Investigation and Management of Fetal/Neonatal Alloimmune Thrombocytopenia (FNAIT)

Recommendation of Practice

Background

- FNAIT is a rare condition characterised by thrombocytopenia in the fetus or neonate. It occurs in approximately 1 in 1000 births. It is a result of maternal IgG alloantibodies to human platelet antigens (HPAs) which are developed as a consequence of maternal-paternal platelet type incompatibility. This causes fetal platelet destruction and possibly suppression of megakaryopoiesis.
- In the Caucasian population, the most common antibodies involved are directed against the HPA-1a antigen, followed by the HPA-5b antigen. Furthermore there has found to be a strong correlation between the HLA allele HLA-DRB3*01:01 and FNAIT outcomes in HPA1bb mothers, with neonates having more significant thrombocytopaenia.
- FNAIT is usually detected as a consequence of investigations for bruising, purpura or poor condition in a neonate. It can also be diagnosed at the time of a significant intracerebral haemorrhage (ICH) of a fetus *in-utero* or as a neonate. Antenatal ICH is a rare presentation of FNAIT occurring in approximately 1:10,000 births. Occasionally, FNAIT will be diagnosed during the investigations carried out due to a close family member having suffered with FNAIT.
- The effects of FNAIT can be devastating and for those families management is complex.

Objective

- To aid planning and management of a pregnancy where there are Maternal Platelet specific Antibodies.

Differential Diagnosis

- Neonatal Thrombocytopenia or ICH secondary to other causes.
- Maternal thrombocytopenia is secondary to auto immune antibodies and is unrelated to FNAIT.

Important History

- Previous pregnancies with affected fetus and /or neonate.
    - Timing and effect in particular:
        - ICH and timing of event
        - Cord/newborn platelet count
        - Any maternal anti-platelet antibody investigation
        - Any maternal therapies

Screening for FNAIT

- Screening for FNAIT in the general population is currently not recommended as there is yet to be convincing evidence that the clinical benefit outweighs the potential harm from over-diagnosis.
- Screening would need to detect FNAIT in the first affected pregnancy in order to reduce the risk of ICH or intrauterine death for that pregnancy and subsequent pregnancies
- The cost effectiveness of screening would primarily be for FNAIT due to anti-HPA-1a, as it is the most common antibody and causes 95% of severe FNAIT

Ultrasound

- Minimal use except to identify an antenatal ICH.
    - 54% of ICH occurs before 28 weeks gestation.

Investigation

These tests are complex to perform and often difficult to interpret. They should be requested by doctors with expertise in this area. Significant anxiety can result when the tests are performed when not indicated or results are not correctly interpreted. MFM Specialists and Transfusion Medicine Specialists (TMS) are available to advise as to whether testing should be considered.

Testing may include:

- Maternal Platelet specific Alloantibodies
    - Platelet genotyping and compatibility of both parents with additional HLA-DRB3*01:01 phenotyping for HPA-1bb mothers
        - note: the lab requests blood from BOTH parents,
- For pregnancies where the father is heterozygous, non-invasive cell-free fetal DNA prenatal testing (NIPT) for fetal platelet typing and compatibility may be considered. This is complex and must be requested in consultation with TMS.
    - An amniocentesis is an alternative investigation, but carries with it a small risk of miscarriage.

Not all platelet antibodies can be detected by the assays available within the New Zealand Blood Service and some samples may need to be sent overseas for MAIPA assay analysis. This should be discussed with the TMS via the MFM Service.

The NIPT and MAIPA samples will be sent to Australia after approval by TMS:

Platelet & Neutrophil Reference Lab
Australian Red Cross Lifeblood
44 Musk Avenue
Kelvin Grove Brisbane QLD 4059
AUSTRALIA

If the fetus is compatible to the mother on-going treatment and surveillance is not required. If there is a strong clinical suspicion of FNAIT and the antibody screening is negative, discuss the results with the Transfusion Medicine Specialists. Antibodies may be negative between pregnancies and even be negative in early pregnancy but re-appear later.

Prognosis

This depends on previous obstetric and neonatal history. If the couple have had a previously affected child there is an 80% chance of significant thrombocytopenia in a future pregnancy without treatment. This condition tends to get worse with each pregnancy without treatment.

On-going Management

See chart below

IVIG and Steroids

- Antenatal treatment should be a shared management plan with the MFM team and the Transfusion Medicine team.
- IVIG has been shown to improve platelet count in fetuses at risk of FNAIT. The dose given and the gestation treatment is started varies significantly between studies. The NZMFMN recommends use 1g/kg/week, starting at 12-16 weeks of gestation in those with a previous affected pregnancy. Doses range between 0.5g/kg/week to 2g/kg/week have been described.
- There has been no high quality studies with strong evidence to support aligning IVIG dose with FNAIT risk stratification eg 0.5-1g/kg/week for lower risk pregnancies (previous FNAIT without ICH) and a higher dose 1-2g/kg/week for higher risk pregnancies (previous FNAIT with ICH). Regimens outside the range of 1g/kg/week and starting at 16-18 weeks should be led by the MFM and Transfusion Medicine Specialists. .
- The addition of steroids could be considered at a dose of 0.5mg/kg/day for women at high risk of poor outcomes if the benefits outweigh the risks as the evidence has not shown it to improved platelet counts significantly. Dexamethasone should not be used because of the associated risk of oligohydramnios.

NZMFMN and NZ Blood Service recommends the following regimens. Please also refer to the BSCH 2019 guidelines

- Women who have had a previous fetus/neonate with FNAIT-related ICH:
    - Start IVIG at 12-16 weeks, at 1-2g/kg/week
- Women who have had a previous fetus/neonate with FNAIT (no ICH):
    - Start IVIG at 20-22 weeks, at 1-2g/kg week

Any doses or regimens outside this range should be led by the MFM and Transfusion Medicine specialists. Note: if 2g/kg/wk is used monitor patients for IVIG-related haemolysis, especially if patient blood group is A, B or AB.

Platelet sampling and transfusions

- Fetal Blood Sampling (FBS) carries a higher risk in a pregnancy at risk of FNAIT due to the risk of bleeding from the puncture site. Transfused platelets have a short half-life of 2-5 days unlike transfused red blood cells. Platelet sampling and transfusion could be considered to guide for timing of delivery planning. If a FBS with platelet transfusion is planned it should be performed in a setting where a move straight to caesarean section delivery is possible.

Mode and timing of delivery

- There has been no high quality studies looking at the safest gestation or mode of delivery for pregnancies complicated by FNAIT. Delivery must be individualised for each pregnancy, taking into account whanāu wishes.
- Mode of delivery would be guided by previous affected pregnancy and progress of current pregnancy.
- In the case of an induction of labour for multiparous women this should occur at 38 weeks gestation with avoidance of rotational or ventouse or forceps delivery, fetal scalp electrode placement or fetal scalp sampling.
- Caesarean section should occur at 37 weeks gestation.

Postnatal management

- The neonatal team and TMS should be notified of a suspected FNAIT case.
- Cord blood for platelet count should be sent immediately after delivery.
- In known cases matched human platelet antigen (HPA)-selected platelets should be on-site and immediately available at time of delivery.
- In an acute situation platelet transfusion can be with unmatched platelets. Transfusion should not be delayed for confirmation by imaging or investigations.
- Cranial USS should be performed within 24 hours of delivery
- Platelets should be monitored, in the absence of treatment, until they normalise.

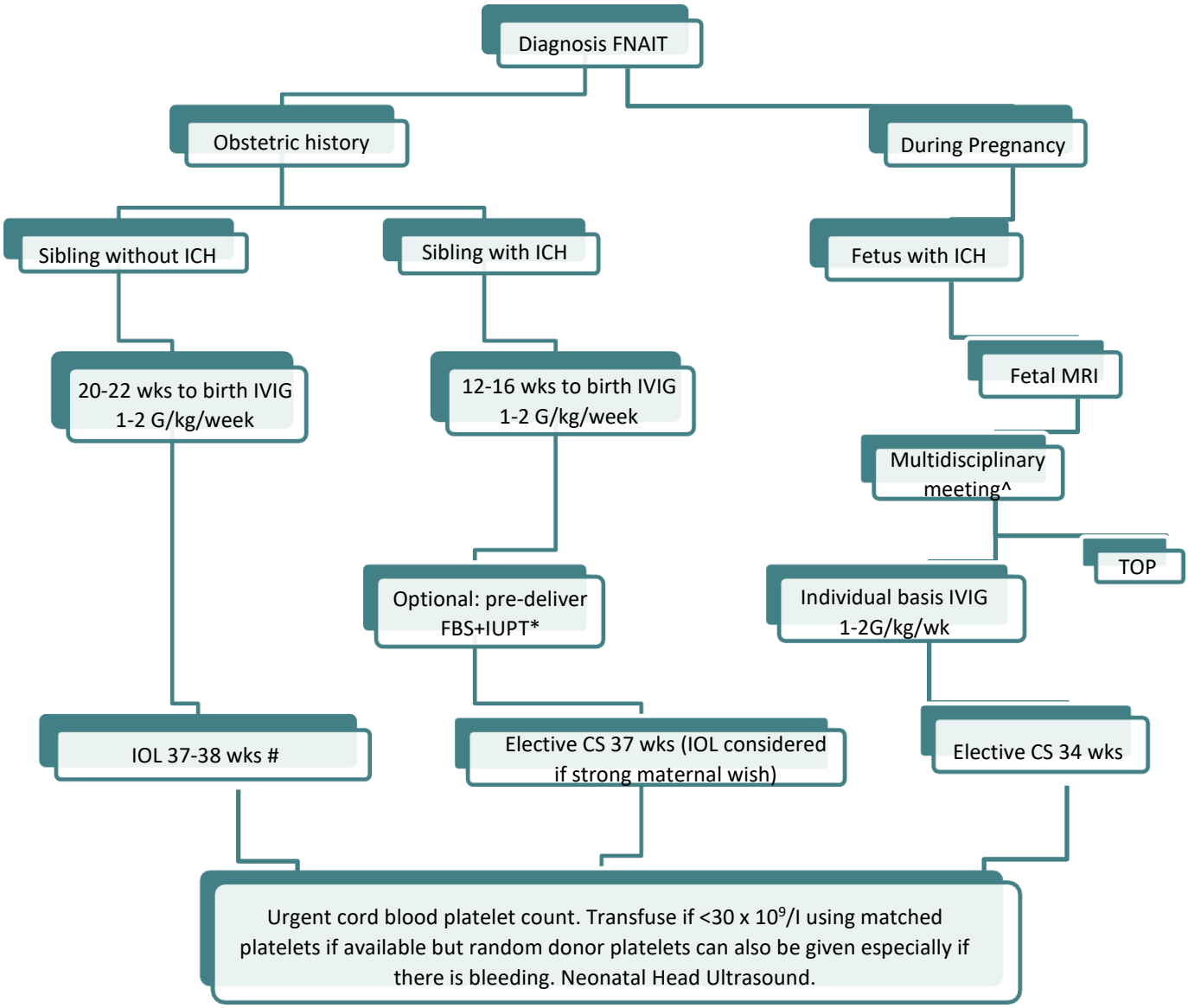
FNAIT Prophylaxis

- Currently there is no prophylaxis options for FNAIT clinically available
- Two potential treatments are in the research phase:
    1. NAITgam: an anti-HPA-1a IgG product which is a human derived prophylaxis similar to anti-D for rhesus disease. It is currently under licensure.
    2. A recombinant high-affinity anti-HPA-1a that also competes for maternal anti-HPA-1a.

This Recommendation of Practice was updated in October 2023 by Drs Jaynaya Marlow and Sally Gundersen from Wāhi Rua and Dr Sonam Mishra from the NZ Blood Service with input from members of Wāhi Rua NZMFM Network.

The most up to date version of this Recommendation of Practice can be found on Healthpoint Wāhi Rua: New Zealand Maternal Fetal Medicine Network (NZMFM) webpages: https://www.healthpoint.co.nz/public/wahi-rua-new-zealand-maternal-fetal-medicine/

Figure 1 - Flowchart for perinatal management of fetal and neonatal alloimmune thrombocytopenia



^Consulting paediatric neurologist, neonatologist regarding outcome
*with platelet transfusion if platelet count <50x109/l
#avoid any potential traumatic events, like scalp electrode, scalp blood sampling or assisted vaginal delivery
ICH=intracranial haemorrhage, IVIG=intravenous immunoglobulins, TOP=termination of pregnancy
CS=caesarean section, FBS=fetal blood sampling, IUPT=intrauterine platelet transfusion

References

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- Lieberman L, Greinacher A, Murphy MF *et al*. Fetal and Neonatal alloimmune thrombocytopenia: recommendations for evidence based practice, an international approach. *BJH*; 2019: 185:549-562
- Liu ZJ, Bussel JB, Lakkaraja M *et al*. Suppression of in vitro megakaryopoiesis by maternal sera containing anti-HPA-1a antibodies. *Blood*; 2015; 126: 1234-1236
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- Tiller H, Kamphuis MM, Flodmark O et al. Fetal intracranial haemorrhages caused by fetal and neonatal alloimmune thrombocytopenia: an observational cohort study of 43 cases from an international multicentre registry. *BMJOpen*; 2013: doi: 10.1136/bmjopen-2012-002490 Winkelhorst D, Murphy M.F, Greinacher, A. *et al*. Antenatal management in fetal and neonatal alloimmune thrombocytopaenia: a systematic review. *Blood*; 2017; 129(11): 1538-1547.

NZBLOOD
Te Ratonga Toto O Aotearoa

REQUEST FOR TISSUE TYPING DIAGNOSTIC TESTING

- **Disease Association**
- **Platelet Tests, Transfusion Reaction Investigation**
- **Hypersensitive Drug Reactions**

National Tissue Typing Laboratory

NZ Blood Service
Private Bag 92071
Victoria Street West
Auckland 1142
NEW ZEALAND

Telephone: (09) 523 5731
Fax: (09) 523 5761

Tissue Typing use only:

Received by _____ Registered by _____

Event No.

FULL AND ACCURATE COMPLETION OF THIS FORM IS ESSENTIAL

Step 1. **PATIENT/DONOR DETAILS** - sections marked * are mandatory

*(Tick box indicating if detail relate to a patient or donor. Attach identification label or complete **all** written details).*

❑ **Patient** ❑ **Donor implicated in TRALI/Transfusion Reaction**

*NHI No. _____ *DOB _____ *Gender _____

*Family Name _____

*Given Names _____

Ethnicity _____

*DHB of Patient _____

*Progesa ID of Donor _____
(TRALI/Transfusion Reaction investigation only)

FOR URGENT TEST REQUESTS PLEASE PHONE TISSUE TYPING – (09) 523 5731

Step 2. **TESTING REQUIREMENTS** – see reverse for sample requirements

Disease Association

❑ B27 (ankylosing spondylitis)
❑ Coeliac Disease (HLA-DQ)
❑ Narcolepsy (HLA-DR,-DQ)
❑ Other – please specify _____

Hypersensitive Drug Reaction

❑ HLA-B*57:01 (Abacavir)
❑ HLA-B*15:02 (Carbamezapine/Tegritol)
❑ Other – please specify _____

Platelet Immunology & TRALI/Transfusion Reaction

❑ Platelet (HPA) antibody screen
❑ NAIT Investigation (includes HPA genotyping and maternal/paternal crossmatch)
❑ Investigation of Platelet Refractoriness (includes HPA/HLA antibody screen and HLA/HPA typing if required)
❑ TRALI/Transfusion Reaction
❑ Other – please specify _____

Step 3. **CLINICAL INFORMATION INCLUDING FACTORS WHICH MAY INTERFERE WITH TESTS**

Step 4. **NAME OF REQUESTING PRACTITIONER / CO-ORDINATOR**

Practitioner / Co-ordinator / Nurse: _____ Signature: _____

Contact ph: _____ Date: _____ DHB: _____

Full Address: _____

Copy report to and Address _____

Step 5. **SPECIMEN COLLECTOR DECLARATION**

* I certify that the blood specimen(s) accompanying this request form was drawn from the patient named above.
* I established the identity of this patient by direct enquiry and/or inspection of their wristband.
* Immediately upon the blood being drawn I labelled and signed the specimen(s) in the presence of the patient.

Date/Time of collection _____ Contact No/Pager _____

SIGNATURE OF COLLECTOR _____ Print Name _____
Doctor/Co-ordinator/Nurse (please circle)

TRIO NZBCL136 05/11 NATIONAL 132F00502

Abbreviation(s)

BMT = Bone Marrow Transplant	MUD = Matched Unrelated Donor	SOT = Solid Organ Transplant
CDC = Complement-Dependent Cytotoxicity	PAA = Platelet Associated Antibody	SPA = Serum Platelet Antibody
HPA = Human Platelet Antigen	PRA = Panel Reactive Antibody	SSP = Sequence Specific Primers
HLA = Human Leucocyte Antigen	SBT = Sequencing Based Typing	

TEST REQUESTS	SAMPLE REQUIREMENTS
Bone Marrow Transplant - patient/donor Initial and confirmatory HLA typing	2 x 10ml CPDA (If cell count low - 4 x 10ml CPDA) 1 x 10ml clotted 1 x 6ml EDTA (with initial typing only)
Solid Organ Transplant - patient/donor Initial and confirmatory HLA typing Lymphocyte crossmatch (Flowcytometry and CDC) Monthly transplant tray sample	 4 x 10ml CPDA; 1 x 10ml clotted and 1 x 6ml EDTA 4 x 10ml CPDA; 1 x 10ml clotted and 1 x 6ml EDTA 1 x 10ml Clotted or, 3 x 5ml or 2 x 7ml Clotted
Disease Association (e.g. B27, Coeliac, Narcolepsy)	1 x 10ml CPDA
Platelet Immunology & TRALI/Transfusion Reactions TRALI/Transfusion Reactions Refractory patients (includes HLA/HPA typing if required) NAIT (includes HPA genotyping and maternal/paternal XM) Platelet Antibody screen (PAA and SPA)	 Donor: 2 x 10ml clotted; Patient: 2 x 10ml CPDA 4 x 10ml CPDA and 2 x 10ml clotted Mother: 4 x 10ml CPDA and 2 x 10ml clotted Father: 4 x 10ml CPDA 4 x 10ml CPDA and 1 x 10ml clotted
Hypersensitive drug reaction (HLA-B*57:01, HLA-B*15:02)	1 x 10ml CPDA

NOTE: FOR YOUNG PATIENT/DONOR WHERE SAMPLE VOLUMES MIGHT BE PROBLEMATIC CONTACT THE TISSUE TYPING LABORATORY AT (09) 523 5731.

SAMPLE LABELLING & ACCEPTANCE CRITERIA

1. Both tube and request form **MUST** contain the following information:
   - Family name and given name(s)
   - NHI No or DOB
   - Date and time of sample collection
2. Request form and sample(s) **MUST** be signed by physician/transplant co-ordinator/nurse who collected the samples.
3. Details on tubes **MUST** match those on the accompanying form.

DELIVERY INSTRUCTIONS FOR TISSUE TYPING TEST REQUESTS

Monday to Friday	After Hours – Weekends and Public Holidays
Tissue Typing Laboratory New Zealand Blood Service 71 Great South Road Epsom AUCKLAND	Blood Bank Auckland City Hospital Park Road AUCKLAND

TURNAROUND TIMES

Bone Marrow Family Study	1 month	Renal Transplant List (HLA and ABO)	2 weeks
MUD Confirmatory HLA typing	2 weeks	Live Donor Renal workup	4 weeks
HLA Type	2 weeks	Other Solid Organ workup	2 weeks
B27 / Disease Association	2 weeks	CDC PRA/Antibody Screen (SOT)	6 weeks
Platelet Refractoriness	*1 day – 1 week	Cadaver Report	4 weeks
NAIT	*1 day – 1 week	Post Transplant Monitoring	2 days
Platelet Crossmatch	*1 day – 1 week		
HPA Genotype	1 week	*Verbal report given within 24 hours	

TESTS PERFORMED	TECHNIQUE
HLA typing uses DNA techniques and is at intermediate resolution except where stated.	
BMT	
Initial HLA Typing: patient HLA-A,-B,-DR or potential related donor HLA-A,-B, and if a HLA-A,-B match HLA-DR	Luminex DNA typing
Confirmatory HLA Typing - HLA-A,-B,-DR	CDC/Luminex/SSP
Patient High Resolution HLA-DR Typing for Unrelated Donor Search	SSP/SBT
High Resolution HLA-A,-B,-C,-DR,-DQ typing for patient and unrelated donor	SSP/SBT
SOT	
Initial HLA Typing patient and donor - HLA-A,-B,-DR	Luminex DNA typing
TRALI/Transfusion Reactions	Luminex
Confirmatory HLA Typing - HLA-A,-B,-DR	Luminex DNA typing
Crossmatch (patient serum v donor cells)	Flow cytometry/CDC
HLA antibody screening	Luminex/CDC
Disease Association	SSP/Luminex DNA typing