

Fetomaternal Alloimmune Thrombocytopenia

Dr Helen Savoia

ROYAL
CHILDREN'S
HOSPITAL



the women's
the royal women's hospital
victoria australia

Overview

- What is FMAIT?
- Fetal and neonatal thrombocytopenia
- Diagnosis
- Consequences
- Antenatal management
- Screening
- Future directions

Platelet Alloantigens

- Target glycoproteins have important biological functions
- 'platelet-specific' but some on other tissues eg HPA-5 on endothelium
- HPA system named in order of discovery
- Bi-allelic system with common (a) and uncommon(b) antigens arising by nucleotide change leading to amino acid substitution

Syndromes Caused by Platelet-Specific Antibodies

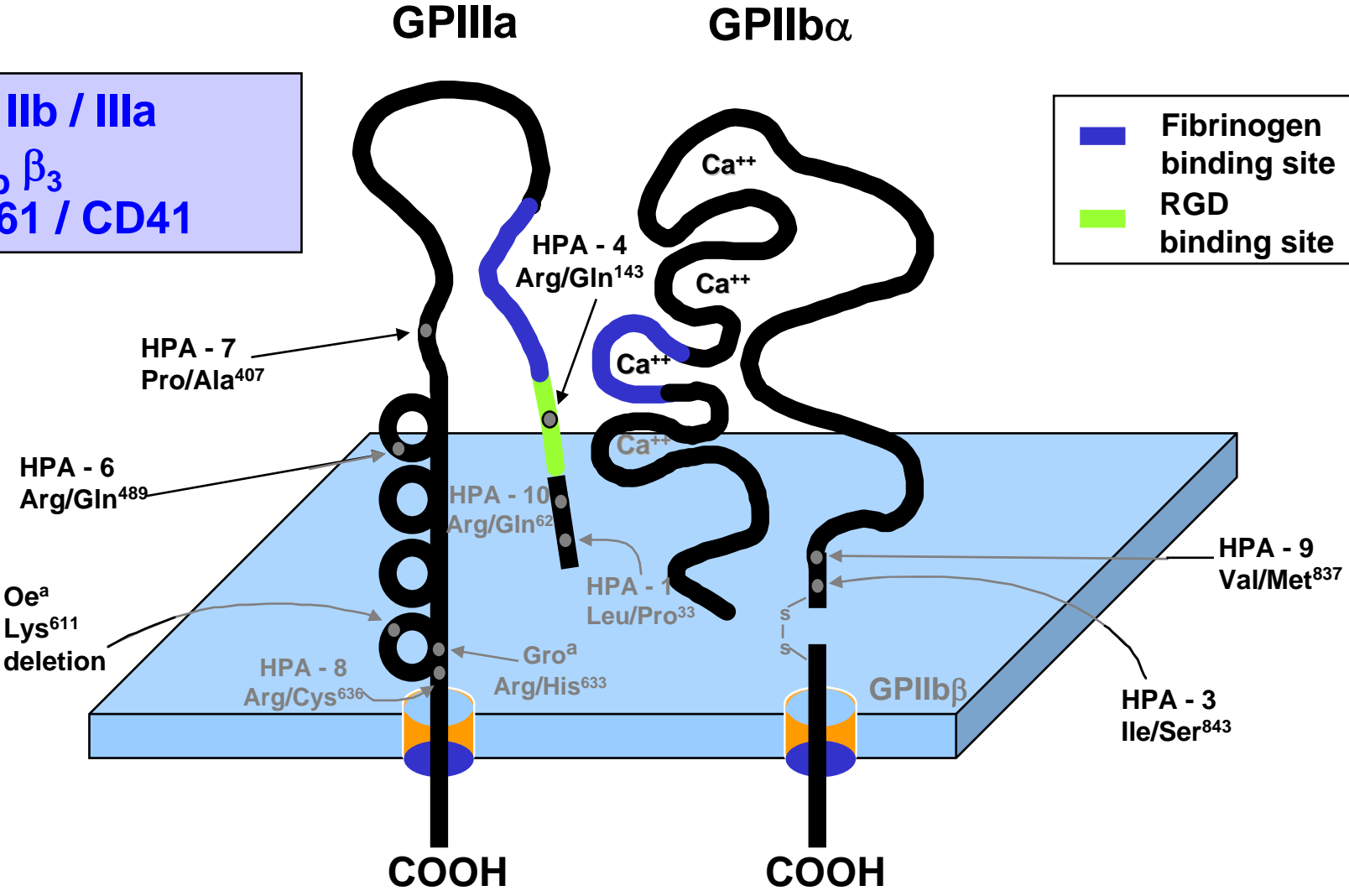
- Fetomaternal Alloimmune Thrombocytopenia (FMAIT)
- Post-Transfusion Purpura (PTP)
- Passive Alloimmune Thrombocytopenia
- Transplantation Associated Thrombocytopenia
- Platelet Transfusion Refractoriness

Human Platelet Antigens (HPA)

Antigen	System	Phenotype frequency	Glycoprotein	Nucleotide change	Amino acid change
HPA-1a	HPA-1	97.9%	GPIIIa	T ¹⁹⁶	Leucine ³³
HPA-1b		28.8%		C ¹⁹⁶	Proline ³³
HPA-2a	HPA-2	>99.9%	GPIb	C ⁵²⁴	Threonine ¹⁴⁵
HPA-2b		13.2%		T ⁵²⁴	Methionine ¹⁴⁵
HPA-3a	HPA-3	80.95%	GPIIb	T ²⁶²²	Isoleucine ⁸⁴³
HPA-3b		69.8%		G ²⁶²²	Serine ⁸⁴³
HPA-4a	HPA-4	>99.9%	GPIIIa	G ⁵²⁶	Arginine ¹⁴³
HPA-4b		<0.1%		A ⁵²⁶	Glutamine ¹⁴³
HPA-5a	HPA-5	99.0%	GPIa	G ¹⁶⁴⁸	Glutamic acid ⁵⁰⁵
HPA-5b		19.7%		A ¹⁶⁴⁸	Lysine ⁵⁰⁵

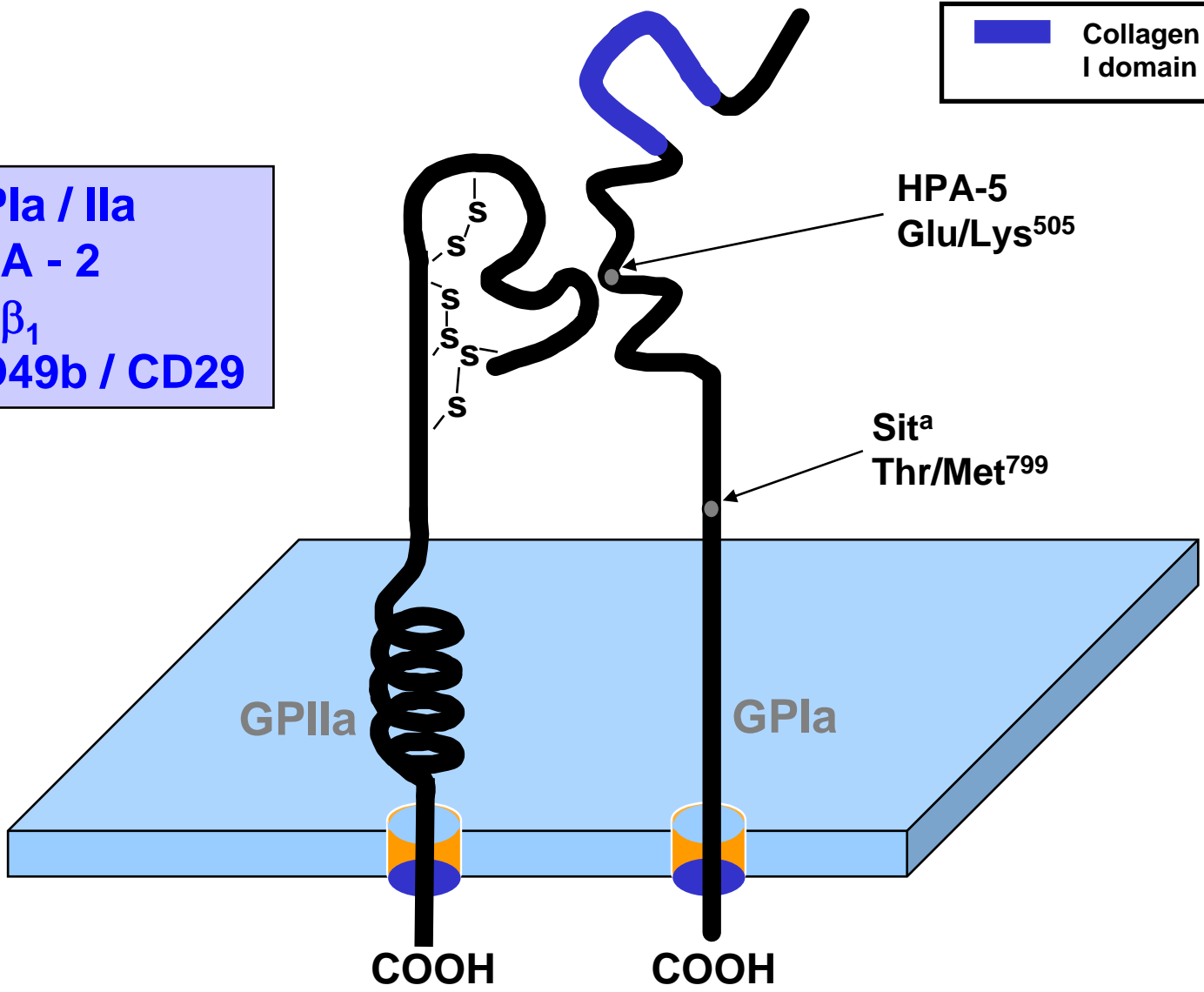
GP IIb / IIIa
 $\alpha_{IIb} \beta_3$
CD61 / CD41

Fibrinogen binding site
RGD binding site



GPIa / IIa
VLA - 2
 $\alpha_2 \beta_1$
CD49b / CD29

 **Collagen binding site**
I domain



HPA-5
Glu/Lys⁵⁰⁵

Sit^a
Thr/Met⁷⁹⁹

GPIIa

GPIa

COOH

COOH

Observed versus Theoretical Frequencies of FMAIT

Target Alloantigen	%Pregnancies at Theoretical Risk of FMAIT	FMAIT Observed Cases
HPA-3b	14.5	0
HPA-1b	10.8	0
HPA-3a	9.3	1
HPA-5b	8.7	6
HPA-1a	1.9	44
HPA-5a	1.1	0

Data from Mueller-Eckhardt et al 1989
serological investigations by a defined protocol over 18 months

Platelet production in the fetus and newborn

- Megakaryocytes in yolk sac from 5 weeks and in liver and spleen from 10 weeks
- Platelets in fetal circulation from 5 weeks, mean count of $187 \times 10^9/l$ at 15 weeks
- Early platelet production in liver and placental circulation
- Platelet numbers at “adult” levels in term and preterm infants
- Increase by 50% in first postnatal week
- 20-25% lower in small for age infants

Fetal and neonatal thrombocytopenia

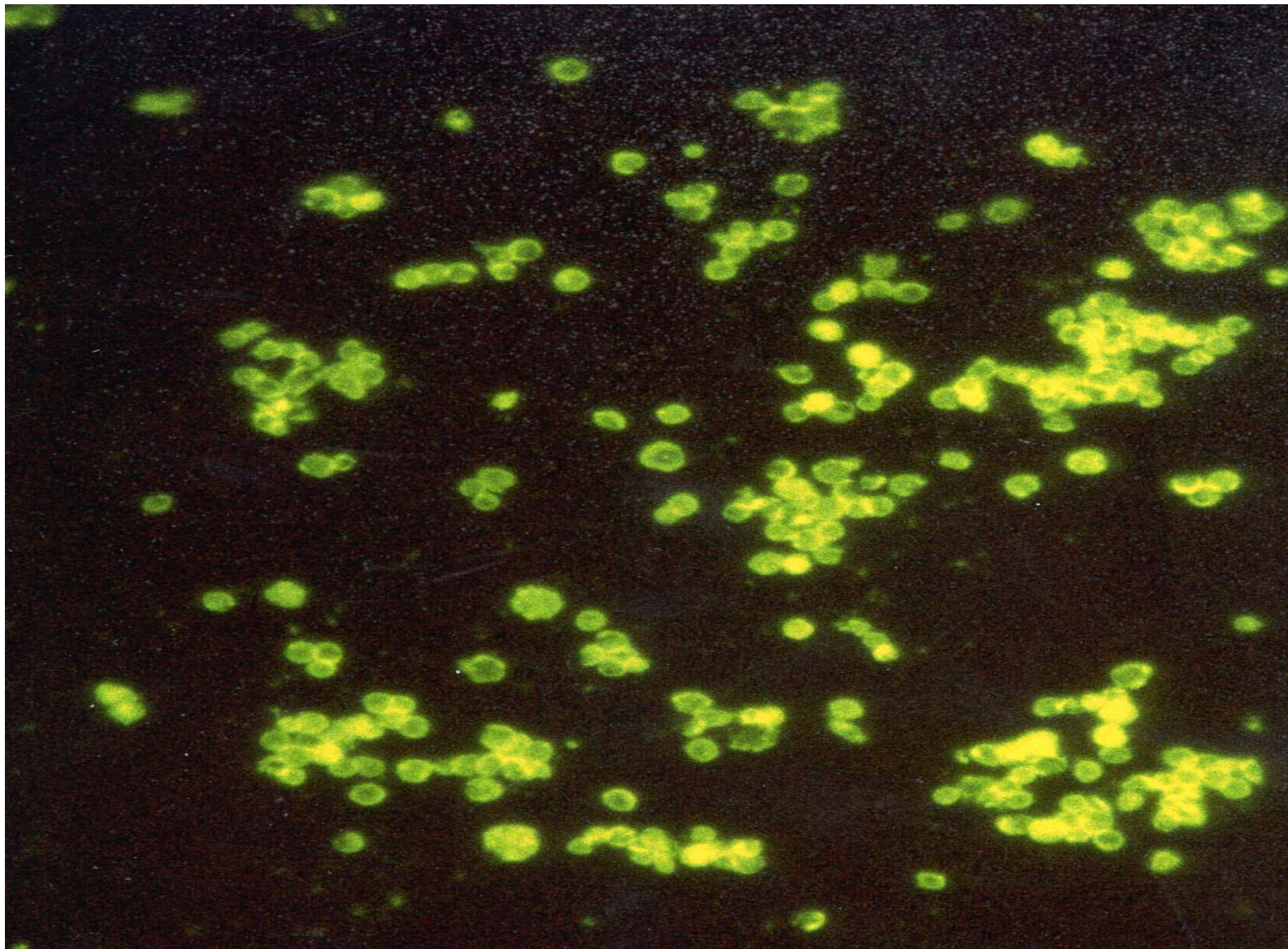
- 5,194 retrospective FBS (Hohlfeld et al Blood 1994)
- 247 fetal counts $< 150 \times 10^9/L$ (4%)
- Severe thrombocytopenia caused by congenital infection, chromosomal abnormalities and immune causes (alloimmune and maternal ITP)
- Mild thrombocytopenia $< 150 \times 10^9/l$ present in cord sample in 4% of 2,200 newborns
- Clinically significant thrombocytopenia $< 50 \times 10^9/L$ 0.12% of 15,000 newborns (Burrows & Kelton NEJM 1993)

Diagnosis

- Clinical presentation
 - Ultrasound evidence of fetal ICH
 - Neonatal bleeding (skin)
 - Incidental finding of neonatal thrombocytopenia

Laboratory Diagnosis of FMAIT

- Demonstration of platelet-specific maternal alloantibody
 - Platelet Immunofluorescence Test (PIFT)
 - monoclonal antibody immobilization of platelet antigens (MAIPA)
- Platelet typing (maternal/paternal)
 - phenotyping (serology, ELISA, flow cytometry)
 - genotyping



FMAIT

- Incidence 1 in 1000-2000 births
- First born 50%
- Most diagnosed after birth (petechiae/purpura)
- Serious bleeding in 25%
- Antenatal ICH in 10%

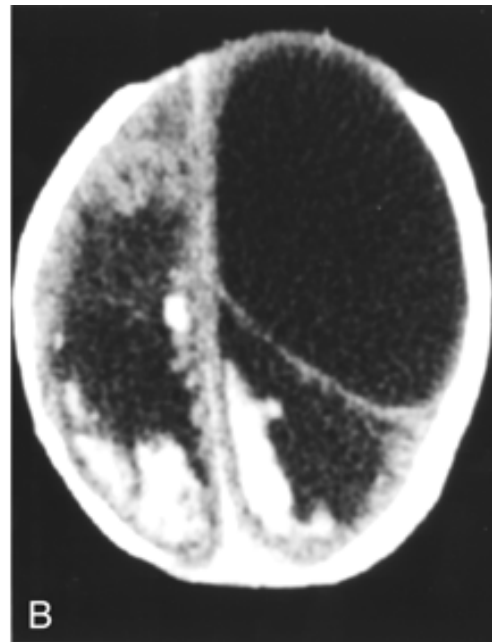
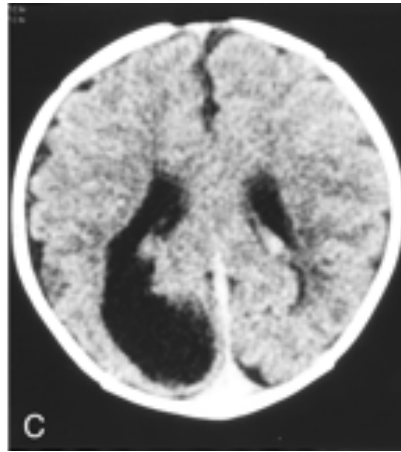






Consequences

- ICH in population-based studies:
 - Low
- ICH in FMAIT
 - 11-26%
 - 7% mortality



Neonatal Management

- Platelet transfusion
 - typed donor platelets HPA-1a neg, 5b neg
 - Random platelets
 - Maternal platelet
- IVIG response rate 75% (delay 24-48 hours)
- Brain imaging- cerebral ultrasound
- Thrombocytopenia usually resolves within 2 weeks, may last up to 6 weeks

Managing the next pregnancy

- Will this fetus be antigen positive?
 - Paternal zygosity
 - Fetal platelet typing (amniocentesis, fetal DNA in maternal plasma)
- What is the risk of antenatal ICH?
 - What was the previous neonatal platelet count?
 - Was there an ICH?
 - Previous ICH – 80% recurrent ICH
 - Previous AIT/no ICH – 7% ICH

History of Antenatal Management

- Early delivery and platelet transfusion
- 1980s FBS and in utero platelet transfusion pre delivery
- 1980s/90s
 - Serial IUT
 - Maternal intravenous immunoglobulin
 - Maternal corticosteroids
 - Combination therapy

Antenatal Management

- Maternal therapy- 67% plts $> 50 \times 10^9/L$
- Serial platelet transfusion- significant complications
- Lower pre treatment platelet counts when previous sibling had ICH or severe thrombocytopenia

Birchall et al 2003

Antenatal Management

- Parallel RCT's of maternal treatment, stratified according to risk
 - HR – IVIG + Prednisolone better than IVIG alone
 - SR – Either IVIG or Prednisolone
 - » Berkowitz et al 2006
- RCT of Empiric Therapy in Standard Risk
 - IVIG +/- Prednisolone
 - Can safely manage without early FBS
 - FBS late, & consider rescue therapy
 - » Berkowitz et al 2007

RWH Case Series 2000-2008

- 15 Pregnancies in 14 patients:

Group	Description	Number
A	Family History, Potential for Incompatibility	2
B	Previous child with Neonatal TCP, no ICH	11 (12)
C	Previous child with Perinatal ICH	0
D	Previous child with Antenatal ICH or FDIU	1

HPA Incompatibility

Antibody Types:

1a	58%
5b	25%
3a	17%

Management

Group (No)	Management Strategy
A (2)	Monthly antibody screen
B1 (3)	Compatible fetus (no treatment)
B2 (9)	IVIG from 12-15/40, FBS Rescue Prednisolone
D (1)	IVIG from 6/40 Prophylactic Prednisolone

Fetal Blood Sampling and Intrauterine Transfusion (00-06)

	Mean	Range
Gestation at first FBS (weeks)	22.3	18 – 28
Number of procedures	4.7	0 – 10
Platelet count at first FBS ($\times 10^9$)	70*	5 - 209

Pregnancy Outcomes

- Gestation at delivery:
 - Mean: 31.8 (Range: 27-35)
 - 3 patients required immediate delivery for fetal bradycardia during IUT (27, 28 & 31weeks)
 - (3/10 cases)

Neonatal

- Platelet count at delivery:
 - Mean: 222 (Range: 10 – 538)
- Mean platelet count at delivery (excluding emerg c/s immediately post transfusion)
 - Mean: 112 (Range: 10 – 235)
- Postnatal treatment:
 - 3 – IVIG (1) + Transfusion (1)
 - 1 – IVIG
 - 1 x IVH – 27/40, Plts = 10

Should we screen for FMAIT?

- Screening for HPA-1a negative women and/or anti-HPA-1a antibody
- Should screening be deferred until optimal antenatal management is better defined?
- Screening programs in some Scandinavian countries
- Women identified through screening offered c/s delivery 2-4 weeks preterm
- Decision tree analysis screening is cost effective (Killie et al 2007)

Discussion

- FMAIT is a rare condition
 - 10 cases in 7 years
 - Birchall et al, BJH 2003
 - » European collaboration – 12 centres, 13 years
 - » 55 cases
 - Berkowitz et al, 2006
 - » American collaboration – 42 centres, 7 years,
 - » 79 cases*
- Risks associated with FBS / IUT

FMAIT National Registry

- ARCBS Funded
- Registry managed by Monash University
Department of Epidemiology & Preventive
Medicine
- Clinical Steering Committee
- Case Ascertainment
 - ARCBS Reference Laboratories
 - Obstetricians
 - Neonatologists

FMAIT National Registry (2)

- Collect information on FMAIT incidence and natural history in Australia
- Document management practices (antenatal and postnatal) and associated outcomes
- Explore factors (clinical, laboratory) affecting clinical outcomes
- Inform & inspire future hypothesis-driven research in this area, and develop a network to facilitate such research

Summary

- The approach of serial FBS & IUT is associated with good long term outcomes, but significant procedure-related risks.
- At RWH, we have moved from an IUT-based approach to a maternal medical treatment approach, in line with current research supporting this model.
- A national registry will facilitate the collection of information on this rare condition and the different treatment strategies, and may serve as a conduit for participation in multicentre studies exploring these questions.