Chapter 3

Noninvasive antenatal management of FNAIT: safe and effective

ABSTRACT

Objective To describe the outcome of pregnancies with fetal and neonatal alloimmune thrombocytopenia (FNAIT) in relation to the invasiveness of the management protocol.

Design Retrospective analysis of prospectively collected data from a national cohort.

Setting Leiden University Medical Centre, the national centre for management of severe red cell and platelet alloimmunisation in pregnancy.

Population Ninety-eight pregnancies in 85 women with FNAIT having a previous child with thrombocytopenia with \( n = 16 \) or without \( n = 82 \) an intracranial haemorrhage (ICH).

Methods Our management protocol evolved over time from (1) serial fetal blood samplings (FBS) and platelet transfusion \( n = 13 \) via (2) combined FBS with maternal intravenous immunoglobulins \( n = 33 \) to (3) completely noninvasive treatment with immunoglobulins only \( n = 52 \) pregnancies, resulting in 53 neonates. Perinatal outcome was assessed according to the three types of management.

Main outcome measures Occurrence of ICH, perinatal survival, gestational age at birth and complications of FBS.

Results All but one of 98 pregnancies ended in a live birth; none of the neonates had an ICH. The median gestational age at birth was 37 weeks (range 32–40). In groups 1 and 2, three emergency caesarean sections were performed after complicated FBS, resulting in two healthy babies and one neonatal death.

Conclusion Noninvasive antenatal management of pregnancies complicated by FNAIT appears to be both effective and safe.
Chapter 3 Noninvasive Antenatal Management

Introduction

Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is caused by maternal antibodies against human platelet antigens (HPA) on fetal platelets. The incidence of FNAIT is estimated to be one in 1000–2000 births. The major complication of severe fetal thrombocytopenia is intracranial haemorrhage (ICH), occurring in 7–26% of untreated pregnancies with FNAIT. In the absence of screening programs, the diagnosis is almost always established after birth of a symptomatic child. To prevent recurrence of FNAIT in a subsequent pregnancy, several interventions have been used. At first, we and others used serial fetal blood sampling (FBS) with often weekly platelet transfusions. After the empirical observation by Bussel et al. in 1988 that antenatal maternal treatment with high-dose intravenous immunoglobulins (IVIG) seemed to prevent ICH in high-risk pregnancies, IVIG became the cornerstone of FNAIT treatment. Several centres in both Europe and the USA advocate the use of FBS for verification of fetal platelet count before and during maternal treatment. Controversy exists whether FBS, with its inherent risks of bleeding, boosting of antibody levels, emergency (preterm) caesarean section and fetal loss, should remain part of the management of FNAIT. In the past 16 years, we gradually changed our management strategy towards a completely noninvasive approach for FNAIT. The aim of this study was to describe our experience with the transition from an invasive strategy via a minimally invasive to an ultimately completely noninvasive strategy.

Methods

The Department of Obstetrics at the Leiden University Medical Centre is the national referral centre for pregnancies complicated by FNAIT in the Netherlands. For this study we extracted data on pregnancy, delivery and neonatal course of all FNAIT pregnancies treated at our centre between March 1989 and December 2005. Maternal and fetal HPA incompatibility was confirmed for all patients by paternal HPA typing. In cases where the father was homozygous for the specific HPA, we assumed that the fetus would be at risk. Where the father was heterozygous for the HPA, amniocentesis was performed for fetal HPA typing.

We divided these pregnancies into three groups, according to the invasiveness of the management protocol used. The first group was managed with FBS and subsequent intrauterine transfusion in case of low platelet count, without the use of IVIG. The second group was treated with IVIG combined with FBS with in-
Fetal thrombocytopenia: preventive strategies

Trauterine transfusion if needed. In all cases of FBS, matched platelets were available for immediate transfusion. Our threshold for platelet transfusion in group 1 was a fetal platelet count < 100 x 10^9/l. In group 2, the nonresponders, defined as fetuses with a platelet count < 50 x 10^9/l after at least 4 weeks of IVIG treatment, received platelet transfusions. In case of predelivery FBS, a threshold of 100 x 10^9/l was used for platelet transfusion. The third group was treated completely noninvasively with IVIG only. Groups 1, 2 and 3 were further subdivided into those pregnancies with a sibling with an ICH and those with a sibling without an ICH.

If the sibling had an ICH, in the second (invasive) group, IVIG was started 4–6 weeks before the estimated time of occurrence of the sibling’s ICH. In the third (noninvasive) group, IVIG was started at 16 weeks of gestation if the sibling did have an ICH and at 32 weeks of gestation if the sibling did not.

In all cases, IVIG was given weekly in a dose of 1 g/kg maternal weight. Further details on our management protocols have been described previously.9,10

If the previous sibling had an ICH, a planned caesarean section was performed around 36 weeks of gestation. In a few cases, in group 2, with an easily accessible cord insertion, predelivery FBS was carried out, with platelet transfusion when needed, followed by induction of labour and vaginal delivery.

If the previous sibling did not have an ICH, IVIG was continued until induction of labour at 38 weeks of gestation, with a caesarean section only for obstetric reasons.

In all groups, serial ultrasounds of the fetal brain were performed. Platelet count at birth was assessed from umbilical cord blood. Neonatal cranial ultrasound was carried out in all children within 24 hours after birth.

The noninvasive management protocol was approved by our institution’s medical ethics committee.

From all pregnancies, we collected the clinically relevant outcome variables: neonatal survival, occurrence of ICH, complications of FBS and gestational age at birth. We consider gestational age at birth as a relevant parameter because a complication during FBS at a viable gestational age is often followed by an emergency caesarean section, resulting in a preterm birth.

RESULTS

Ninety-nine fetuses from 98 pregnancies in 85 women were treated at our centre during the study period. HPA-1a antibodies were the leading cause of FNAIT,
**Table 1:** Characteristics and outcome of 98 pregnancies (99 fetuses) treated for FNAIT at Leiden University Medical Centre from March 1989 till December 2005

<table>
<thead>
<tr>
<th></th>
<th>Sibling with ICH</th>
<th>Sibling without ICH</th>
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</thead>
<tbody>
<tr>
<td><strong>Treatment</strong></td>
<td>Group 2</td>
<td>Group 3</td>
</tr>
<tr>
<td></td>
<td>IVIG+ FBS+</td>
<td>IVIG without FBS</td>
</tr>
<tr>
<td></td>
<td>(invasive)</td>
<td>(non-invasive)</td>
</tr>
<tr>
<td></td>
<td>n=11</td>
<td>n=5</td>
</tr>
<tr>
<td></td>
<td>IVIG+ FBS+</td>
<td>IVIG without FBS</td>
</tr>
<tr>
<td></td>
<td>(invasive)</td>
<td>(non-invasive)</td>
</tr>
<tr>
<td></td>
<td>n=13</td>
<td>n=22</td>
</tr>
<tr>
<td></td>
<td>n=48*</td>
<td></td>
</tr>
<tr>
<td><strong>In utero</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median platelet count sibling (range) x 10^{9/l}</td>
<td>20 (2-36)</td>
<td>12 (6-12)</td>
</tr>
<tr>
<td>Median GA at first IVIG treatment (weeks, range)</td>
<td>27 (12-30)</td>
<td>16 (16)</td>
</tr>
<tr>
<td>Median number of IVIG treatments (range)</td>
<td>11 (5-24)</td>
<td>20 (19-21)</td>
</tr>
<tr>
<td>Median number of FBS (range)</td>
<td>2 (5-9)</td>
<td>-</td>
</tr>
<tr>
<td>Median platelet count at first FBS (range) x 10^{9/l}</td>
<td>26 (2-125)</td>
<td>-</td>
</tr>
<tr>
<td>Median number of platelet transfusions (range)</td>
<td>2 (0-9)</td>
<td>-</td>
</tr>
<tr>
<td><strong>At delivery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal delivery (n,%)</td>
<td>7 (64%)</td>
<td>0</td>
</tr>
<tr>
<td>Median platelet count at birth (range) x 10^{9/l}</td>
<td>180 (55-377)^a</td>
<td>15 (10-199)</td>
</tr>
<tr>
<td>Platelet count at birth ≤ 50 x 10^{9/l} (n,%)</td>
<td>0</td>
<td>4 (80%)</td>
</tr>
<tr>
<td>Emergency delivery due to FBS (n,%)</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Neonatal death secondary to FBS (n,%)</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Delivery before 34 weeks (n,%)</td>
<td>1 (9%)</td>
<td>0</td>
</tr>
<tr>
<td>Median GA at delivery (weeks, range)</td>
<td>36 (32-38)</td>
<td>37 (34-37)</td>
</tr>
</tbody>
</table>

*48 neonates, 47 pregnancies (1 twin)
^ after intrauterine transfusion

FNAIT: fetal and neonatal alloimmune thrombocytopenia
FBS: fetal blood sampling
GA: gestational age
present in 76 of 85 women (89%); the remaining patients had HPA-5b \((n = 7)\) or HPA-3a \((n = 2)\) antibodies. In six pregnancies, a combination of HPA-1a with HPA-3a or HPA-5b was found. In 22 pregnancies, fetal HPA typing by amniocentesis showed that the fetus was positive for the HPA. Overall perinatal survival was 99% (98 of 99 fetuses). None of the neonates had an ICH. Median gestational age at birth was 37 weeks (range 32–40). Three emergency deliveries because of fetal distress after FBS occurred at 38, 37 and 34 weeks of gestation, two with good outcomes. One fetus died immediately after the emergency delivery at 38 weeks of gestation with an umbilical arterial pH of 6.88. Sixty-two of the 98 pregnancies ended in a vaginal delivery.

Thirteen pregnancies (group 1) were managed with FBS and platelet transfusions if needed, without the use of IVIG, of which none had a sibling with ICH. Thirty-three pregnancies (group 2) were treated with IVIG combined with FBS and intrauterine transfusions if needed. Fifty-two pregnancies (group 3), resulting in 53 neonates, were treated completely noninvasively, of which five had a sibling with an ICH.

In Table 1, the characteristics and the outcome of all 98 pregnancies are given, with the three groups subdivided in having a sibling with or without an ICH.

**DISCUSSION**

In this cohort study of a relatively large series of consecutive pregnancies complicated by FNAIT, the gradual change over time from an invasive management protocol to a completely noninvasive approach resulted in excellent outcome for all noninvasively treated patients. These findings encourage us to continue, and recommend to others, the noninvasive strategy that we have suggested in previous publications.9,10

To support this view further, the clinically important outcome data from our series compare favourably with two recently published studies describing results from more invasive management protocols. Birchall *et al.* reported on an observational study from 12 European centres, with a total of 50 women with 55 pregnancies and 56 fetuses, all with HPA-1a alloimmunisation treated between 1988 and 2001.11 Multiple management options were described, all after an initial FBS. ICH occurred in 5% of the children \((3/56)\). FBS-related adverse outcome occurred in 18% of the fetuses \((10/56)\), with two fetal losses and eight deliveries before 34 weeks of gestation. In addition, in 9% \((5/56)\) an emergency delivery after 34 weeks of gestation had to be performed following FBS. Maternal treat-
ment with IVIG was used in 18 patients, combined with one or more FBS. Four of these 18 neonates were born before 34 weeks, one fetal loss occurred and one emergency caesarean section was performed, both associated with FBS. The mean platelet count at birth in this group was $80 \times 10^9/l$ with six of the 18 neonates having a platelet count $< 50 \times 10^9/l$. None of their cases were treated completely noninvasively.

Berkowitz et al. performed a randomised multicentre study stratifying 79 pregnancies into high-risk and low-risk arms. All women underwent initial FBS at 20 weeks of gestation. High-risk cases ($n = 40$) were defined as either a sibling with peripartum ICH or an initial platelet count $< 20 \times 10^9/l$. Randomisation was between IVIG and prednisone, or IVIG only. Low-risk cases were randomly assigned to IVIG or prednisone. A second FBS was used to adapt the medication dose in nonresponders. Platelet transfusions were given in an unknown number of cases. ICH occurred in three cases (4%). In 13% (10/79) of the pregnancies, emergency deliveries related to FBS were required and 24% (19/79) of the neonates were born before 34 weeks. One fetus died because of a complication of FBS and two pregnancies ended in unexplained fetal demise. A total of 175 FBS were carried out, with serious complications occurring in 6%. Mean platelet count at birth in the high-risk group was $99 \times 10^9/l$ in the IVIG group and $69 \times 10^9/l$ in the IVIG combined with steroids group. In the low-risk group, 15% (6/39) of fetuses had a platelet count $< 50 \times 10^9/l$.

In conclusion, the studies by Birchall et al. and Berkowitz et al. describe a considerable number of complications and adverse outcomes associated with FBS. However, such risks could be acceptable if the invasive management would result in a better overall outcome when compared with a completely noninvasive approach. This, as our data suggest, does not seem to be the case. For none of the clinically relevant outcome parameters, including survival, ICH and gestational age at birth, our noninvasively managed series shows worse results than in the other studies. Platelet counts at birth, although arguably a surrogate measure, were similar in our group.

Our data as well as our comparison with the other two studies should be interpreted with some care. All three studies described fewer than 100 patients, over a considerable period of time, managed with different protocols. Patient populations in the three studies differed slightly, although the possible bias this could introduce would not weaken our main conclusions. In the study by Berkowitz et al., patients with the most severe forms of FNAIT (sibling with ICH or platelet count $< 20 \times 10^9/l$) were excluded, while we included all patients referred to us.
As far as can be ascertained, the severity of the disease in patients in our series was at least comparable with the other two studies. The level of evidence for the suggestion that FBS can be avoided in all pregnancies with FNAIT would obviously be stronger with properly controlled study designs. However, given the rarity of this disease, the data presented here represent the best possible evidence currently available. In our view, these limited data suggest that there seems to be no benefit in the use of diagnostic FBS in addition to treatment with IVIG in the management of FNAIT, irrespective of the severity of the disease.

The perceived advantages of FBS are to optimise the indication for IVIG treatment and identify nonresponders for treatment adjustment, and in case of predelivery sampling, to select patients that might safely deliver vaginally. The serious and, in this particular disease, even greater risks of FBS\textsuperscript{13,14} have to be balanced against unnecessary IVIG treatment. Omitting FBS means starting IVIG treatment ‘blindly’, based only on the history of the disease in a previous child. With noninvasive management, adaptation of the dose, or adding steroids in case of insufficient response is obviously not possible. Compelling evidence that such adaptations lead to improved outcome however is lacking. Moreover, highdose prednisone is known to cause serious maternal adverse effects.\textsuperscript{5} Because IVIG in a dose of 1 g/kg/week has been shown to have minimal, if any, adverse effects both for mother and fetus,\textsuperscript{15,16} and excellent outcome, the risk of superfluous treatment in some pregnancies by starting IVIG blindly may well outweigh the risks of pretreatment FBS.

Apart from the immediate risks of exsanguination or haematoma formation during FBS, a more long-term negative effect might be a boosting of antibodies especially with transplacental procedures.\textsuperscript{17} We speculate that this mechanism could have contributed to the lower platelet counts at birth in the patients with a sibling without an ICH described by Birchall \textit{et al.} compared with our noninvasively managed patients. In future studies, changes in antibody titres could be monitored in order to address this important issue.\textsuperscript{18}

Predelivery FBS to allow vaginal birth in case of a sufficient platelet count would be a logical intervention if caesarean section is considered safer in fetuses with low platelet counts, an assumption not based on any evidence. In a recent study we found no peripartum ICH in any neonate with FNAIT born vaginally.\textsuperscript{19}

Although we do realise that the absolute number of patients treated completely noninvasively is still limited, we conclude that based on our data and the currently available literature, there seems to be no advantage to the use of
FBS in the management of pregnancies complicated by FNAIT. For clinically relevant endpoints, the noninvasive management strategy using IVIG without pretreatment or confirmatory FBS seems both effective and safe. Adherence to the principle of *primum non nocere* means, in our view, that potentially hazardous diagnostic procedures should only be employed when proven to do more good than harm.

Further improvement of treatment strategies is certainly warranted, as we still observed fetuses and neonates with low platelet counts at risk for ICH. Future studies could be directed at the optimal time to start treatment and optimising the dose, possibly stratifying patients according to antibody levels or functional bioassays and obstetric history. Because FNAIT is a potentially devastating but rare disease, rapid advances in our insights to improve management can only be made by multicentre collaboration. We would therefore like to encourage all colleagues caring for these patients to consider participating in international trials and registries. Information on one of these initiatives can be found on www.noich.org.

REFERENCES


Fetal thrombocytopenia: Preventive strategies


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