Fetal and Neonatal Alloimmune Thrombocytopenia (FNAIT)

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• Professor of Pediatrics
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Antenatal and Postnatal Diagnosis and Management of Fetal and Neonatal Alloimmune Thrombocytopenia

A 35 Year Saga
Collaborators from 1983 until now

Richard Berkowitz
Maternal Fetal Medicine

Janice McFarland
Director Platelet Diagnostic Laboratory
Alloimmune Thrombocytopenia (AIT): What is it?

Platelet Equivalent of Rh (HDFN) disease

- Mother lacks platelet antigen possessed by father; she is exposed to it by fetal platelets; could also be by GPIIIIA on syncytiotrophoblasts
- Mother makes a (strong) IgG antibody against fetal platelet antigen, e.g. anti-HPA-IA (PL^A1)
- The IgG anti-platelet antibody crosses the placenta, destroys fetal platelets, and results in an often early, severe thrombocytopenia
Current Schematic Diagram of the Platelet Membrane Glycoprotein Polymorphisms that can cause Alloimmune Thrombocytopenia

GPla-IIa (α2β1)
- A vWF-like A(dhesion) domain (blue ball) is inserted between β-propellers 2 and 3 of the α subunit.
- The Br polymorphism is located between β-propellers 5 and 6 and is homologous to αSer523.

GPIIb-IIIa (αIIbβ3)

PJIa (Leu33Pro)
PJIb (Val837Met)
Bak (Ile843Ser)
Max (Val37Met)
Sit (Thr799Met)

GPIbα (β3)
Ko (Thr145Met)

Mo (Pro407Ala)
La (Arg62Gln)
Duv (Thr140Ile)
Pen (Arg143Gln)

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Science 294:316, 2001, with permission
Current Schematic Diagram of the Platelet Membrane Glycoprotein Polymorphisms that can cause Alloimmune Thrombocytopenia

GPIa-IIa (α2β1)
A vWF-like A(dhesion) domain (blue ball) is inserted between β-propellers 2 and 3 of the α subunit. The Br polymorphism is located between β-propellers 5 and 6 and is homologous to α5 Ser523.

GPIib-IIIa (αIibβ3)

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ANTIGEN CAPTURE ELISA

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ANTIGEN CAPTURE ELISA II

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MODIFIED ANTIGEN CAPTURE ELISA

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PLATELET ANTIBODY SCREEN BY FLOW CYTOMETRY (PATIENT SERUM):

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<th>IgG</th>
<th>IgM</th>
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<td>JB</td>
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PLATELET TYPE: MOTHER

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PLATELET TYPE: FATHER

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CLASSICAL FINDINGS FOR PLA1(HPA-1A) INCOMPATIBILITY.
Cases identified by screening all pregnancies

- Disease incidence is higher than in cases which are clinically identified (1:500-1000)
- First fetus is not often affected; sensitization occurs 75% at delivery of the 1st pregnancy
- ICH rate is <<1% and birth platelets are mildly low
- Severity may not increase so second baby is also often mildly affected
- Management is by C/S at 37-38 weeks (Norway)
Schism in Description of FNAIT

Cases clinically-identified by bleeding due to neonatal thrombocytopenia

- Disease incidence is lower (1:5000-10,000)
- In 60+%, the first fetus is affected; thus sensitization mostly occurs during the 1\textsuperscript{st} pregnancy
- The ICH rate is 11-21%; 75% of ICHs occur in utero
  - Birth platelet counts are very low: 50% of 107 fetuses were $< 20,000/\mu l$ by 24 weeks of gestation
- Recurrence approaches 100% of antigen+ fetuses and 42% of FBS plt cts in 2\textsuperscript{nd} fetus before treatment were $< \text{than birth platelet counts of 1}\textsuperscript{st} \text{affected fetus}$
Why focus on fetal and neonatal alloimmune thrombocytopenia?

FNAIT is the most common cause of:

• A) IntraCranial Hemorrhage (ICH) in term neonates

• B) Severe thrombocytopenia in all neonates

FNAIT has special treatment considerations:

• Will recur in next affected pregnancy and typically be more severe so maternal treatment to mitigate fetal thrombocytopenia in next affected pregnancy is required

• Neonate may need IVIG with platelets: ideally would get matched platelets
Many Etiologies of Neonatal Thrombocytopenia

- Infections: Torch, HIV, Parvo, Sepsis
- Asphyxia: DIC, Reduced Plt Production
- Liver Disease: low TPO, hypersplenism
- Thrombosis: consumption--Renal Vein, CVL
- Respiratory Distress: almost anything
- Syndromes: Trisomies: 13, 18, 21
- Amegakaryocytic: CAMT, TAR, CTRUS
- Inherited Thrombocytopenias: eg MYH9-RD, WAS, many others
Clinical Diagnosis of NAIT

Algorithm for bedside diagnosis of AIT
2005, Pediatric Blood & Cancer:
1. Neonatal (day 1) platelet count < 50,000/ul
2. Unexplained thrombocytopenia
3. Family history of neonatal thrombocytopenia
4. Not failure to respond to random platelets
5. Persistence of thrombocytopenia suggests an inherited TP eg CAMT, MYH9, WAS
Clinical Diagnosis of FNAIT

Algorithm for bedside diagnosis of FNAIT

Neonatal (day 1) platelet count < 50,000/ul

A) 90% of FNAIT babies have birth platelet count < 50,000

B) 25-50% of babies with platelets < 50,000 on day 1 are FNAIT

C) 50% of FNAIT babies have day 1 platelet counts < 20,000/ul but 75-90% of these babies are FNAIT
Fetal Alloimmune Thrombocytopenia

Figure 1. Initial Platelet Count as a Function of Gestational Age in 107 Fetuses with Alloimmune Thrombocytopenia. Diamonds denote fetuses with an older affected sibling who had had a perinatal intracranial hemorrhage, circles fetuses with an older affected sibling who had had an antenatal intracranial hemorrhage, and open squares fetuses with an older affected sibling who had not had an intracranial hemorrhage. Where solid squares appear, a circle or diamond overlaps an open square. Fifty percent of the platelet counts were 20,000 per cubic millimeter (broken line).
Treatment of Neonatal Thrombocytopenia

- **Cranial Ultrasound or CT or MR**
- Random Platelet transfusions: Mainstay
- Matched platelets: 1) Mother 2) Unrelated
- IVIG
- Steroids (low dose to avoid sepsis)
- **Not Anti-D**: could cause jaundice
Antenatal Management of Fetal and Neonatal Alloimmune Thrombocytopenia (FNAIT)

Treating the second affected pregnancy in a woman to avoid severe fetal thrombocytopenia and especially fetal intracranial hemorrhage
The First Patient (1983): consultation with the parents

- Previous (only) child born at 38 weeks with count of 3k. ICH caused death; CT scan and autopsy revealed ICH had begun at 32 wks.
- Tests showed HPA-1a (PI^{A1}) incompatibility; father homozygous HPA-1aa
- Both parents 40+ years old
- Clearly a standard approach for this pregnancy (elective C/S at 38 weeks of gestation) already at 12 weeks of gestation was not going to work
Figure 1. Platelet Counts in the Fetuses of Patients 2 through 7. Circles denote blood sampling, and squares denote birth. Patient 6 was not treated between the first and second blood samples (dashed line). Patient 5 underwent initial sampling only, and Patient 1 did not undergo sampling at all.
Figure 2. Serial Platelet Counts in Eight Initially Untreated Fetuses with Alloimmune Thrombocytopenia. The solid circles denote fetuses with PlA1 incompatibility, the squares a fetus with Br4 incompatibility, the triangles a fetus with Bak4 incompatibility, and the open circles a fetus with an undetermined antigen incompatibility.
## High Risk (n=41)

<table>
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<th>IVIG (1gm/kg/wk) vs. IVIG (1gm/kg)+Pred (1mg/kg)</th>
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<tr>
<td>Median Plt Counts</td>
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<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; FBS</td>
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<tr>
<td>-------------------</td>
</tr>
<tr>
<td>IVIG 1/kg N=22</td>
</tr>
<tr>
<td>IVIG+Pred N=19</td>
</tr>
</tbody>
</table>
Intracranial hemorrhage in alloimmune thrombocytopenia: Stratified management to prevent recurrence in the subsequent affected fetus.


Am J OBGYN, 2010; 203(2): 1
IVIG + Pred to Prevent Recurrent ICH in Next FNAIT Pregnancy

37 pregnancies in 33 women:

- All but 1 with HPA-1a incompatibility
- All 33 had had a sibling suffer an ICH at least 29 of which occurred in utero
- There were only 2/37 > grade 1 ICH’s that were treatment failures (both would be handled differently today)
- 2 ICH from fetal sampling with cts > 100k and 1 grade 1 ICH (clinically irrelevant)
Long-Term Effects of Fetal and Neonatal Alloimmune Thrombocytopenia and Its Antenatal Treatment on the Medical and Developmental Outcomes of Affected Children.

Ward MJ, Pauliny J, Lipper EG, Bussel JB.

Am J Perinatology, 2006; 23:
Mechanisms of IVIG Effect in Fetal Alloimmune Thrombocytopenia

Bussel, JB, Berkowitz, RL, and McFarland, JG

Transfer of anti-D antibodies across the isolated perfused human placental lobule and inhibition by high-dose intravenous immunoglobulin: a possible mechanism of action

Urbaniak SJ, Duncan JI, Armstrong-Fisher SS, Abramovich DR and Page KR.

Br J Haem, 1997; 96: 186-193
Transfer of anti-D antibodies across the isolated perfused human placental lobule and inhibition by high-dose intravenous immunoglobulin: a possible mechanism of action

Fig 1. Schematic representation of the dually perfused placenta maintained under closed-circuit perfusion conditions.

Br J Haem, 1997; 96: 186-193
FNAIT: What Has Happened With Treatment Since 2012?

1. We performed one more randomized trial looking at the comparison of IVIG + a second IVIG per week versus IVIG + prednisone.

2. In both arms we asked for fetal blood sampling at 32 weeks of gestation: if the fetal platelet count is < 50k increase treatment.
Alloimmune thrombocytopenia: Fetal and neonatal losses related to cordocentesis.


Omission of Fetal Sampling in Treatment of Subsequent Pregnancies in Fetal-Neonatal Alloimmune Thrombocytopenia.


Both treatment arms increased BPC to greater than or equal to 50k in the fetus/neonate in ~85% of cases.

Figure 1: Fetal BPC\(^1\) for Arm A versus Arm B

<table>
<thead>
<tr>
<th>BPC ≥ 50k</th>
<th>BPC &lt; 50k</th>
</tr>
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<tbody>
<tr>
<td>Arm A</td>
<td>48</td>
</tr>
<tr>
<td>Arm B</td>
<td>43</td>
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</table>

\(^1\): Birth Platelet count
Salvage reverses fetal thrombocytopenia by increasing treatment intensity

BPC in severely affected cases (FPC\textsuperscript{2} ≤50) on 2 regimens; salvage therapy (IVIG 2g/kg/wk) + Prednisone 0.5mg/kg/d and no salvage therapy (IVIG 2g/kg/wk or IVIG 1g/kg/wk + pred 0.5mg/kg/d) = continuing the same treatment (no change)

BPC\textsuperscript{1}: Birth Platelet count; FPC\textsuperscript{2}: Fetal Platelet Count; *g/kg/wk: grams/kilogram/week; †mg/Kg/d: mg/kg/day
New Developments in FNAIT: What Has Happened Since 2012?

1. Screening of all pregnancies to identify the 2.5% of the population who is HPA-1bb
2. Clarify the role of DRB3*0101 in the sensitization and severity of FNAIT
3. Development of “NAITGAM”: prophylactic IVIG to mimic for HPA-1a anti-RhD
4. New treatments: inhibition of FcRn to block transfer of anti-HPA-1a across the placenta
Screening for FNAIT

Any country that screens at first prenatal visit for Rh status (for hemolytic disease of the fetus and newborn HDFN) can use the same sample to screen for HPA-1A.

Using molecular testing, high throughput screening is possible.

If HPA-1a is not appropriate, then which Ags should be screened for and is there a NAITGAM available for that Ag eg HPA-4a?

Is screening cost effective? How should it be done (includes role of DRB3*0101)?
Role of DRB3*0101 in FNAIT

1. As far as we know, DRB3*0101 is only important for anti-HPA-1a

2. Recent evidence suggests that HPA-1a incompatibility will have 3-4 times as many affected neonates with maternal DRB3*0101 as without it

3. Key question is relative severity: preliminary data requiring confirmation suggests non-DRB3*0101 cases are milder and homozygotes are most severe

4. If this holds up, it would simplify care
Prophylaxis with “NAITGAM”

Slow development from cost restrictions: FNAIT affects 1/10th as many newborns as HDFN
Initial studies have been done: the mouse work looks good but no clear demonstration of efficacy in humans—only safety studies
Efficacy studies are planned but funding is a major issue: very promising meeting with FDA as far as how to go forward
A lot of NAITGAM (a hyper-immune IVIG) has been made as proof of principle from high titer mothers’ plasma
Blockade of FcRn

- FcRn is the Fc receptor that transports maternal IgG across the placenta to the fetus.
- Normal term newborn IgG levels are 110% of the mother’s IgG level.
- FcRn also recycles all IgG in people of all ages.
- Blocking FcRn not only would prevent transport of maternal “bad” IgG, ie anti-HPA-1a, to the fetus but also greatly shorten the half-life if IgG so IgG levels, including anti-HPA-1A levels would fall dramatically---also transports albumin.
- 4 different anti-FcRn’s are in clinical trial.
Role of FcRn in FNAIT

1. No clinical data in pregnant humans
2. Two preparations have been effective in ITP in people and lowered IgG dramatically down to levels like 200 (normal 639-1600)
3. Ideally weekly or biweekly dosing would prevent any anti-HPA-1a from going across the placenta and simultaneously lower the mother’s anti-HPA-1a levels
4. Issues: a) fetus will be born very hypogamma-globulinemic----is one dose of IVIG at birth sufficient  b) will mother get infections?
Summary of New Developments in FNAIT

Screening all pregnancies for mothers who are HPA-1bb is entirely feasible.

Development of NAITGAM is underway and also seems feasible but there are funding issues.

It appears that DRB3*0101 is more important than we had thought if all seriously affected FNAIT cases are positive and especially if the most severely affected (ICH) cases are homozygous DRB3*0101.

Blockade of FcRn has considerable potential to revolutionize treatment of women affected by FNAIT.
New Developments in FNAIT: Pathophysiology and Testing

A study lead by Martha Sola-Visner showed that anti-HPA-1a antibodies not only destroy platelets but also damage megakaryocytes and inhibit platelet production---this explains the greater severity of thrombocytopenia and the difference from the neonate of the mother with ITP.

At least for HPA-1A, free fetal DNA in the mother’s circulation can be tested to see if the fetus is HPA-1a -this would be in circumstances in which the father is not available, away ie in the armed forces, or uncertain.
Summary of Current Approach to Antenatal Management of AIT

A) No Fetal Blood Sampling
B) No prolonged high dose Prednisone
C) Treat according to outcome of previous affected siblings starting at 12 or 20-24 weeks
D) Individualize treatment choice for standard risk based on blood type and steroid tolerance:
E) Augment treatment automatically at 32 wks
F) Delivery by C/section (?)
G) Have matched platelets available
Management when the affected mother is pregnant again?

- In 1980: schedule the mother for a Caesarian section at 38 weeks
- In 2018: provide stratified therapy to the mother during pregnancy based on the previous affected sibling = whether or not they had had an ICH
Thanks to many many people

Affected women and their families
MFMs who entered their patients on studies
Nurses who managed the patients and infused them
Nurses and NPs and Fellows who worked with me: especially Megan Wissert
Coordinators who helped collect and analyze the date: especially Madhavi Lakkaraja
My family: My wife Charlotte and my daughter Kiki
The King Faisal Prize and its board