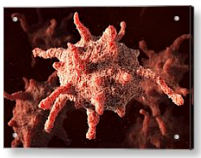
# Fetal/ Neonatal Allo Immune Thrombocytopenia



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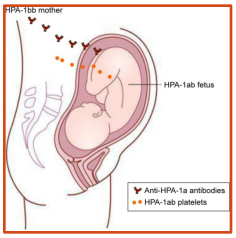
FETAL MEDICINE UPDATE- NOV 16-17, 2018

## Objectives

- ✓Summary of what we know about F/NAIT
- ✓Open questions:
- ✓What's the best management?
- ✓Can we predict the severity of F/NAIT?
- ✓Can we prevent F/NAIT?

## F/NAIT what we know

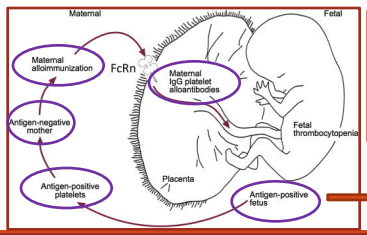



## F/NAIT

- ✓F/NAIT is the most common cause of early onset severe isolated **thrombocytopenia** and/or intracranial hemorrhage (ICH) in term newborns
- ✓**Rare condition**: The incidence is reported to be **1/1,000-1/1,500** births
- ✓**Rare severe consequences**: 20% risk of severe ICH associated with severe sequelae or death: **1/11,000** newborns

*Mueller-Eckhardt C et al, Lancet 1989; Bussel JB et al, NEJM 1997.; Kamphuis MM et al, Pediatrics 2014.*

## FNAIT-Pathogenesis




FNAIT results from the destruction of fetal platelets (PLTs) by maternal alloantibodies that cross the placenta and target fetal PLT antigens inherited from the father (HPAs).

Antigens on fetal platelet inherited from the father and lacking in the mother

## FNAIT vs Rh alloimmunization

| SIMILARITIES |
|---|
| **FNAIT and Rh alloimmunization** |
| Like RBC, platelets have specific surface antigens. |
| Fetus inherits paternal antigens that the mother lacks (platelet antigen incompatibility). |
| Mother develops antibodies (sensitized) to fetal PLT antigens during pregnancy. |
| Maternal IgG antiPLT Abs cross the placenta and coat fetal PLT, resulting in sequestration and destruction of platelets in the fetal reticuloendothelial system. |

| DIFFERENCES | |
|---|---|
| **FNAIT** | **Rh alloimmunization** |
| First pregnancy (first born children affected 20-60%) | Second pregnancy |
| Thrombocytopenia/ICH | Hemolytic anemia |
| Maternal Ab titers do not predict severe outcomes | Maternal Ab titers predict pregnancy outcomes |
| No prophylaxis (diagnosed at delivery of a first affected pregnancy) | Prophylaxis |

## FNAIT: the frequency of HPAs varies worldwide

| HPAs | | FNAIT |
|---|---|---|
| HPA 1a | 97-98% Caucasian population<br>(68% 1a-1a Homozygotes; 29% 1a-1b Heterozygotes)<br>rare in Asian and African population<br>Only 10% of HPA-1a negative pregnant women develop anti-HPA-1a IgG antibodies | most severe |
| HPA 5a | second leading cause in Caucasian population | less severe |
| HPA 5b<br>HPA 4b | More frequent in Asian population | |
| HPA 2a | low frequency | no classical FNAIT (miscarriage but no neonatal bleeding) |
| HPA 3a | low frequency | 3-5% severe FNAIT miscarriages |

## FNAIT-Natural History

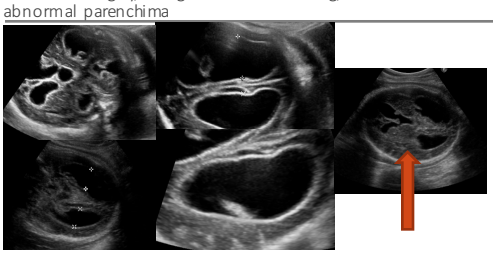
**Variable clinical manifestations**

From mild asymptomatic thrombocytopenia to minor skin lesions (petechiae) to severe thrombocytopenia leading to ICH with potentially severe perinatal morbidity and mortality

80% ICH occurs in utero and 50% <30 weeks (fetal PLT Ag expressed since 16 weeks)


## 36 yo, G1P0 36 weeks

Ventriculomegaly, echogenic ventricular lining, Clot in the Rt ventricle, abnormal parenchima



## Perinatal Outcome and Long-Term Neurodevelopment after Intracranial Haemorrhage due to Fetal and Neonatal Alloimmune Thrombocytopenia

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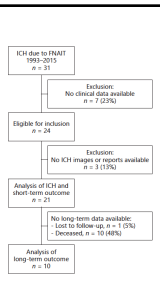



**Table 1.** Demographic characteristics of the study population ($n$ = 21)

| | |
|---|---|
| Maternal age, years | 30 (21–41) |
| Obstetric history | |
| Sibling with ICH | 1 (5%) |
| Sibling with FNAIT | 2 (10%) |
| Miscarriage | 10 (48%) |
| HPA type | |
| HPA-1a | 18 (86%) |
| HPA-5b | 2 (10%) |
| HPA-5a | 1 (5%) |
| Obstetric characteristics | |
| Singleton pregnancy | 20 (95%) |
| First pregnancy | 5 (24%) |
| First-born child | 12 (57%) |
| Antenatal treatment, IVIG 1 g/kg/week | |
| after antenatal detection of ICH | 4 (19%) |
| Gestational age at delivery, weeks[a] | 36[+6] (30[+0]–41[+0]) |
| Delivery[1] | |
| Vaginal | 6 (33%) |
| Ventouse | 3 (17%) |
| Caesarean section | 9 (50%) |
| Neonatal characteristics | |
| Male sex | 13 (62%) |
| Birth weight, g[1] | 2,408 (1,178–4,080) |
| Platelet count, $\times 10^9$/L[1] | |
| Without antenatal IVIG | 158 (133–164) |
| With antenatal IVIG | 11 (6–29) |

21 cases

short term outcomes

3/21 (14%) treated

7/21 (33%) perinatal death

3/21 (14%) TOP

| Child No. | GA at birth | Antenatal IVIG | ICH location | Associated lesions | Mortality | Obstetric history |
|---|---|---|---|---|---|---|
| 1 | 33+4 | no | extensive subarachnoid and unilateral parenchymal frontal/temporal/occipital | – | yes, neonatal | G1P0 |
| 2 | 35+0 | no | unilateral intraventricular and parenchymal | hydrocephalus | yes, neonatal | G2P1 healthy child |
| 3 | 31+3 | no | bilateral parenchymal | – | yes, neonatal | G1P0 |
| 4 | 36+5 | no | extensive bilateral parenchymal | | yes, neonatal | G3P1 healthy child, miscarriage |
| 5 | 38+1 | no | extensive bilateral parenchymal | hydrocephalus | yes, fetal | G2P0 miscarriage |
| 6 | 22+5 | no | bilateral parenchymal | hydrocephalus | yes, TOP | G2P0 miscarriage |
| 7 | 32+1 | no | extensive subarachnoid | | yes, neonatal | G2P1 child with trisomy 21 |
| 8 | 36+0 | no | bilateral intraventricular and parenchymal | hydrocephalus | yes, neonatal | G3P0 miscarriage, one TOP |
| 9 | 19+0 | no/ | extensive bilateral parenchymal | – | yes, TOP | G4P1 two healthy children, one child with FNAIT |
| 10 | 19+3 | no | unilateral parenchymal and intraventricular | – | yes, TOP | G1P1 healthy child, miscarriage |
| 11 | 38+1 | no | unilateral parenchymal, occipital | – | no | G1P0 two miscarriages |
| 12 | 36+0 | no | unilateral parenchymal, temporal | hydrocephalus, VPD | no | G1P0 |
| 13 | 35+0 | no | bilateral parenchymal, temporal | porencephalic cyst hydrocephalus, VPD | no | G1P0 miscarriage |
| 14 | 36+1 | no | bilateral parenchymal, temporal, and occipital | porencephalic cyst hydrocephalus, VPD | no | G2P0 miscarriage |
| 15 | 35+0 | yes, from 30 weeks | extensive bilateral intraventricular, parenchymal, and cerebellar hemorrhage | bilateral porencephalic cyst, cerebellar destruction hydrocephalus, VPD | no | G2P1 healthy child |
| 16 | 36+0 | yes, from 28 weeks | unilateral parenchymal, occipital, and cerebellar | – | no | G4P1 two miscarriages, one child with FNAIT |
| 17 | 40+0 | no | bilateral parenchymal, parietal, temporal, and occipital | bilateral porencephalic cyst hydrocephalus, VPD | no | G1P0 |
| 18 | 41+2 | no | unilateral parenchymal, frontotemporal | – | no | G1P0 |
| 19 | 37+0 | yes, from 28 weeks | unilateral parenchymal, intraventricular, and bilateral cerebellar | hydrocephalus, unilateral porencephalic cyst | no | G4P2 immature delivery at 17 weeks, child with ICH, TOP |
| 20 | 41+2 | no | bilateral frontal parenchymal and intraventricular | hydrocephalus, bilateral porencephalic cysts | no | G2P0 molar pregnancy |
| 21 | 37+0 | no | extensive bilateral intraventricular | – | no | G2P1 healthy child |

11 cases

long term outcomes

6/11 severe neurodev impairment (NDI)

| Child No. | Associated lesions | Age at evaluation | Cerebral palsy | Developmental test | Total IQ | Long-term outcome | Severe NDI |
|---|---|---|---|---|---|---|---|
| 1 | none | 8 years | – | WISC-III | 86 | attention deficit hyperactivity disorder | no |
| 2 | hydrocephalus, VPD | 2, 8, and 14 years | spastic tetraplegia, GMFCS level V | Bayley-III, Reynell-Zinkin, KID-N | 49 | bilateral blindness, severe cognitive and motor delay, epilepsy | yes |
| 3 | porencephalic cyst hydrocephalus, VPD | 20 years | spastic tetraplegia, GMFCS level V | not tested due to severe impairment | 49 | bilateral blindness, severe cognitive and motor delay, epilepsy | yes |
| 4 | porencephalic cyst hydrocephalus, VPD | 23 years | spastic tetraplegia, GMFCS level V | not tested due to severe impairment | 49 | bilateral blindness, hearing impairment, severe cognitive and motor delay | yes |
| 15 | bilateral porencephalic cyst, cerebellar destruction hydrocephalus, VPD | 3 years | spastic diplegia, GMFCS level IV | SON | 60 | severe cognitive and motor delay | yes |
| 16 | none | 5 years | – | WPPSI-III | 110 | | no |
| 17 | bilateral porencephalic cyst hydrocephalus, VPD | 1 year | spastic hemiplegia, GMFCS level IV | KID-N | 49 | visual impairment, severe cognitive and motor delay, epilepsy | yes |
| 18 | none | 7 years | – | WISC-III | 112 | | no |
| 19 | hydrocephalus, unilateral porencephalic cyst | 5 years | spastic hemiplegia, GMFCS level II | WPPSI-III | 85 | problems with behaviour and attention regulation | no |
| 20 | hydrocephalus, bilateral porencephalic cysts | 8 years | spastic diplegia, GMFCS level II | SON | 50 | severe cognitive and motor delay, epilepsy | yes |
| 21 | none | loss of contact information, no long-term follow-up available | | | | | |

## FNAIT Diagnosis

In the absence of a population-based screening, F/NAIT is suspected in case of bleeding problems

- During fetal life (Brain US abnormalities) 1st pregnancy — **RARELY**
- After the delivery of an infant with thrombocytopenia or fetal/neonatal ICH — **MOST COMMONLY**
- Via family Hx — **RARELY but IDEAL**

**Indications for Testing:**

- Neonate with petechiae and ecchymosis, unexplained thrombocytopenia.
- Fetus with unexplained ICH, hydrocephalus, or porencephalic cyst
- Woman incidentally found to be HPA-1a negative
- Family history of NAIT

**Diagnostic Criteria:**

Fetal or neonatal thrombocytopenia (< 150 x$10^9$/L) plus identification of a paternal, fetal, or neonatal platelet antigen with identification of maternal antibodies to that specific antigen

## What's the best management

FNAIT

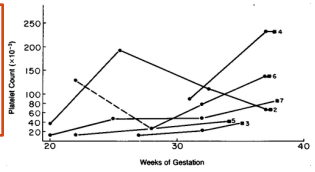
- Preventive antenatal measures, including maternal IVIG, with or without prednisone, and *in utero* platelet transfusions (platelet IUT) after fetal blood sampling (FBS) have been proposed.
- Currently, there is **no consensus regarding the optimal antenatal treatment strategy**
- The lack of randomized control trials presents a problem in establishing a framework for 'best practice' management of FNAIT

## Antenatal Treatment of Neonatal Alloimmune Thrombocytopenia

N Engl J Med 1988; 319:1374-1378

James B. Bussel, M.D., Richard L. Berkowitz, M.D., Janice G. McFarland, M.D., Lauren Lynch, M.D., and Usha Chitkara, M.D.

7 treated fetuses had platelet counts above 30X10$^9$ at birth, and none had an intracranial hemorrhage
7 untreated siblings, who had lower platelet counts and three of whom had intracranial hemorrhages (antenatal in two infants).




## Mechanism of action of IVIG

The exact mechanism of action is uncertain but is considered to be a combination of:

- dilution of the anti-HPA antibodies,
- blockade of placental receptors with a decrease in transplacental passage of antibody
- reduction in the destruction of antibody-coated platelets in the fetal circulation
- induction of T/B cell tolerance
- inhibition of dendritic cell function

## Dose

The most effective dosage regimen of IVIG is uncertain:

- 0.5-1.0 g/kg/week (Sweden-Nederland)
  - lower dose for no Hx of ICH
- 1/g/kg/weeks or 2g/kg/week (USA)
  - in higher risk pregnancy

This lack of high-level evidence on the optimal dosage regimen to administer remains a concern, and all studies published to date have not had the statistical power to show a significant difference, mainly because of the rarity of FNAIT.

Antenatal management in fetal and neonatal alloimmune thrombocytopenia: a systematic review

Dian Winkelhorst, Michael F. Murphy, Andreas Greinacher, Nadine Shehata, Tamam Bakchoul, Edwin Massey, Jillian Baker, Lani Lieberman, Susano Tanael, Heather Hume, Donald M. Arnold, Shoma Baidya, Gerald Bertrand, James Bussel, Mette Kjaer, Cécile Kaplan, Jens Kjeldsen-Kragh, Dick Oepkes and Greg Ryan

Blood 2017 blood-2016-10-739656; doi: https://doi.org/10.1182/blood-2016-10-739656

First line weekly maternal IVIG is the recommended management, with no consistent evidence found in the use of additional steroids.

Invasive fetal therapy resulted in a 11% risk of adverse outcome per treated pregnancy, particularly associated with preterm emergency caesarean section

**Management and Neonatal Outcomes of Pregnancies with Fetal/Neonatal Alloimmune Thrombocytopenia: A Single-Center Retrospective Cohort Study**

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## Aim of the study

We retrospectively reviewed the management and neonatal outcomes of pregnancies with a previous history of F/NAIT which were followed at our center from 1993-2016.

We specifically looked for:

- The fetal blood sampling (FBS)-related risks.
- The characteristics of cases in which there was a response to in-utero medical therapy (Responders), compared to those in which there was no response (Non-Responders) (i.e. required intrauterine platelet transfusion).
- The rate of caesarean delivery in our cohort.

## Methods

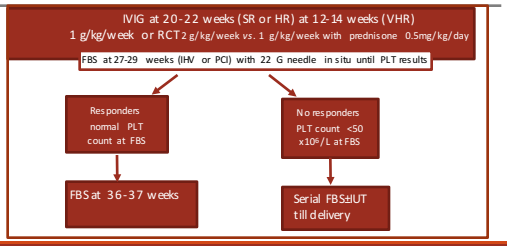
- We included all pregnancies with a previous history of F/NAIT and confirmed maternal/fetal HPA incompatibility.
- When the father was heterozygous, an amniocentesis to determine fetal HPA typing was performed
- When the same patient was followed in more than one pregnancy, we selected the pregnancy which occurred immediately after the index case so that each patient was only represented once in this series.

## Stratifying risk and prenatal therapy

Stratification of NAIT cases according to risk of intracranial haemorrhage [2].

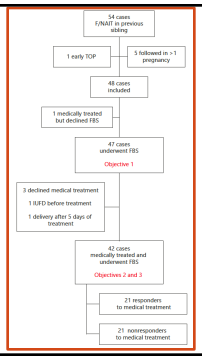
| Stratum | Definition | Risk |
|---|---|---|
| 1 | History of previous fetus or newborn with thrombocytopenia or intracranial haemorrhage of unknown aetiology; no HPA antibody detected. | Unknown |
| 2 | History of previous fetus or newborn with serologically confirmed fetal or neonatal alloimmune thrombocytopenia having only thrombocytopenia and no evidence of an intracranial haemorrhage. | Standard |
| 3 | History of serologically confirmed fetal or neonatal alloimmune thrombocytopenia and previous fetus or newborn with intracranial haemorrhage at 28 weeks of gestation or more (includes peripartum and neonatal intracranial haemorrhage). | High |
| 4 | History of serologically confirmed fetal or neonatal alloimmune thrombocytopenia and previous fetus with intracranial haemorrhage at less than 28 weeks. | Very High |

## Protocol for management of pregnancy with previous F/NAIT at FMU-MSH



## Results

### Population




## Results

Table 1

**Risks of fetal intervention (Objective 1)**

- fetal exsanguination
- PPROM
- IUFD
- pre-term labor (<34 weeks)
- abnormal fetal heart rate tracing requiring immediate delivery

| Fetal interventions: (FBS / platelet IUT) | N=47 |
|---|---|
| # FBS median, IQR, (range) | 2, 1 (1-8) |
| 1 FBS n/N (%) | 10/47 (21%) |
| 2 FBS n/N (%) | 16/47 (34%) |
| 3 FBS n/N (%) | 13/47 (28%) |
| ≥3 FBS n/N (%) | 8/47 (17%) |
| Total number FBS's | 119 |
| Patients who underwent platelet IUT | 23/47 (49%) |
| # platelet IUTs median, IQR (range) | 2, 2 (1-8) |
| 1 platelet IUT n/N (%) | 8/23 (35%) |
| 2 platelet IUTs n/N (%) | 5/23 (22%) |
| 3 platelet IUTs n/N (%) | 7/23 (30%) |
| ≥3 platelet IUTs n/N (%) | 3/23 (13%) |
| Total # platelet IUTs | 55 |
| FBS-related fetal loss | 1/119 (0.8%) |
| Unplanned delivery within 7 days of FBS | 1/119 (0.8%) |
| Total # FBS-related adverse events | 2/119 (1.6%) |

79%

## FBS-related risk

Our single FBS-related fetal loss (0.8%) occurred due to severe abdominal hemorrhage during FBS in a severely thrombocytopenic fetus (PLT count of 1 ×10⁹/L) in an (IVIG) untreated pregnancy. This was also prior to the recognition of the crucial importance of always having PLTs ready for transfusion at any FBS of a potentially thrombocytopenic fetus, which became routine practice following the report of Paidas et al. [14–16]. There were no fetal losses in any of the IVIG-treated cases

Appendix 1:

**Risks of FBS related fetal loss and adverse pregnancy outcome in F/NAIT**

| | Single/Multi Center (n) | FBS related Fetal loss N (%) | FBS Adverse pregnancy outcomes | Delivery <34 weeks |
|---|---|---|---|---|
| Radder et al 2003 (17) | Single | 0/24 fetuses (0%) | 1/24 fetuses (4.2%) Emergency CS for fetal bradycardia | NA |
| Overton et al 2002(18) | Single | 2 /12 fetuses (16.6%) 2/86 procedures (2.4%) 1 exsanguination during FBS and 1 fetal IUFD 7 days after parent IUT | 0/12 fetuses (0%) 0/86 procedures (0%) | 9/11 (75%) |
| Bichel et al 2003 (19) | Multicenter (12) | 2/58 fetuses (3.4%) 1 exsanguination post FBS 1 unexplained — 1 day after IUT | 14/58 fetuses (24%) Emergency CS for fetal bradycardia, infection, exsanguination/bleeding , cord thrombosis, needs dislodged. | 24/58 (41.4%) |
| Berkowitz et al 2006 (20) | Multicenter (42) | 1/79 fetuses (1.3%) 1/175 procedures (0.6%) 1 IUFD - trauma 4 days after FBS | 11/79 (14%) 11/175 (6%) Emergency CS at FBS, pPROM | 19/79 (24%) |
| Van den Akker et al 2007 (12) | Single | 1/46 fetuses (2.2%) NND after emergency CS at 36 wks post FBS for fetal bradycardia | 3/46 fetuses (6.5%) Emergency deliveries for fetal distress after FBS | 1/46 (2.2%) |
| Lakkaraju et al 2016 (9) | Multicenter (36) | 0/60 fetuses (0%) | 10/80 fetuses (12.5%) CS for fetal bradycardia, premature labor or pPROM <2 weeks after procedure | 6/80 (7.5%) |
| Present study, 2018 | Single | 1/47 fetuses (2.1%) 1/119 procedures (0.8%) 1 exsanguination during FBS | 1/47 fetuses (2.1%) 1/119 fetuses (0.8%) premature labor 5 days after FBS | 1/47 (2.1%) |

## Results

**Table 2 (Objective 2):**

**Characteristics of Responders (R) *vs.* Non-Responders (N-R)**

| Medically treated N= 42 | Responders N=21 | Non-Responders N=21 | p |
|---|---|---|---|
| **Maternal characteristics:** | | | |
| **Maternal age** (years, Median, (IQR) | 32 (3.5) | 31 (8) | *0.75* |
| **Gravida** Median (IQR) | 3 (2) | 2 (1) | *0.47* |
| **Para** Median (IQR) | 1(0) | 1(0) | *1.00* |
| **Blood group A** n/N (%) | 8/19 (42) | 12/18 (67) | *0.13* |
| **Blood group O** n (%) | 6/19 (32) | 5/18 (28) | *0.80* |
| **Group of severity UR** n/N (%) | 3/21 (14) | 1/21 (5) | *0.29* |
| **Group of severity SR** n/N (%) | 15/21 (71) | 14/21 (66) | *0.74* |
| **Group of severity HR** n/N (%) | 2/21 (10) | 1/21 (5) | *0.55* |
| **Group of severity VHR** n/N (%) | 1/21(5) | 5/21 (24) | *0.08* |
| **HPA-1a** n/N (%) | 13/18 (72) | 20/20 (100)* | **0.01** |
| **HPA-3a** n/N (%) | - | - | - |
| **HPA-5a** n/N (%) | 5/18 (28) | 2/20 (10)* | *0.16* |
| **Index case characteristics (in previous sibling):** | | | |
| **Platelet count at birth** ($x10^9$/L, Median, IQR) | 20 (35) | 9 (11) | **0.02** |
| **Male sex** n/N (%) | 12/18 (67) | 13/17 (76) | *0.52* |
| **ICH** n/N (%) | 5/21 (24) | 6/21 (29) | *0.72* |
| **Platelet count at birth in neonates with ICH** ($x10^9$/L Median, IQR) | 20.5 (15.5) | 7.5 (4.5) | **0.001** |
| **Adverse Outcome** n/N (%) | 4*/21 (19) | 4**/21 (19) | *0.94* |

* In few patients >1HPA antibodies were detected

## Results

**Table 2 (Objective 2):**

**Characteristics of Responders (R) *vs.* Non-Responders (N-R)**

| Medically treated N= 42 | Responders N=21 | Non-Responders N=21 | p |
|---|---|---|---|
| **Current pregnancy: medical and invasive therapy** | | | |
| **GA when treatment commenced** (weeks, Mean±SD) | 22.3 ± 4.1 | 21.5 ± 6.2 | *0.81* |
| **IVIG** n/N (%) | 19/21 (90) | 21/21 (100) | *0.15* |
| **1 g/kg/d** n/N (%) | 15/19 (79) | 14/21 (67) | *0.38* |
| **2 g/kg/d** n/N (%) | 4/19 (21) | 7/21 (33) | *0.38* |
| **Increased 1 to 2 g/kg/d** n/N (%) | 0/19 | 3/21 (14) | *0.09* |
| **Prednisone added to IVIG** n/N (%) | 3/19 (14) | 19/21 (90) | **0.001** |
| Prednisone added to 1g/kg/d | 3/19 (14) | 12/21 (57) | **0.007** |
| Prednisone added to 2g/kg/d | 0/19 | 7/21 (33) | **0.006** |
| **Prednisone only***** n/N (%) | 2/21 (9) | 0/21 | *0.15* |
| **Duration of treatment at 1st FBS** (weeks, Mean±SD) | 7.6 ± 3.9 | 6.6 ± 2.9 | *0.36* |
| **GA at 1st FBS** (weeks, Mean ± SD, ) | 29.1 ± 3.8 | 27.2 ± 4.2 | *0.13* |
| **Number of FBS** (median, IQR) | 2 (1) | 3 (1.5) | **0.001** |
| **1 FBS** n/N (%) | 7/21 (33) | 1/21 (5) | **0.02** |
| **2 FBS** n/N (%) | 10/21 (48) | 4/21 (19) | **0.04** |
| **≥3 FBS** n/N (%) | 4/21 (19) | 16/21 (76) | **0.001** |
| **# Platelet IUT's** (median, IQR) | | 2 (2) | |
| **1 Platelet IUT** n/N (%) | | 6/21 (29) | |
| **2 Platelet IUT's** n/N (%) | | 5/21 (24) | |
| **≥3 Platelet IUT's** n/N (%) | | 10/21 (48) | |

## Results

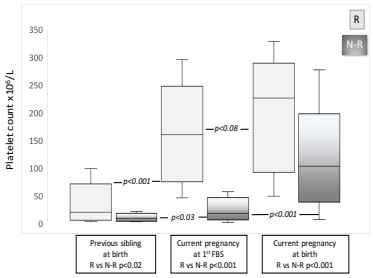
**Table 2 (Objective 2):**

Characteristics of Responders (R) *vs.* Non-Responders (N-R)

| Medically treated N= 42 | Responders N=21 | Non-Responders N=21 | p |
|---|---|---|---|
| **Current pregnancy: Delivery and neonatal outcomes** | | | |
| **GA at birth** (weeks, mean±SD) | 36.5 ± 2.1 | 36.0 ± 1.2 | *0.32* |
| **Birth < 32 weeks** n/N (%) | 1/21 (5) | 0/19 | *0.33* |
| **Birth < 34 weeks** n/N (%) | 2/21 (9) | 1/19 (9) | *0.92* |
| **Duration of treatment** (weeks, Mean±SD) | 14.7 ± 4.6 | 14.6 ± 6.2 | *0.96* |
| **SVD** n/N (%) | *16/21 (76)* | *10/20 (50)* | *0.08* |
| **CS** n/N (%) | *5/21 (24)* | *10/20 (40)* | *0.08* |
| **Birth weight (g) Mean ± SD** | 2955 ± 561 | 2796 ± 628 | *0.42* |
| **Male sex** n/N (%) | 7/21 (33) | 10/19 (53) | *0.22* |
| **PLATELET count at birth** | | | |
| **<50 x $10^9$/L** n/N (%) | 1/21 (5) | 3/19 (16) | *0.25* |
| **<20 x $10^9$/L** n/N (%) | 0/21 | 2/19 (10) | *0.13* |
| **Post natal treatment** n/N (%) (IVIG or platelet transfusion) | 2/21 (9) | 8/19 (42) | **0.02** |
| **ICH** n/N (%) | 0/21 | 0/21 | - |

## Results

Median platelets count of previous sibling at birth, in the current pregnancy at the first FBS and at birth for Responders and Non Responders




## Results

**Table 3 (Objective 3):**

**Actual CS rate *vs.* anticipated CS rate if no fetal procedure had been done**

| | Responders N=21 | Non-Responders N=18 | Total N=40 |
|---|---|---|---|
| **CS rate** n/N (%) | 5/21 (24) | 10/20 (40) | 15/41 (36.7) |
| **Indication:** | | | |
| **Elective repeat CS (no labor)** n/N (%) | 2/5 (40) | 6/10 (60) | |
| **CS in labor** n/N (%) | 2/5 (40) | 1/10* (10) | |
| **Breech presentation** n/N (%) | 1/5 (20) | 1/8 (10) | |
| **Pre-eclampsia** n/N (%) | - | 1/8* (10) | |
| **IUGR & abnormal Dopplers** n/N (%) | - | 1/8 (10) | |
| **Anticipated CS rate if FBS had not been done** n/total n (%) | 9/21 (43) | 12/20 (60) | 21/41 (51.2) |

* CS as mother refused FBS to assess suitability for vaginal delivery

## Conclusions

- Maternal IVIG treatment of pregnant patients with a previous history of F/NAIT is effective but associated with a non-uniform fetal platelet response
  - Despite similar duration of maternal IVIG treatment and dosage, 50% (n=21) fetuses remained thrombocytopenic (platelets < 50 x $10^9$/L), requiring fetal platelet transfusions
- A combination of medical treatment and serial platelet IUT's for non-responders results in a significant increase in fetal platelet count at birth, associated with no cases of ICH or neonatal bleeding

## Conclusions

- A previous sibling with severe thrombocytopenia at birth and the presence of HPA-1a antibody in the maternal circulation represent the two main clinical risk factors associated with a lack of fetal response.
- However the two prognostic factors are not enough to predict a priori non responders: we should be cautious before abandoning invasive fetal procedures in F/NAIT.
- Caregivers in experienced tertiary or quaternary level centers with a good track record of FBS-related adverse outcomes should continue to discuss and offer fetal testing to allow mothers the option of a safe vaginal delivery.

## Open questions

### F/NAIT: Guidance to Reduce the Risk of Intracranial Bleeding

International panel (pediatric hematology, maternal fetal medicine (MFM), neonatology, methodology, transfusion medicine, and a patient representative)

convened by the International Collaboration for Transfusion Medicine Guidelines (ICTMG)

**What's the best management?**

**Women with FNAIT in a previous pregnancy or sisters of women with FNAIT should be referred to MFM centers.**

**Fetal HPA typing** (e.g. HPA-1a/1b) should be performed in HPA-immunized pregnant women when the paternity is unknown or the partner is heterozygous or unavailable for testing. Prenatal HPA-1 typing should preferentially be performed by **a non-invasive method** e.g. cell-free fetal DNA (cffDNA) in maternal plasma if adequately quality assured.

**Antenatal IVIG administration:** initiated at 12-16 weeks gestation for all cases with previous fetus or neonate with F/NAIT related ICH. For all other pregnancies with a previous neonate with FNAIT (without ICH), administering antenatal IVIG to the mother should be discussed prior to a subsequent pregnancy or when pregnancy with maternal fetal incompatibility is confirmed.

If corticosteroids are used with IVIG, dexamethasone should not be used because of the associated risk of oligohydramnios.

Open questions

F/NAIT

**Can we predict the severity of the disease?**

- Anti HPA1a and HPA 3a Abs are associated with more severe disease compared with HPA 15a or 1b: no recommendations or guidelines exist to advice on different antenatal management strategies with different types of alloimmunization
- Ab titers: While high anti-HPA-1a levels correlate with more severe disease, pregnancies with barely detectable antibody levels and a severely affected fetus or neonate have been described as well

Maternal HPA-1a antibody level and its role in predicting the severity of Fetal/Neonatal Alloimmune Thrombocytopenia: A systematic review

*M.Kjaer, G.Bertrand, T. Bakchoul, E.Massey, J.M.Baker, L.Lieberman, S.Tanod, A.Greinacher, M.F. Murphy, D.M. Arnold, S.Baidya, J.Bussel, H.Hume, C.Kaplan, D.Oepkes, G.Ryan, H.Savoia, N.Shehata, J.Kjeldsen-Kragh on behalf of International Collaboration for Transfusion Medicine Guidelines* **2018**

To review results from previous published studies to examine whether the maternal antibody level to HPA-1a could be used to identify high-risk pregnancies

**The maternal antibody level** (measured by the monoclonal antibody immobilization of platelet antigen (MAIPA)) **correlated with the risk for severe thrombocytopenia**.

The prospective studies reported high negative predictive values (88-95%), which would allow for the use of maternal anti-HPA-1a antibody level as a predictive tool in a screening setting, in order to identify cases at low risk for FNAIT.

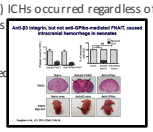
However, due to low positive predictive values reported in prospective as well as retrospective studies (54-97%), the maternal antibody level is less suited for the final diagnosis and for guiding antenatal treatment

Open questions

F/NAIT

**Is ICH associated with more severe thrombocytopenia?**

In animal model (F/NAIT mouse model) ICHs occurred regardless of platelet counts and HPA-1a antibodies inhibited **angiogenic signaling**, induced endothelial cell apoptosis, and decreased vessel density in affected brains as well as retinas.



In addition, very recently a retrospective study assessing human FNAIT sera reported the occurrence of ICH to be related to the presence of endothelial-specific anti-HPA1a antibodies, the anti-αVβ3 subtype

*Yougbare I et al, J Clin Invest 2015; Santoso S et al, Arterioscler Thromb Vasc Biol 2016*

## Future research: crucial topics

To define the optimal approach to antenatal management of the next affected pregnancy.

To develop biomarkers of fetal severity.

To prevent this disease creating a comprehensive screening to identify HPA-1b1b women at risk of FNAIT

naitbabies.org
neonatal alloimmune thrombocytopenia