopenic bleeding. Neonates without bleeding and a PC above $50 \times 10^9/L$ may be closely observed without transfusions (Blanchette, 2000).

Our protocol in Leiden advises not administer platelets when PC is above 30 and more recently even $20 \times 10^9/L$ without any sign of bleeding.

There are two distinct treatment groups; those treated with IVIG prenatally and those diagnosed after birth in the presence of clinical symptoms. In the prenatally treated group a rapid rise in PC after one HPA-matched transfusion can be expected (te Pas *et al.*, 2007) without the need of administering IVIG. In postnatally diagnosed cases random platelet transfusions can be used until

matched platelets are available. A study of Kiefel *et al.* (2006) showed that serial random donor platelets could successfully be used in the majority of cases pending the availability of matched platelets.

Transfusion of HPA-1a/5b-negative platelets, if available from stock, will be effective in more than 95% of the cases seen in a Caucasian population (Blanchette, 2000). Our bloodbank organisation can provide such units within a few hours anywhere in the country. IVIG could be added to increase and prolong the response to transfusions (te Pas *et al.*, 2007). The use of corticosteroids is not supported by any evidence (Bussel, 1991)

CONCLUSION

The optimal prenatal therapy to prevent ICH in pregnancies complicated by FNAIT is still unclear. All published treatment modalities are associated with a significant percentage of failing to keep the PC in the safe range, which is above 30 or $50 \times 10^9/L$. However, the true goal of preventive measures is to prevent bleeding complications. In particular in the group of FNAIT pregnancies with a previous child without ICH, treatment with 1.0 g/kg IVIG appears highly successful. In this group, there is insufficient evidence for additional benefit of FBSs or steroids. Only small studies have been done using maternal medical treatment in FNAIT pregnancies with a previous child with ICH. IVIG with or without steroids was successful in this high-risk group as well, although not 100%. Large prospective, preferably randomised studies are needed to provide evidence for optimal strategies.

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