Chapter 4

IVIG without initial and follow-up cordocentesis in FNAIT at high risk for intracranial hemorrhage

ABSTRACT

Objective To report on a less invasive treatment strategy in alloimmune fetal and neonatal thrombocytopenia (FNAIT) at high risk for either in utero or neonatal intracranial hemorrhage (ICH).

Methods In seven pregnancies, with a history of ICH in the older sibling, weekly intravenous immunoglobulin (IVIG) therapy to the mother (1 g/kg) without initial cordocentesis was started at a median gestational age of 16 weeks.

Results In four pregnancies cordocentesis was avoided. One predelivery cordocentesis with platelet transfusion was performed in three further cases. Although none of the cases had a platelet count of > 50 x 10^9/l at cordocentesis, predelivery or birth, no ICHs were observed. The neonatal periods of the infants were uncomplicated.

Conclusion IVIG treatment alone might be considered in patients with both severe platelet alloimmunization and an increased risk for morbidity and mortality at cordocentesis.
INTRODUCTION

Platelet alloimmunization, resulting in severe fetal or neonatal thrombocytopenia (FNAIT), is a rare but potentially devastating condition. The major complication of severe thrombocytopenia in the fetus or newborn is intracranial hemorrhage (ICH), resulting in either perinatal mortality or serious morbidity. In Caucasians, the immunodominant antigen is the human platelet antigen (HPA) 1α, responsible for approximately 85% of FNAIT cases. Two percent of pregnant Caucasian women are HPA-1a negative. Severe thrombocytopenia is estimated to occur in 6–12% of the HPA-1a-negative mothers with antibodies. The reported frequency of ICH in FNAIT varies from 7 to 26%, of which the large majority is presumed to occur in utero. After the birth of a child with ICH, the recurrence rate in the subsequent offspring carrying the offending antigen is estimated to be as high as 79%.

The accepted treatment to reduce the risk of both severe thrombocytopenia and ICH is maternal intravenous immunoglobulin (IVIG) administration and serial cordocentesis from 20 weeks onwards, and if thrombocytopenia persists, intrauterine platelet transfusions (IUP1). It is recognized that cordocentesis is a hazardous procedure, especially for patients with thrombocytopenia. Based on a review of the literature, the complication rate of cordocentesis in FNAIT pregnancies was calculated as 1.6% fetal loss and 2.4% other complications. According to two recent studies, 6% of pregnancies were lost because of serial cordocentesis.

Application of high-dose maternal immunoglobulins (1 g/kg body weight/week) has become increasingly important in the management of alloimmune thrombocytopenia of pregnancy. In addition to increasing fetal platelet counts, reported in 70% of the cases, the treatment seems to reduce the incidence of ICH, even when severe thrombocytopenia persists. In alloimmunized women with an older infant with severe thrombocytopenia, but without ICH, we have shown that weekly administration of immunoglobulins without cordocentesis is safe. Balancing the risk for serious complications from cordocentesis on one hand and ICH on the other, we designed a protocol to further reduce invasive procedures in patients with the highest risk for fetal ICH. We describe the protocol and the results of the first eight consecutive pregnancies thus treated.
**Figure 1:** Flow chart of the management protocol in HPA-1a immunized women, used at Leiden University Medical Centre.

- Obstetric History
  - Sibling with ICH and thrombocytopenia
    - IvIG from 16 weeks onwards
  - Sibling without ICH, but with thrombocytopenia
    - IvIG from 28-34 weeks

- Posterior placenta
  - FBS / IUPT from 24-28 weeks onwards
  - Elective CS ≤ 36 weeks

- Anterior placenta
  - FBS / IUPT is option, after parental consent
  - One single FBS / IUPT* (pre-delivery)
  - Elective birth at 32-38 weeks

- No FBS / IUPT
  - Elective CS ≤ 38 weeks
  - Elective birth ≤ 38 weeks

§ = Defined as a neonatal platelet count of < 100 x 10⁹/l;
* = in case of a fetal platelet count < 100 x 10⁹/l;

ICH = intracranial hemorrhage;
IVIG = intravenous immunoglobulins;
FBS = fetal blood sampling;
IUPT = intrauterine platelet transfusion;
CS = cesarean section.
PATIENTS AND METHODS

Between June 1998 and December 2003, six HPA-1a alloimmunized women with eight pregnancies with a prior child with ICH were treated at the Leiden University Medical Center (LUMC). The LUMC is the Dutch national referral centre for the management of severe alloimmune pregnancy disorders. One patient opted for follow-up cordocentesis, based on her experience in a previous pregnancy. This case will be excluded in this report. Therefore, seven cases without initial and follow-up cordocentesis will be described here. The six partners were homozygous HPA 1a/1a. The characteristics of the pregnancies are depicted in table 1. In all but one of the six siblings, ICH occurred in utero and before labor. In the elder sibling of cases 3 and 4 (table 1), a massive subarachnoid bleeding was diagnosed and the growth-retarded neonate died early in the neonatal period. Two of the six siblings survived, both with severe physical and mental handicaps. Case 3 (tables 1, 2) has been previously published, in the series described by Radder et al.18.

Before the current pregnancy, all the couples were counseled extensively about the known risks of a subsequent pregnancy. They were informed about the treatment thus far8 and the pros and cons of a management strategy, including repeated cordocentesis. The couples were also informed about the new management protocol (fig. 1). All of the couples decided to attempt a new pregnancy and agreed to follow the protocol.

During the current pregnancy, IVIG was started early in the second trimester (table 2) and continued until delivery. Detailed ultrasound examinations of the fetal brain were performed weekly. Cordocentesis with IUPT was performed once in three pregnancies, just before a planned delivery. In the other four pregnancies, cordocentesis was avoided. The local medical ethical commission approved the protocol.

RESULTS

Serial ultrasound examinations during pregnancy revealed no ICH in the fetus. The median gestational age at the start of IVIG was 16 weeks (range 16–29 weeks) based on the estimated gestational age when ICH occurred in the sibling. In two pregnancies of the same woman (cases 3 and 4 in table 2), IVIG treatment was initiated later, because the older sibling had a subarachnoid bleeding instead of ICH and was growth retarded. The total number of weekly IVIG infusions ranged from eight to twenty-one (table 2).
**Fetal Thrombocytopenia: Preventive Strategies**

**Table 1:** Characteristics of the pregnancies

<table>
<thead>
<tr>
<th>Mother</th>
<th>Case no.</th>
<th>Timing of ICH in sib (weeks GA)</th>
<th>Sib died? When?</th>
<th>PLC of sib (x 10⁹/l)</th>
<th>BW sib (gram)</th>
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<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>&lt; 33</td>
<td>yes, 1 day pp</td>
<td>33</td>
<td>2750</td>
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<td>&lt; 33</td>
<td>yes, 1 day pp</td>
<td>33</td>
<td>2750</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>33</td>
<td>yes, directly pp*</td>
<td>11</td>
<td>1200</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>33</td>
<td>yes, directly pp*</td>
<td>11</td>
<td>1200</td>
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<tr>
<td>5</td>
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<td>&lt; 36</td>
<td>no, multiple handicaps</td>
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<td>2200</td>
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<td>&lt; 33</td>
<td>no, multiple handicaps</td>
<td>11</td>
<td>2390</td>
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<td>&lt; 35</td>
<td>yes, antenatal</td>
<td>20</td>
<td>2730</td>
</tr>
</tbody>
</table>

* Extensive subarachnoid bleeding, uncertain when occurred, with severe intrauterine growth retardation

ICH: intracranial hemorrhage  
Sib: sibling  
GA: gestational age  
pp: postpartum  
PLC: platelet count  
BW: birth weight
Table 2: Characteristics of the treatment with immunoglobulins, placenta localization and birth outcome

<table>
<thead>
<tr>
<th>Mother</th>
<th>Case no.</th>
<th>First IVIG (GA) (weeks)</th>
<th>IVIG (n)</th>
<th>Placenta localisation</th>
<th>Birth (GA) (weeks)</th>
<th>PLC at birth (x 10⁹/l)</th>
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<tr>
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<td>1</td>
<td>16</td>
<td>20</td>
<td>Posterior</td>
<td>36</td>
<td>39</td>
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<tr>
<td></td>
<td>2</td>
<td>16</td>
<td>21</td>
<td>Anterior</td>
<td>37</td>
<td>14</td>
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<tr>
<td>2</td>
<td>3</td>
<td>28</td>
<td>10</td>
<td>Fundal</td>
<td>38</td>
<td>26*</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>29</td>
<td>8</td>
<td>Anterior</td>
<td>38</td>
<td>41*</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>18</td>
<td>19</td>
<td>Posterior</td>
<td>37</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>16</td>
<td>19</td>
<td>Posterior</td>
<td>34§</td>
<td>10</td>
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<tr>
<td>5</td>
<td>7</td>
<td>19</td>
<td>19</td>
<td>Anterior</td>
<td>37</td>
<td>49*</td>
</tr>
</tbody>
</table>

* Platelet count at fetal blood sampling predelivery, before intrauterine platelet transfusion
§ Elective cesarean section because of hydrothorax and fear for internal bleeding; after birth: infant with Down syndrome without signs of internal bleeding

IVIG: intravenous immunoglobulins
GA: gestational age
PLC: platelet count
Elective cesarean section was performed in four pregnancies between a gestational age of 34 and 37 weeks. In the other three pregnancies, labor was induced between 37 and 38 weeks, within three days after IUPT.

Although none of the cases had a platelet count of > 50 x 10^9/l, after several weeks of IVIG treatment (table 2), no ICH was diagnosed in antenatal or neonatal ultrasound examinations. Four neonates were given one platelet transfusion shortly after birth. None of the neonates received IVIG. The neonatal platelet counts for the first five days are depicted in figure 2. Strikingly, although some neonates experienced an initial thrombocytopenia, recurrence was not observed subsequently (fig. 2). At follow-up three months after birth, all of the infants were doing well.

**Figure 2:** Fetal and neonatal platelet counts
DISCUSSION

The present series describes the use of weekly immunoglobulins to the mother without initial or confirmatory cordocentesis in FNAIT with an older sibling with ICH. In seven alloimmunized pregnancies with an older sibling with severe internal bleeding, serial IUPT were avoided. With the less invasive approach, ICH did not recur in any of the cases. The cornerstone of therapy was maternal administration of immunoglobulins (1 g/kg bodyweight/week). Cordocentesis was only considered when the procedure did not pose an unacceptable risk. In our current protocol, women are given the option of cordocentesis after at least four weeks of IVIG treatment, when the placenta is anteriorly located. Although the placenta was anteriorly located in three of the cases, IVIG was administered as the sole treatment, and this was continued until term.

In general, procedure-related complications of cordocentesis are associated with factors such as experience of the operator, gestational age, indication for the procedure, and location of the placenta. In fetuses with severe thrombocytopenia, cordocentesis is a procedure that poses a high risk for bleeding. Especially, puncture of a free loop or posteriorly located umbilical cord insertion may lead to either excessive fetal bleeding or cord hematoma.

Three patients delivered vaginally after cordocentesis and platelet transfusion. The other four underwent an elective cesarean section. The rationale to perform elective cesarean section in these patients was that we did not dare to attempt vaginal delivery in these high-risk cases for bleeding, without knowledge of the platelet counts. Although all infants had platelet counts of < 50 x 10^9/l at birth or before a predelivery IUPT, no ICH was observed in the neonates. In addition, four newborns needed a single platelet transfusion shortly after birth and all had normal and stable platelet counts after birth. This observation is in concordance with earlier reports that IVIG therapy might prevent ICH in nonresponders to IVIG. The reported recurrence risk of ICH in the next pregnancy of women with an older affected child is 79% (CI: 61–97%). Given this risk, approximately six cases of ICH would be expected in our series. This suggests a beneficial effect of IVIG on the recurrence of ICH, despite the presence of low platelet counts in utero. This may be the result of a specific protective effect of IVIG for bleeding in severe alloimmune thrombocytopenia. Potential disadvantages of IVIG are the generally mild side effects and the high costs of the treatment. Although the longterm side effects for mother and child treated with high dose IVIG are still unclear, reports thus far are satisfactory. At present cordocentesis, with or
without pretreatment with IVIG, and, in case of persisting thrombocytopenia, IUPT, given weekly, is the treatment of first choice in patients at high risk for in utero ICH. This approach is effective but has a significant risk, even in experienced hands. In a recent publication of the European Fetomaternal Alloimmune Thrombocytopenia Study Group, five problems occurred in the 33 fetuses that were treated with serial IUPT. Two fetuses died, one from exsanguination during cordocentesis and one on the day after IUPT. In the remaining three cases, delivery occurred before 32 weeks’ gestation due to cordocentesis-related complications.

The results of the present series show that the effectiveness of maternally administered IVIG allows a further avoidance of cordocentesis in the most severe cases of FNAIT. However, we acknowledge that our series is small and that in the group of alloimmunized women at extreme high risk for ICH, IVIG therapy alone may not entirely eliminate the risk of ICH. There are anecdotal reports in the literature of cases where IVIG treatment failed to prevent ICH. It is, therefore, extremely important to initiate a collaborative database of cases of FNAIT to investigate the risk of invasive versus noninvasive treatment.
REFERENCES


10 Radder CM, Brand A, Kanhai HH: 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: 318–325.


FETAL THROMBOCYTOPENIA: PREVENTIVE STRATEGIES


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