


Fetal Hydrops


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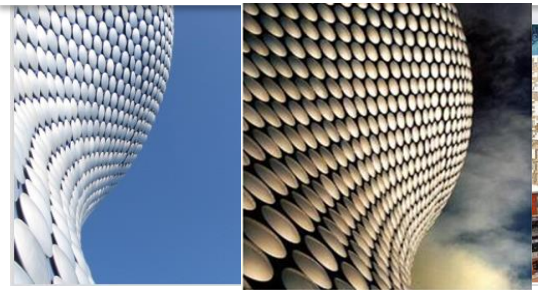
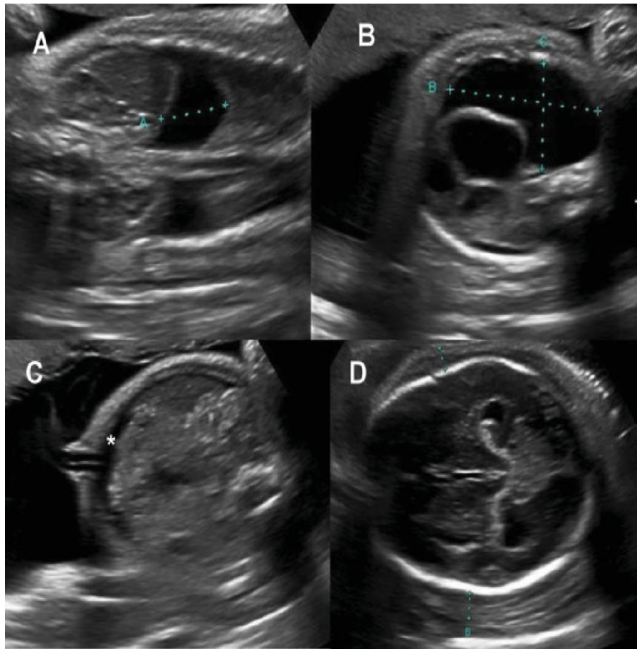



BMUS Obstetric Study Day, 6th October 23
(Some slides courtesy of Mark D Kilby)

Fetal hydrops

- The pathophysiology of immune and nonimmune fetal hydrops is multifactorial and complex.
- Fetal hydrops is a sign, not a diagnosis, and should prompt the question “What is the cause?”
- The fetal component signs of hydrops, usually identified by ultrasound imaging, are:
  - skin oedema (usually over the cranium), and/or
  - the presence of other serous effusion collections (ascites, pericardial, hydrothorax), and/or
  - polyhydramnios, and/or
  - increased placental thickness (> 6 cm in depth)



Maternal features

- In addition to the fetal morbidity and mortality associated with fetal hydrops, a secondary maternal “mirror syndrome” can occur, with findings of:
  - maternal dilution anaemia
  - oedema
  - proteinuria
  - hypertension

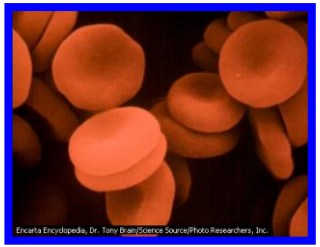
Two aetiological groups

Immune fetal hydrops:

- Hydrops with circulating antibodies in maternal serum against RBC antigens
- 10-15%, decreasing incidence of RhD
- Others E,c, Kell and less common Fya (Duffy) and Jka (Kidd)

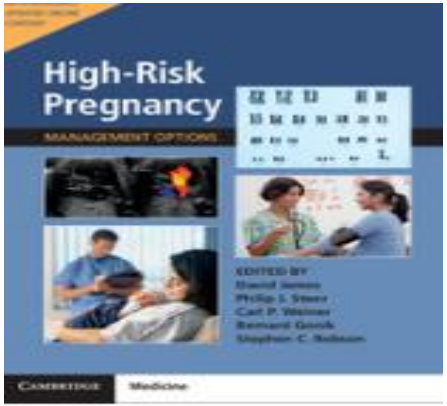
Nonimmune fetal hydrops:

- Hydrops with no circulating RBC antibodies
- 85-90% of cases
- Causes:
  - Genetic
  - Structural malformations
  - Infection
  - Metabolic causes
  - MC twin vascular anomalies



Non-immune fetal hydrops

- 1 in 1500-4000 deliveries (3 per 10,000 births)
- Idiopathic – generally considered rare, but a recent cohort study identified “unknown” at 17.8%
- Maternal conditions associated with NIFH:
  - Diabetes, thyroid, hypoalbuminaemia, alpha-thal, hypoxia and anaemia, hypertension
- Placental and umbilical cord conditions associated with NIFH (5.6%):
  - MC vascular complications
  - Chorioangioma
  - Umbilical vein thrombosis
  - Cord cysts
- Fetal conditions:
  - cardiovascular (21.7%)
  - hematologic (10.4%)
  - maternal/fetal infection (6.7%)
  - thoracic malformations (6.0%)
  - lymphatic dysplasia (5.7%)
  - fetal other (8.4%)
- Genetic processes:
  - chromosomal (13.4%) – T21/18/13/15/16, 45X0 -1%
  - genetic syndromes (4.4%) - Noonan
- Secondary disruptive processes:
  - infection (6.7%) – CMV, coxsackie, Parvovirus B19



High-Risk Pregnancy

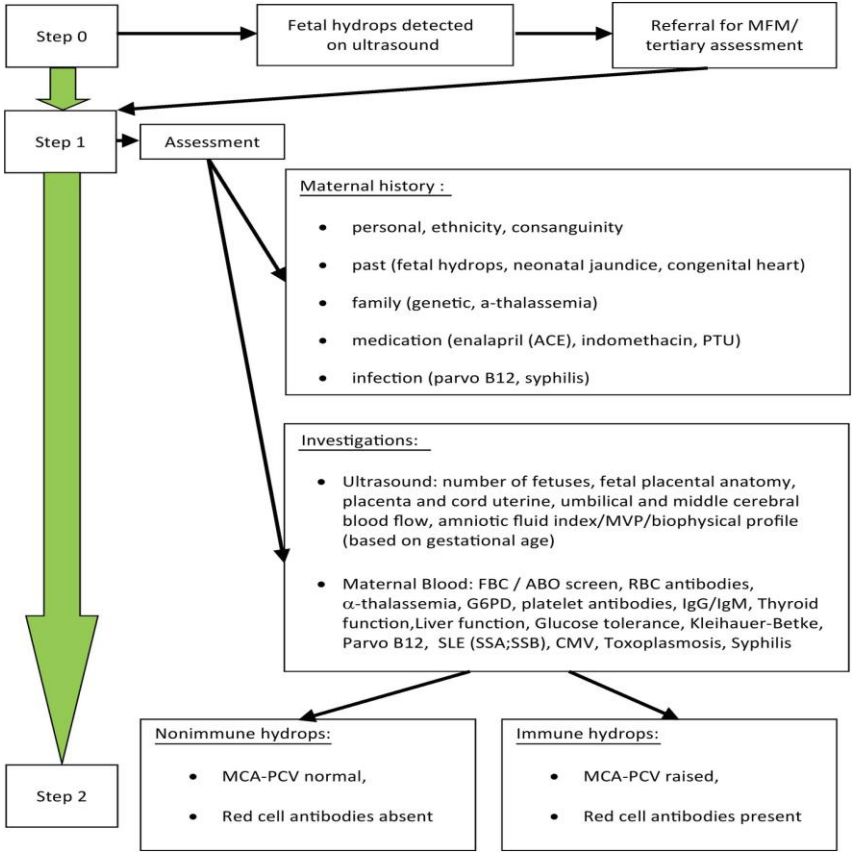
Management Options

Fetal conditions

Mechanism/system (% contribution to BelliniReference Bellini and Hennekam[11]/SMFMReference Norton, Chauhan and Dashe[1] cohorts)	Diagnosis/condition/process	Genetics, recurrence, treatment
Cranial-neck/CNS (–/–)	•Intracranial hemorrhage •Vein of Galen aneurysm •Cerebral tumor/angioma •Encephalocele •Porencephaly •Absent corpus callosum •Sacrococcygeal teratoma •Cystic hygroma (N karyotype) •Hypothyroidism •Hyperthyroidism, fetal/Graves' disease	All conditions are rare (< 1%) Encephalocele recurrence risk reduced with first-trimester folic acid
Thoracic/pulmonary (11.7%/6%)	•CPAM pulmonary sequestration •Pulmonary tumor •Bronchogenic cyst •Pulmonary hypoplasia •Mass/teratoma/leimyosarcoma •CHAOS/laryngeal atresia	All conditions are rare (< 1%) and multifactorial in etiology
	•Diaphragmatic hernia	
	•Chylothorax •Pulmonary lymphangiectasis	

Cardiovascular (21.7%/17–35%)	•AV septal defect •AV septal with heterotaxia •Tricuspid dysplasia/Ebstein's anomaly •RV outflow obstruction/pulmonary valve •Truncus arteriosus •Premature closure of FO •LV outflow obstruct/aortic valve •Hypoplastic left/right heart •AV canal defect •Teratology of Fallot •Transposition of great vessels •Cardiopulmonary hypoplasia/hydrothorax •Premature closure DA/lung hypoplasia	Multifactorial 1–5%, genetic 75% (autosomal dominant 50%, autosomal recessive 25%)
	•Wolf–Parkinson–White syndrome	
	•Atrial flutter •Supra ventricular tachycardia	
	•Sinus bradycardia •Complete heart block	
	•High-output cardiac failure - Large AVM	Rare (< 1%)
	•Rhabdomyoma •Hemangioma •Hamartoma •Intrapericardial teratoma	All conditions are rare (< 1%)
	•Cardiomyopathy Dilated •Restrictive	
	Myocarditis	Rare (< 1%)
	Infarction	Rare (< 1%)
	Arterial calcification	25% recurrence estimate

Investigations

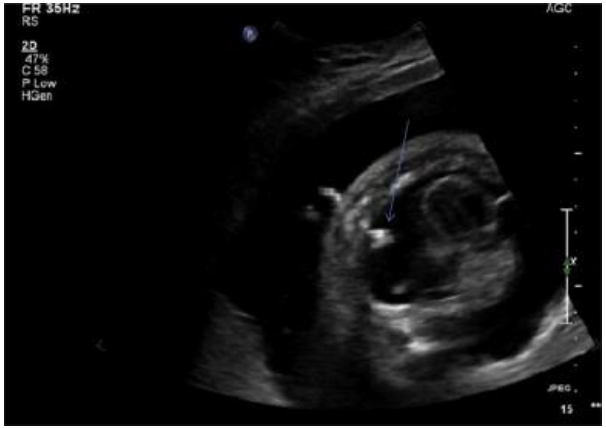


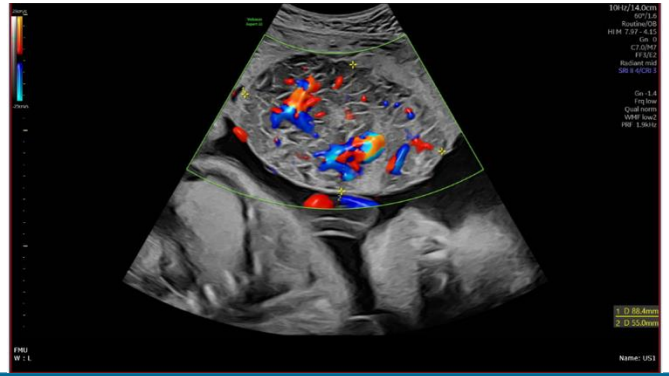
Step 3:

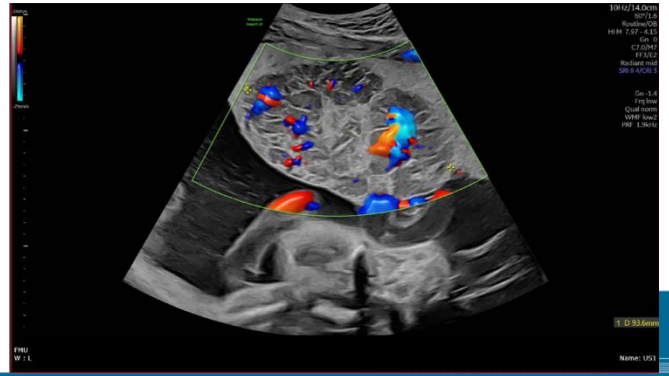
- Treatment if appropriate
- Plan management of pregnancy, labour and delivery
- Post delivery planning:
  - Neonatal management and investigations
  - Counselling for placental and post-mortem if relevant

Management options NIFH

- IUT if anaemia
- Laser or RITA for vessel abnormalities
- Antiarrhythmic drugs
- Thoracocentesis or shunt insertion
- Corticosteroids for CPAM
- Fetal antithyroid medications for fetal thyrotoxicosis







Survival by aetiology

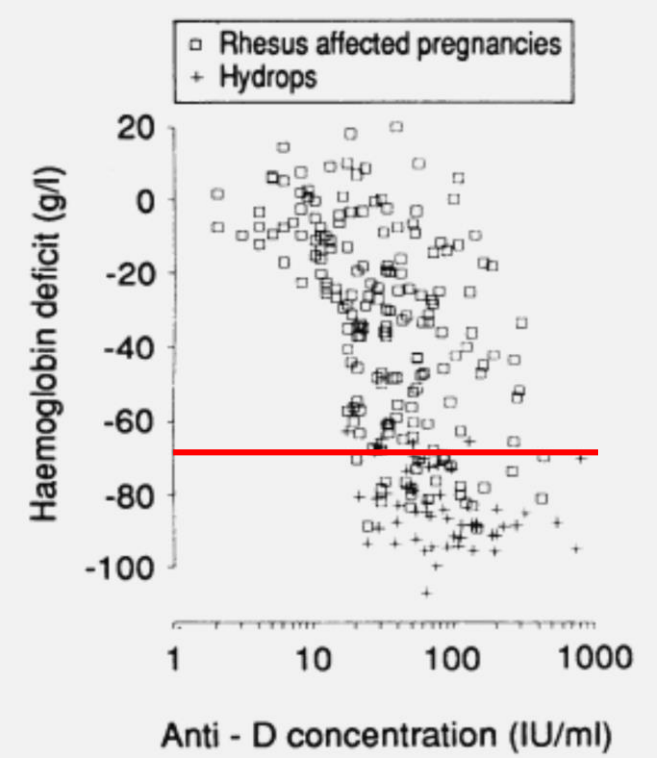
Table Survival by final aetiology (Gilby *et al.*) – single centre n=131 cases

Etiology	Number survived/total cases (%)
Chylothorax	3/3 (100%)
Infection	4/8 (50%)
Alloimmune	2/4 (50%)
Other	2/5 (40%)
Structural (non-cardiac)	7/18 (39%)
Idiopathic	9/41 (22%)
Cardiac	6/27 (20%)
Syndromal	3/25 (12%)
Total survival	**36/131 (27%)**

Rhesus disease: Fetal Anaemia

Ultrasound assessment

Hydrops ≡ Hb ≤5g/dl



Antibody titre

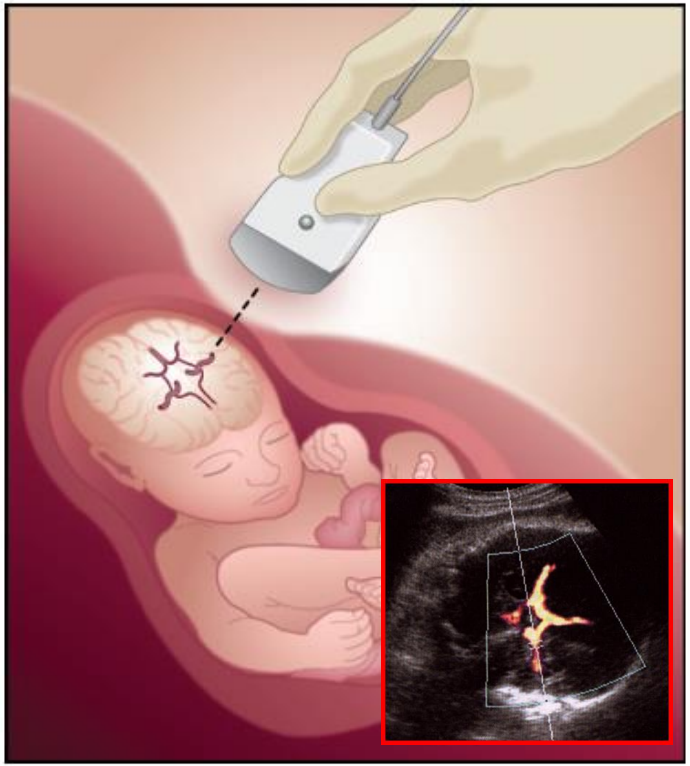
Potential for anaemia at >15iu/ml (or >1:128)

Refer at 10iu/ml or 1:64

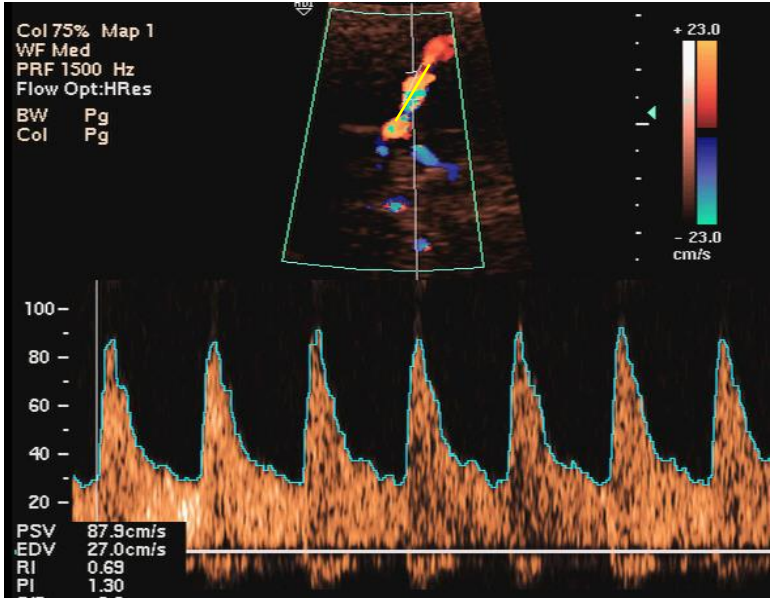
(Thilaganathan B et al. AmJOG 1988)

Prediction of Fetal Anaemia

Doppler assessment



Middle Cerebral Artery PSV



Mari G *et al.* NEJM 2000

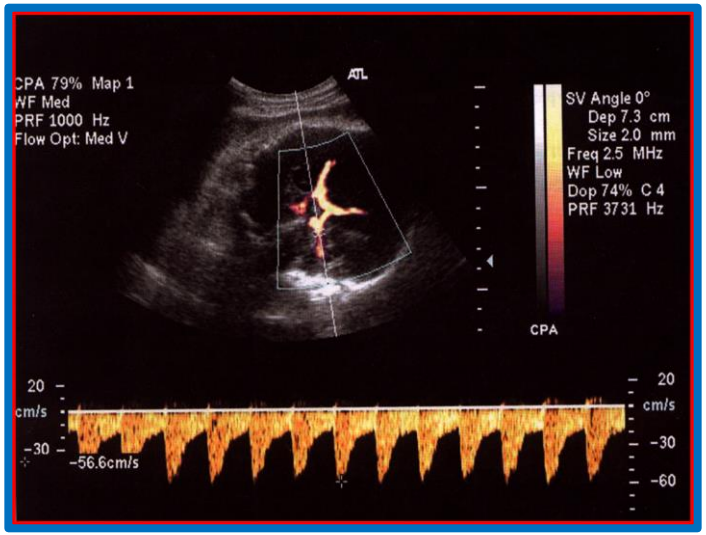
Pretlove SJ *et al*. BJOG. 2009 ;116(12):1558-67

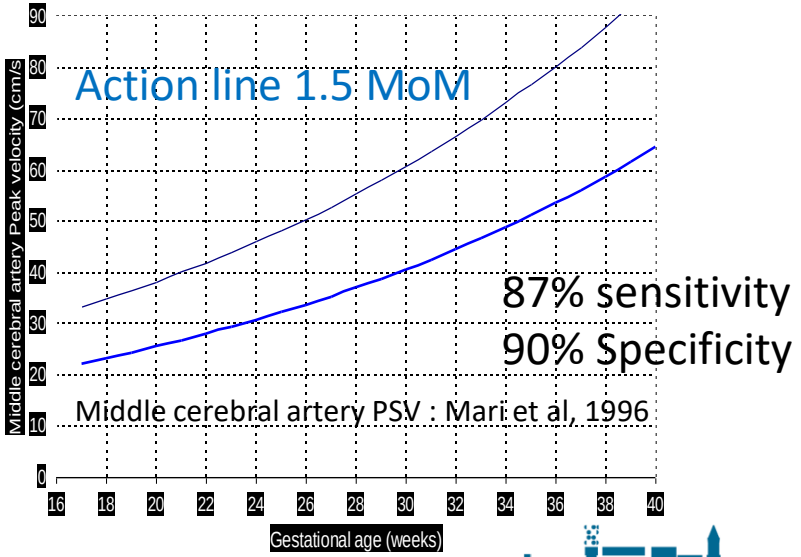
Noninvasive methods of detecting fetal anaemia: a systematic review and meta-analysis

SJ Pretlove,[a] CE Fox,[b] KS Khan,[b] MD Kilby[a,b]

[a] Fetal Medicine Centre, Birmingham Women's Foundation Trust, Edgbaston [b] School of Clinical and Experimental Medicine (Reproduction, Genes and Development), College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK
Correspondence: Dr SJ Pretlove, Birmingham Women's Hospital, Metchley Park Road, Edgbaston, Birmingham B15 2TG, UK.
Email sampretlove@doctors.net.uk

Pretlove S et al, BJOG. 2009;116:1558–1567





87% sensitivity
90% Specificity

Middle cerebral artery PSV : Mari et al, 1996

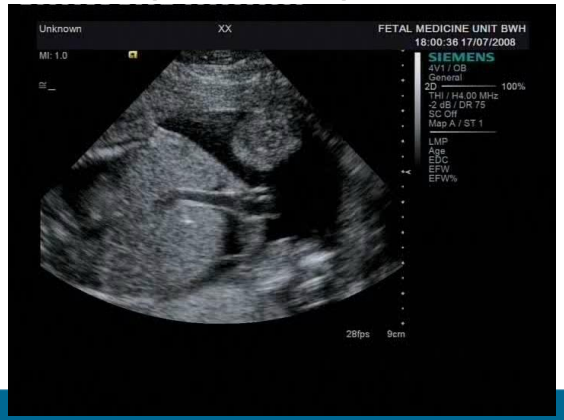
Non-invasive detection of anaemia : all aetiologies

Fetal IUTs : Outcome

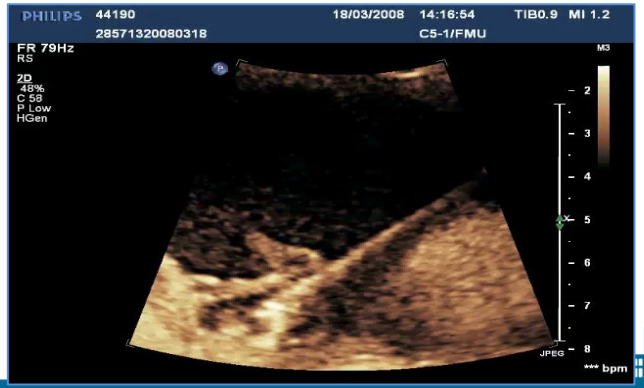
% Live births:	Overall	Non-hydrops	Hydrops
BWH, 1999-2019	98%	99%	94%
Literature (1998)	84%	94%	74%

Over an 8-year period, 1997-2004, 221 in-utero transfusions were performed for fetal anaemia *(Somerset et al. Fetal Diagn Ther. 2006;21(3):272-6).*

Intrahepatic vein puncture



Placental cord root



Prenatal, in-utero transfusion Ultrasound Obstet Gynecol 2017; 50, 180-186

Complications of intrauterine, intravascular blood transfusion:

- 1988 – 2015 in Netherlands
- 1678 IUTs were performed in 589 fetuses.
- Improvement in survival (1988 at 88.6% *vs* 2015 at **97.0%**, *P < 0.001*).
- Decline in total procedure-related complications per fetus (1988 at 9.8% vs 2015 at **3.3%**, *P = 0.001*).
- Procedure-related perinatal loss declined from 4.7% (1988) to **1.8% per fetus** in 2015 (*P = 0.053*).
- Improvements secondary to:
  - routine use of short acting fetal paralysis.
  - Increased use of intrahepatic vein at transfusion site.
  - Avoidance of umbilical arterial puncture.

DOI: 10.1111/1471-0528.12063
www.bjog.org

Increased perinatal loss after intrauterine transfusion for alloimmune anaemia before 20 weeks of gestation

ITM Lindenburg,[a] IL van Kamp,[a] EW van Zwet,[b] JM Middeldorp,[a] FJCM Klumper,[a] D Oepkes[a]

- **Fetal hydrops**
- **Small vessel size**

(more technically challenging)

- **Haemodynamic response to IUT**

	<20 weeks	≥ 20 weeks	*P*-value	OR (95% CI)
Per fetus, *n* (%)	(*n* = 29)	(*n* = 462)		
Perinatal loss	7 (24)	35 (8)	0.002	3.9 (1.4–10.4)
Per procedure, *n* (%)	(*n* = 37)	(*n* = 1385)		
Procedure-related	2 (5)	17 (1)	0.08	4.6 (0.0–21.9)
Not procedure-related	4 (11)	19 (1)	<0.001	8.7 (2.4–29.3)
Total perinatal loss	6 (16)	36 (3)	<0.001	7.3 (2.5–19.7)

(BJOG. 2013;120(7):847-52)

Other methods of delaying IUT

- Other transfusion methods (intraperitoneal)
- Plasmopheresis (mainly historical)
- **Potential medical options**

Medical options

- **There are four potential mechanisms of action for medical management of red cell alloimmunization.**
  - **Reduce** the amount of circulating maternal IgG antibody by preventing its production.
  - A molecule might **eliminate IgG** from the maternal or fetal circulation.
  - **Prevent IgG** against red cell antigen from crossing the placenta (via FcRn) into the fetal circulation.
  - Target the antibody–antigen complex and **alter the interaction** between the antibody and target fetal antigen.
- **Potential unwanted effects and cost**.
  - Maternal (or fetal) immunosuppression can lead to life-threatening infectious morbidity.
  - Maternal immune therapies may be expensive, time consuming, and demanding on healthcare resources.

Maternal immunoglobulin

Most commonly given IV at dose 0.4 - 2g/Kg

- IVIG is a plasma protein product derived from the pooled human plasma of between 3000 and 10,000 healthy donors.
- Process to inactivate/or remove bacterial and viral pathogens.
- The supply of immunoglobulin is limited
- IVIG are available in strengths of 3% to 12%
- Immunoglobulin has also been shown to be effective in a wide range of diseases where 'modulation' of the immune system.
- Adverse reactions (type III hypersensitivity) Headache / rash

Vox Sang 1991;61:181–189

0042–9007/91/0613–0181 $2.75/0

High-Dose Intravenous IgG for the Treatment of Severe Rhesus Alloimmunization

Miguel Margulies, Liliana S. Voto, Elena Mathet, Máximo Margulies

Department of Maternal-Fetal Medicine, Juan A. Fernández Hospital, University of Buenos Aires School of Medicine, Buenos Aires, Argentina

- 24 patients with 'severe' Rhesus disease.
- Three groups : i) <20 wk. ii) 20-28wks. iii) >28 weeks
- All in Liley zone III : 'pathologic'.
- 0.4g/Kg for 5 consecutive days & monthly until delivery.
- Three IUDs associated with 'hydrops' (12.5% were 'non-responders').
- All showed a fall in Anti-D levels & 'haemolysis'
- IVIG treatments were:

- <20 wks 3.5±2.5; 20-28wks 3.6±1; >28wks 2.5±0.5.
- All 21 (87.5%) survivors delivered >32 weeks in good condition

OBSTETRICS

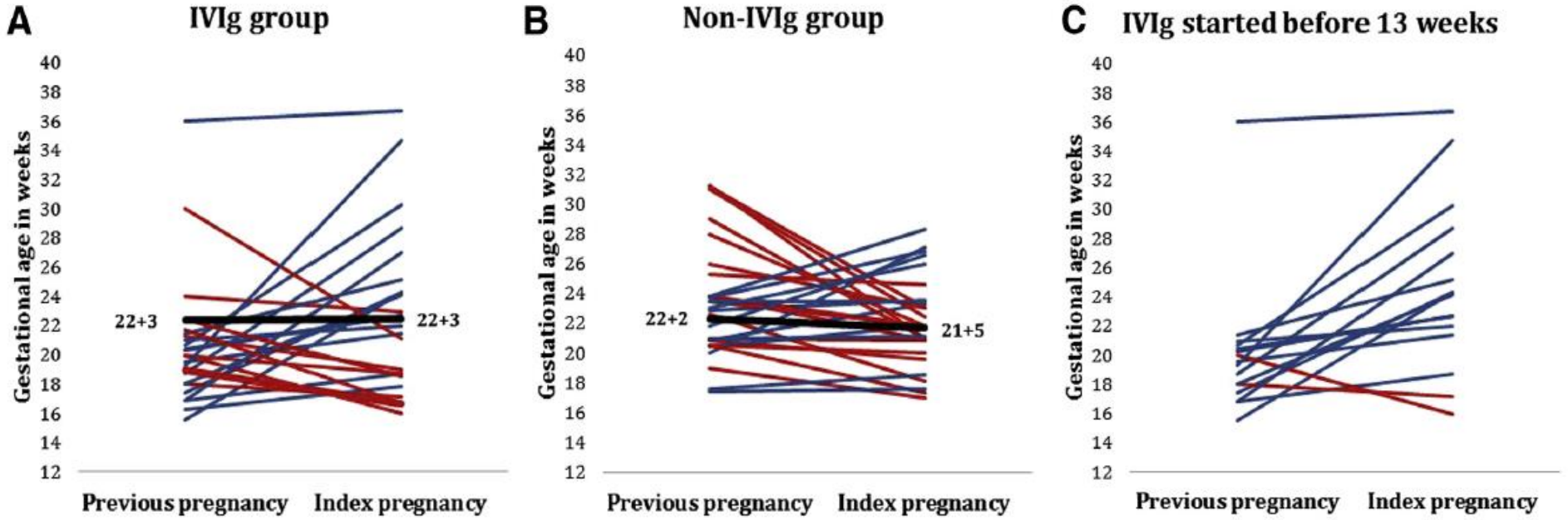
Postponing Early intrauterine Transfusion with Intravenous immunoglobulin Treatment; the PETIT study on severe hemolytic disease of the fetus and newborn

Carolien Zwiers, MD; Johanna G. van der Bom, MD, PhD; Inge L. van Kamp, MD, PhD; Nan van Geloven, PhD; Enrico Lopriore, MD, PhD; John Smoleniec, MD, PhD; Roland Devlieger, MD, PhD; Pauline E. Sim, BSc; Marie Anne Ledingham, MD, PhD; Eleonor Tiblad, MD, PhD; Kenneth J. Moise Jr, MD, PhD; Karl-Philip Gloning, MD, PhD; Mark D. Kilby, MD, PhD; Timothy G. Overton, MD; Ditte S. Jørgensen, MD; Katrine V. Schou, MD; Bettina Paek, MD; Martin Walker, MD; Emma Parry, MD; Dick Oepkes, MD, PhD; Masja de Haas, MD, PhD

- Consecutive pregnancies with RBC alloimmunisation
- Past history of severe disease (fetal anaemia ≤ 24 weeks).
- Index pregnancy managed with IVIG (n = 24)
- Managed without IVIG treatment (n = 28)

(Am J Obstet Gynecol. 2018;219(3):291.e1-291.e9)

PETIT study



- In 'index' pregnancies **with IVIG**, **fetal anemia developed** **average 15 days later** compared to the previous
- pregnancy without IVIG [8% less often <20 weeks].
- In pregnancies **without IVIG**, **anaemia developed** **9 days earlier** compared to previous pregnancy.
- **Starting IVIG <13 weeks significantly prolonged GA prior to anemia** & hydrops (p=0.01)

PETIT Study

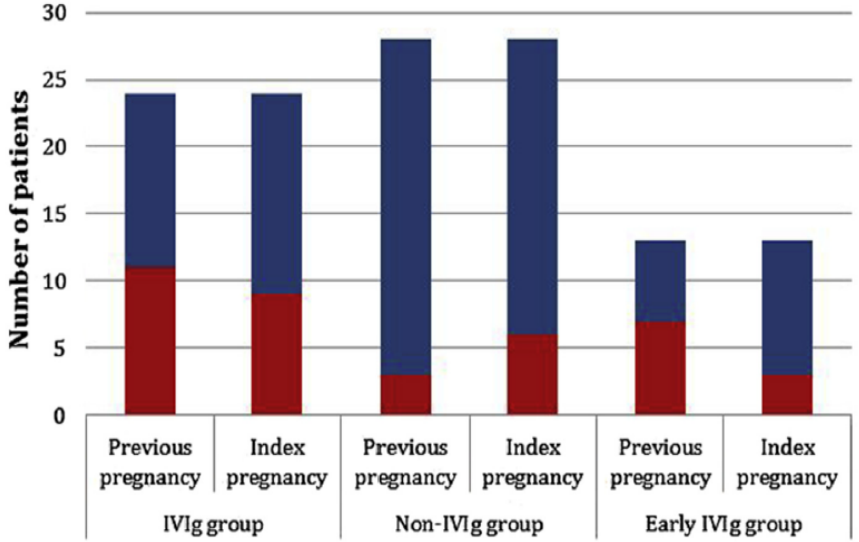
In the subcohort in which IVIG treatment was started <13 weeks, anaemia developed 25 days later & 31% less <20 weeks' gestation (54% compared to 23%) than in the previous pregnancy.

Fetal hydrops occurred in 4% of iIVIG-treated pregnancies and in 24% of those without IVIG treatment (odds ratio, 0.03; 95% confidence interval, 0-0.5; P = .011).

Exchange transfusions were given to 9% of neonates born from pregnancies with and in 37% without IVIG treatment
(OR, 0.1; 95% confidence interval, 0-0.5; P = .009).

(Am J Obstet Gynecol. 2018;219(3):291.e1-291.e9)

FIGURE 2
Onset of fetal anemia <20 weeks and >20 weeks gestation in previous and index pregnancies



Onset of severe anemia <20 weeks' gestations (red bars) and anemia >20 weeks' gestation (blue bars).

IVIg, intravenous immunoglobulin.

Zwiers et al. Prenatal intravenous immunoglobulin seems to improve course of alloimmunized pregnancies. Am J Obstet Gynecol 2018.

MOMENTA

- **FMC BWC NFT**
- **FMC UCL**

Momenta was founded in 2001 based on technology discovered and developed at the Massachusetts Institute of Technology (MIT)

A Multicenter, Open-Label Study to Evaluate the Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics of M281 Administered to Pregnant Women at High Risk for Early Onset Severe Hemolytic Disease of the Fetus and Newborn (HDFN)

ClinicalTrials.gov Identifier: NCT03842189

OBJECTIVES

Primary:

- To evaluate the **safety** in mother and neonate/infant of M281 administered to pregnant women at high risk for early onset severe HDFN (EOS-HDFN).
- To evaluate the **efficacy** of M281 as measured by proportion of patients with **live birth** at or after gestational age (GA) **32 weeks without intrauterine transfusion (IUT).**

Secondary:

- To evaluate the efficacy of M281 on antenatal management and outcome as measured by GA at **first fetal IUT, frequency of fetal IUT, and frequency of live birth.**
- To evaluate the efficacy of M281 on **postnatal management and outcome** as measured by severity of hyperbilirubinemia, phototherapy, exchange transfusions, and transfusions in the first 12 weeks of life.
- To evaluate the **PD activity** of M281 as measured by effects on maternal FcRn occupancy, and maternal and neonatal/infant levels of total IgG and alloantibodies.
- To evaluate the **PK** of M281 in human pregnancy.

UNITY clinical trial – baby outcome

- 12 out of 13 participants experience a live birth
- In pregnancies that met the primary endpoint of a live birth at gestational age of or after 32 weeks without IUTs (54 percent; n=7/13), one infant required a simple (blood) transfusion.
- In pregnancies requiring an IUT (n=6/13), all live-born infants (n=5/5) required a simple transfusion. Among the 12 live-born infants, one infant required an exchange (blood) transfusion.
- The median gestational age at the first IUT was 28 and 3/7 weeks (range: 24 1/7 – 31 5/7 weeks) for those with live births.
- There were no reports of fetal hydrops.
- One fetal demise following IUT at 22+5

Conclusion

- Rhesus is an uncommon disease – fetal mortality/morbidity
- Early-onset disease is highly problematic
- In women at risk of early-fetal IUT (<20 weeks) consider ‘medical management’ as adjuvant therapy.
- IV γ–immunologlobulin (especially <13 weeks) maybe useful.
- New “monoclonal antibodies” require evaluation.
- Need to investigate combination therapy IVIG and MAB by RCT

*Thank you for the invitation to give the **lecture** and for your attention!*