Neonatal Alloimmune Thrombocytopenia: Antenatal Management

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32 yo, G2P1, 12 wk of gestation

OB Hx:

G1- Vaginal delivery @ 38wk, petechiae at birth,
PLT-30,000
Outline

• How is NAIT diagnosed?
• What is the antenatal management?
• Can severity of NAIT be predicted?
• What is the management in cases of previous ICH?
• What should be the mode of delivery?
• What is the management in cases of previous thrombocytopenia/ICH of unknown etiology?
• Should we screen for NAIT?
• Is it possible to prevent HPA alloimmunization?
How is NAIT diagnosed?
NAIT-Diagnosis

- Previous child with unexplained thrombocytopenia
- Maternal-Paternal HPA incompatibility
- Maternal HPA antibodies against the corresponding HPA antigen
### Table 1. Platelet-specific alloantigens that are associated with AIT

<table>
<thead>
<tr>
<th>HPA system name</th>
<th>Antigen</th>
<th>Familiar name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polymorphisms of glycoprotein IIIa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPA-1</td>
<td>HPA-1a</td>
<td>P1\textsuperscript{A1}, Zw\textsuperscript{a}</td>
</tr>
<tr>
<td></td>
<td>HPA-1h</td>
<td>P1\textsuperscript{A2}, 7w\textsuperscript{b}</td>
</tr>
</tbody>
</table>

### Table 2. Human platelet alloantigen frequencies.

<table>
<thead>
<tr>
<th>Antigens</th>
<th>Percentage frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Caucasian</td>
</tr>
<tr>
<td>HPA-1a</td>
<td>97.9</td>
</tr>
<tr>
<td>HPA-1b</td>
<td>28.6</td>
</tr>
<tr>
<td>HPA-2a</td>
<td>&gt;99.9</td>
</tr>
<tr>
<td>HPA-2b</td>
<td>13.2</td>
</tr>
<tr>
<td>HPA-3a</td>
<td>80.9</td>
</tr>
<tr>
<td>HPA-3b</td>
<td>69.8</td>
</tr>
<tr>
<td>HPA-4a</td>
<td>&gt;99.9</td>
</tr>
<tr>
<td>HPA-4b</td>
<td>0.0</td>
</tr>
<tr>
<td>HPA-5a</td>
<td>99.0</td>
</tr>
<tr>
<td>HPA-5b</td>
<td>19.7</td>
</tr>
</tbody>
</table>

n.t., not tested.
The fetus is at risk

Amniocentesis for fetal HPA typing

Fetal HPA-typing using free fetal DNA in maternal plasma

Scheffer et al., BJOG 2011
Maternal IgG Alloantibodies to PLT antigens

Cross the placenta

Fetal platelets

Removed by RES

Fetal thrombocytopenia
Only around 10% of HPA-1a negative pregnant women produce HPA-antibodies despite carrying an HPA-1a positive fetus

Association between maternal HLA and tendency to produce these antibodies
Neonatal Alloimmune Thrombocytopenia

- Incidence: 1:1000-1:2000 (varies by ethnicity)
- Can occur in the first pregnancy
- Diagnosis is usually made following delivery of an affected child
Neonatal Alloimmune Thrombocytopenia

- Rate of recurrence among subsequent infants is 90%
- Tends to worsen in subsequent pregnancies???
  Killie et al., Haematologica 2008
- 10%-20% affected infants have ICH
What is the antenatal management?
Antenatal management is aimed at maintaining fetal platelet count on a safe level

The optimal antenatal management has not been defined:

- Serial fetal platelet transfusions:
  The half life of transfused platelets is very short

- IVIG ± steroids
Maternal: dilution of anti-HPA antibodies

Placenta: blockage of the receptor (Fc-R)

Fetus: blockage of the Fc-receptors on the macrophages

No dose-effect studies have been done
• Headache
• Fever
• Chest pain
• Laryngeal edema
• Renal failure
• Aseptic meningitis
• Thrombotic complications
NAIT – Antenatal management

**Invasive:** FBS in order to diagnose fetal thrombocytopenia before therapy and to evaluate subsequent fetal response

- High risk of hemorrhagic complications from cordocentesis (5%)
- Risk for boosting the alloimmunization

**Non-invasive:** Empiric IVIG for women with a fetus at risk for NAIT

FBS-indicated therapy and empiric therapy have never been prospectively compared in a randomized trial
Fetal blood sampling at 20-22 weeks

If PLT<100,000 start IVIG
If PLT>100,000 FBS every 6-8 weeks

FBS after 4-6 wk to evaluate therapy

Lynch et al., Obstet Gynecol 1992
IUT-Complications
NAIT – Invasive approach

• 11 (6%) serious complications after 175 FBS:
  – 9 emergent CS
  – 1 IUFD 4 days post FBS
  – 1 PPROM 4 days post FBS

• 19 (24%) delivered <34 wk

Berkowitz et al., Obstet Gynecol 2006
NAIT – Non-invasive approach

Rationale: - High recurrence rate of NAIT
- Desire to avoid risks of FBS

Advantages
- Highly effective
- Avoids risks of FBS

Disadvantages
- Overtreatment in some cases
- Inadequate therapy in other cases

Does these concerns outweigh the negative side effects of repeated FBS?
Antenatal noninvasive treatment of patients at risk for alloimmune thrombocytopenia without a history of intracranial hemorrhage

Yoav Yinon, MD,a,* Maya Spira, MD,a Ofira Solomon, MD,b Boaz Weisz, MD,a Benjamin Chayen, MD,a Eyal Schiff, MD,a Shlomo Lipitz, MD,a

Objective

To evaluate a non-invasive management of alloimmune thrombocytopenia, in which treatment included only blind administration of immunoglobulin
22 women, 41 pregnancies at risk of NAIT
All fetuses antigen-positive

35 pregnancies: IVIG treatment

6 pregnancies: Refused treatment

• Weekly administration of IVIG 1 gr/kg without monitoring platelet counts
• Started in 18-24 gestational week and continued until delivery

Yinon et al., AJOG 2006
<table>
<thead>
<tr>
<th>Characteristic (n=35)</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLT @ 1&lt;sup&gt;st&lt;/sup&gt; pregnancy</td>
<td>18,000 (8000-70,000)</td>
</tr>
<tr>
<td>PLT @ birth</td>
<td>90,500 (11,000-320,000)</td>
</tr>
<tr>
<td>PLT&lt; 30,000</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>GA @ delivery</td>
<td>38 (31-40)</td>
</tr>
<tr>
<td>Mode of delivery: VD</td>
<td>11 (31%)</td>
</tr>
<tr>
<td></td>
<td>CS</td>
</tr>
<tr>
<td></td>
<td>24 (69%)</td>
</tr>
</tbody>
</table>

Yinon et al., AJOG 2006
## NAIT – Non-invasive approach

<table>
<thead>
<tr>
<th></th>
<th>FBS+IUT (n=13)</th>
<th>IVIG+FBS (n=22)</th>
<th>IVIG only (n=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plt @ birth</td>
<td>145</td>
<td>180</td>
<td>137</td>
</tr>
<tr>
<td>Plt &lt;50,000 at birth</td>
<td>3 (23%)</td>
<td>0</td>
<td>6 (13%)</td>
</tr>
<tr>
<td>Emergency CS d/t FBS</td>
<td>0</td>
<td>3 (14%)</td>
<td>0</td>
</tr>
<tr>
<td>GA @ delivery</td>
<td>38</td>
<td>37</td>
<td>38</td>
</tr>
</tbody>
</table>

Van den Akker et al., BJOG 2007
### NAIT – Non-invasive approach

<table>
<thead>
<tr>
<th></th>
<th>Number of fetuses</th>
<th>Dose</th>
<th>ICH (n)</th>
<th>PLT at birth</th>
<th>PLT &lt;50000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berkowitz (2007)</td>
<td>37</td>
<td>2</td>
<td>1</td>
<td>169</td>
<td>14%</td>
</tr>
<tr>
<td>Yinon (2006)</td>
<td>24</td>
<td>1</td>
<td>0</td>
<td>118</td>
<td>8%</td>
</tr>
<tr>
<td>Van den Akker (2007)</td>
<td>45</td>
<td>1</td>
<td>0</td>
<td>136</td>
<td>16%</td>
</tr>
<tr>
<td>Bertrand (2011)</td>
<td>27</td>
<td>1</td>
<td>0</td>
<td>89</td>
<td>44%</td>
</tr>
</tbody>
</table>

Kamphuis and Oepkes, Prenatal Diagnosis 2011
10-20% of fetuses do not seem to respond

There is currently no explanation for this phenomenon

The non-responders may be at risk for ICH although it seems extremely rare in IVIG treated fetuses

IVIG may aid in protection against bleeding
NAIT – Non-invasive approach

- Non-invasive management of NAIT is highly effective and seems safe.

- The value of performing cordocentesis and platelet transfusion is doubtful in view of its risk for the fetus, and the fact that immunoglobulin therapy so effectively improves the fetal platelet count.
Cost effectiveness of empiric IVIG

- For every 1000 women empiric therapy compared with FBS-indicated treatment:
  - Decreased perinatal deaths from 31.7 to 11.8
  - Increased number of infants with long-term neurologic deficits from 6.1 to 9.6

Empiric IVIG therapy is a cost-effective strategy when the rate of perinatal ICH is less than 28%

Thung and Grobman, AJOG 2005
Can the severity of thrombocytopenia in NAIT be predicted?
Prediction of the fetal status in noninvasive management of alloimmune thrombocytopenia

Gerald Bertrand, Moustapha Drame, Corinne Martageix and Cecile Kaplan

<table>
<thead>
<tr>
<th>Maternal antibody concentration, IU/Ml</th>
<th>PLT&lt; 50000</th>
<th>PLT ≥ 50000</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 28</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>≥ 28</td>
<td>13</td>
<td>2</td>
</tr>
</tbody>
</table>

PPV- 86.7%, NPV-76.9%
NAIT – Prediction of severity

• Higher anti-HPA level correlated with a more severe disease

• Severe disease can occur even with low antibody titers

• Antibody titer can fluctuate over time

History of previous ICH is the strongest predictor

Sainio et al, Transfusion Medicine 2013
Does a previous good response to IVIG treatment predicts a similar response in the next affected pregnancy?
Yinon et al., ISUOG 2011
What is the antenatal management in cases of previous ICH?
NAIT and Intracranial Haemorrhage

NOICH registry

592 pregnancies
43 cases of ICH

39 HPA-1a
4 HPA-5a-5b

5 dead in utero
1 dead during labour
9 dead after birth
28 survivors

23 severe neuro disabilities
5 alive and well

Tiller et al., BMJ Open 2013
The majority of bleedings (54%) occurred before 28 wks.
The first born child was affected in most cases (63%).
Median PLT count was 8000 (1000-27000).
Antenatal treatment was given in 4/43 (9%) cases.

Tiller et al., BMJ Open 2013
NAIT and previous ICH

37 pregnancies with previous ICH

- **Extremely high risk**
  - Sibling ICH prior to 28 wks (n=8)
  - Salvage treatment 5/8
  - ICH 1/8

- **Very high risk**
  - Sibling ICH at 28-36 wks (n=17)
  - Salvage treatment 13/17
  - ICH 2/17

- **High risk**
  - Sibling ICH in perinatal period (n=12)
  - Salvage treatment 7/12
  - ICH 2/12

Bussel et al., AJOG 2010
<table>
<thead>
<tr>
<th>Patient group</th>
<th>Initial treatment and GA at start</th>
<th>Birth GA, wk</th>
<th>Grade and timing</th>
<th>Platelet count, $10^3$/mL</th>
<th>Additional factors</th>
<th>Outcome (disability)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EHR</td>
<td>IVIG 1 g/kg/wk + prednisone 1 mg/kg/d, 13 wk</td>
<td>19</td>
<td>III-IV in utero</td>
<td>7</td>
<td>Failed treatment</td>
<td>Fetal demise at 21 wk(^a)</td>
</tr>
<tr>
<td>HR</td>
<td>IVIG 1 g/kg/wk 22 wk</td>
<td>36</td>
<td>I perinatal</td>
<td>14</td>
<td>Premature labor</td>
<td>Living(^b)</td>
</tr>
<tr>
<td>HR</td>
<td>IVIG 1 g/kg/wk + prednisone 1 mg/kg/d, 25 wk</td>
<td>28</td>
<td>III-IV in utero</td>
<td>18</td>
<td>Delayed treatment by 13 wk; should have been in EHR group</td>
<td>Fetal demise at 31 wk(^c)</td>
</tr>
</tbody>
</table>

\(^a\) From previous ICH study published in Bussel et al., AJOG 2010.
Antenatal management of NAIT and previous ICH (US)

Previous fetus with ICH > 28 wks
- IVIG 1g/kg/wk at 12 wks
- At 20 wks increase IVIG to 2g/kg/wk or
  Add prednisone 0.5 mg/kg/day
- At 28 wks IVIG 2g/kg/wk and prednisone 0.5 mg/kg/day

Previous fetus with ICH < 28 wks
- IVIG 2g/kg/wk at 12 wks
- At 20 wks add prednisone 1 mg/kg/day

Pacheco et al., Obstet Gynecol 2011
Antenatal management of NAIT and previous ICH (Europe)

Diagnosis of NAIT

Sibling without ICH
- IVIG 0.5 gr/kg/wk
- Start at 28 wks

Sibling with ICH
- IVIG 1 gr/kg/wk
- Start at 16 wks

Kamphuis and Oepkes, Prenatal Diagnosis 2011
What should be the mode of delivery?
NAIT – Mode of delivery

- Elective CS

- Pre-delivery FBS in double set-up → Vaginal delivery if PLT > 50,000

No evidence that when PLT < 50,000, VD increases the risk for ICH
Our protocol (Sheba)

Diagnosis of NAIT

Sibling without ICH
- IVIG 1 gr/kg/wk
  Start at 22 wks

Sibling with ICH
- IVIG 2 gr/kg/wk
  Start at 12 wks
  +prednisone start at 20 wks

Elective CS or pre-delivery FBS at 37 wks
• Most cases resolve spontaneously

• Neonates without bleeding and PLT > 50000 may be closely observed without transfusions

• HPA-matched transfusion when PLT < 30000

• IVIG could be added to increase and prolong the response to transfusions
History of previous newborn with thrombocytopenia or ICH of unknown etiology
33 Y.O, G2P1, 25 wk

OB Hx:
G1 (2007): US @ 30 wk – severe ICH.
PLT – 38,000
Autopsy- massive subdural and subarachnoid hemorrhage.
Case Presentation

Work-up:
Mom: HPA-3b3b
Dad: HPA-3a3b
Fetus: HPA- 3a3b

No anti-HPA-3a antibodies were detected

Should we treat with IVIG?
Should we do FBS?
Previous thrombocytopenia of unknown etiology

Incompatibility at HPA loci
No maternal anti-HPA antibodies

Repeat maternal anti-HPA antibody testing and cross-match with paternal platelets at 12, 24, 32 weeks
Negative
No further evaluation

No incompatibility at HPA loci
No maternal anti-HPA antibodies

Test for maternal antibodies and cross-match with paternal platelets at 30 weeks
Negative
No further evaluation

Pacheco et al., Obstet Gynecol 2011
Should we screen for NAIT?
A screening and intervention program aimed to reduce mortality and serious morbidity associated with severe neonatal alloimmune thrombocytopenia

HPA 1 typing in 100,448 pregnant women

2.1% were HPA 1a negative

Anti-HPA-1a was detected in 10.6% of these

170 pregnancies were managed according to the intervention program

55 had severe thrombocytopenia

3 had ICH
Screening for NAIT

- The prevalence of HPA-1a negative is 1-2%

- Only 10% of these patients will develop anti-HPA-1a antibodies

- Of those, only 30% of neonates will have severe thrombocytopenia

- 10-20% of them will develop ICH

Prevent 6 cases of ICH for 100,000 women screened
Is it possible to prevent HPA-1a alloimmunization?
Toward a prophylaxis against fetal and neonatal alloimmune thrombocytopenia: induction of antibody-mediated immune suppression and prevention of severe clinical complications in a murine model

Heidi Tiller, Mette Kjaer Killie, Pingguo Chen, Mariana Eksteen, Anne Husebekk, Bjorn Skogen, Jens Kjeldsen-Kragh, and Heyu Ni

Prophylactic administration of PLT antibodies induces antibody-mediated immune suppression and prevents poor pregnancy outcome in a murine model of NAIT

Tiller et al., Transfusion 2012
Prevention of HPA-1a alloimmunization

Tiller et al., Transfusion 2012
Recombinant HPA-1a antibody therapy for treatment of fetomaternal alloimmune thrombocytopenia: proof of principle in human volunteers

In cases in which there is antihuman platelet antigen incompatibility and IVIG cannot be administered, PGD is a reliable alternative to enable birth of unaffected children.
Summary

• Testing for NAIT should be done for any fetus or neonate with an unexplained ICH or thrombocytopenia

• Preferred antenatal management:
  Non-invasive approach of empiric IVIG therapy

• Management should be based on risk stratification:
  More intensive treatment for patients with a history of ICH

• Pre-delivery FBS allows vaginal delivery in most patients
Research agenda

• Non-invasive method to predict severity of fetal thrombocytopenia

• The role of screening of the HPA-status of pregnant women

• Prevention of HPA-1a alloimmunization by HPA-1a antibody therapy
Thanks for your attention