NHS
Blood and Transplant

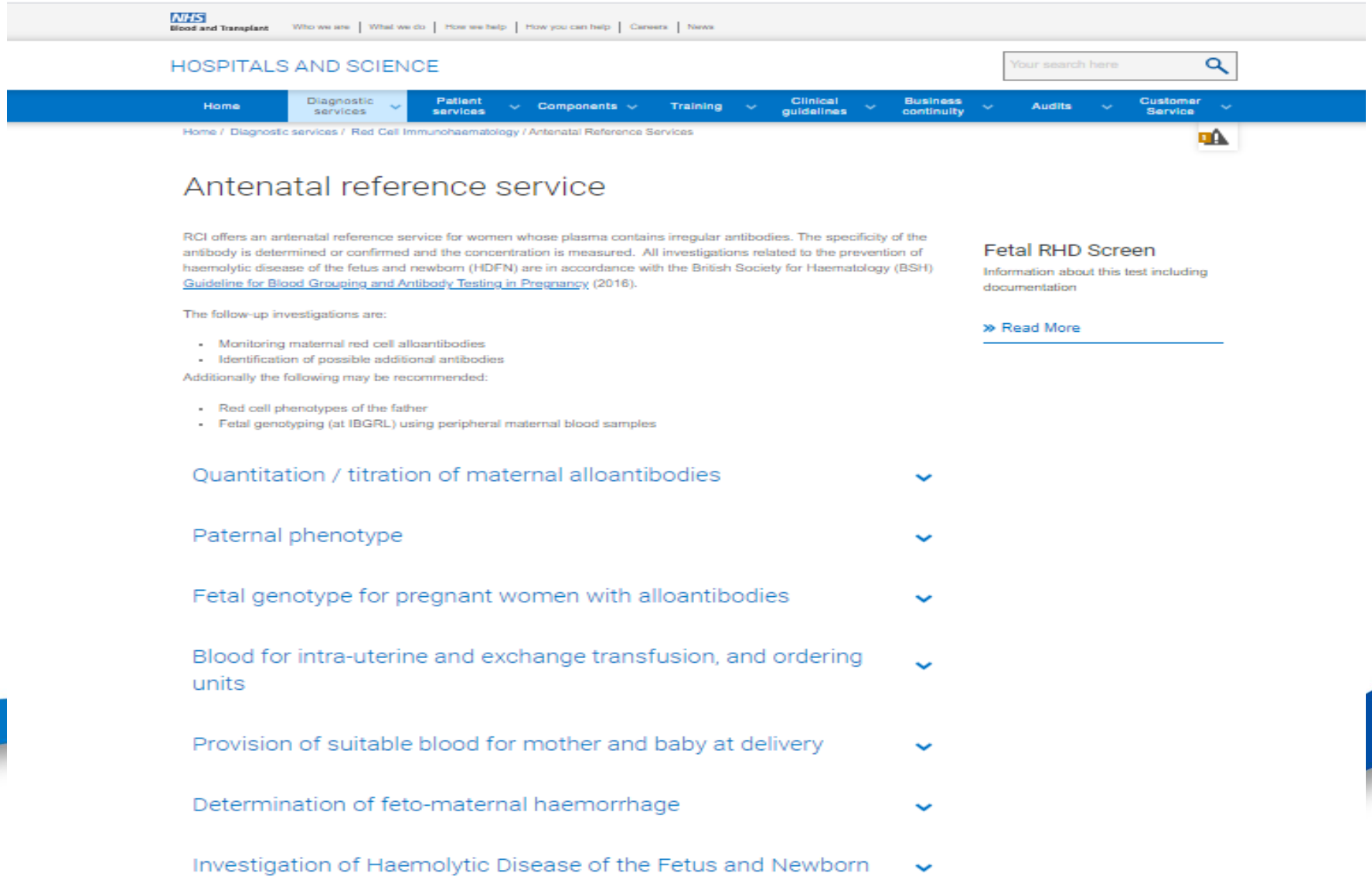
Are you ‘c’- rious?

Helen Thom

BMSEDG#7

Antenatal Referrals

NHS Blood and Transplant



Follow-up Recommendations

Anti-D, anti-c and Kell system antibodies most likely to cause significant HDFN

- BSH guidelines recommend sample taken and referred:
  - Every 4 weeks until 28 weeks' gestation
  - Every 2 weeks until delivery

Other clinically significant alloantibodies:

- Refer at booking and 28 weeks

At delivery:

- Direct Antiglobulin Test (DAT)
- Haemoglobin and Bilirubin monitored

Placental Transfer of Maternal IgG Antibodies

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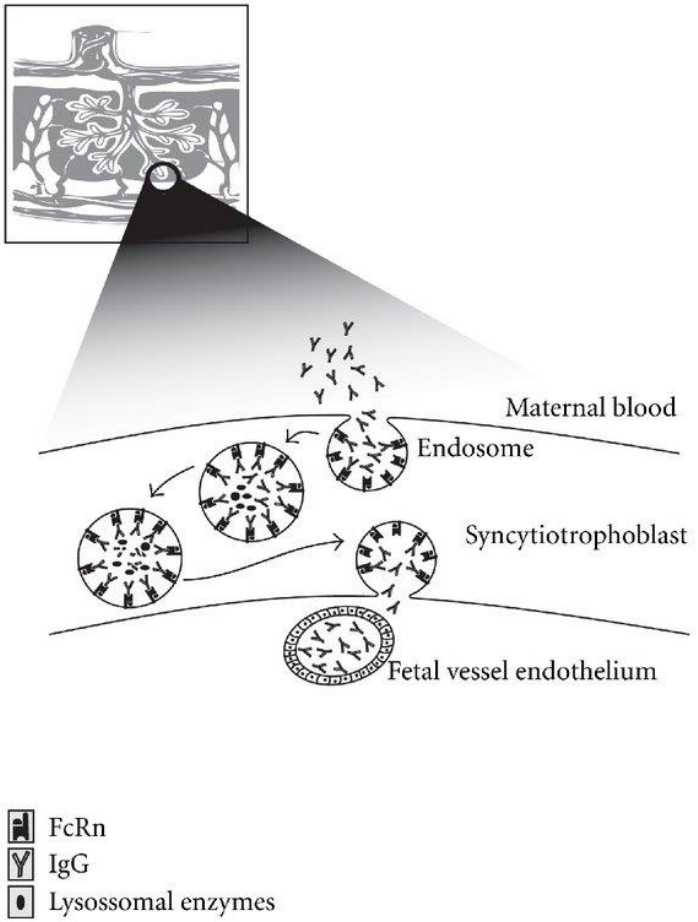
- Provides protection
- Fetus' immune response is inefficient
- IgG is the only antibody class which significantly crosses the human placenta
- FcRc expressed on syncytiotrophoblast cells



What is HDFN?

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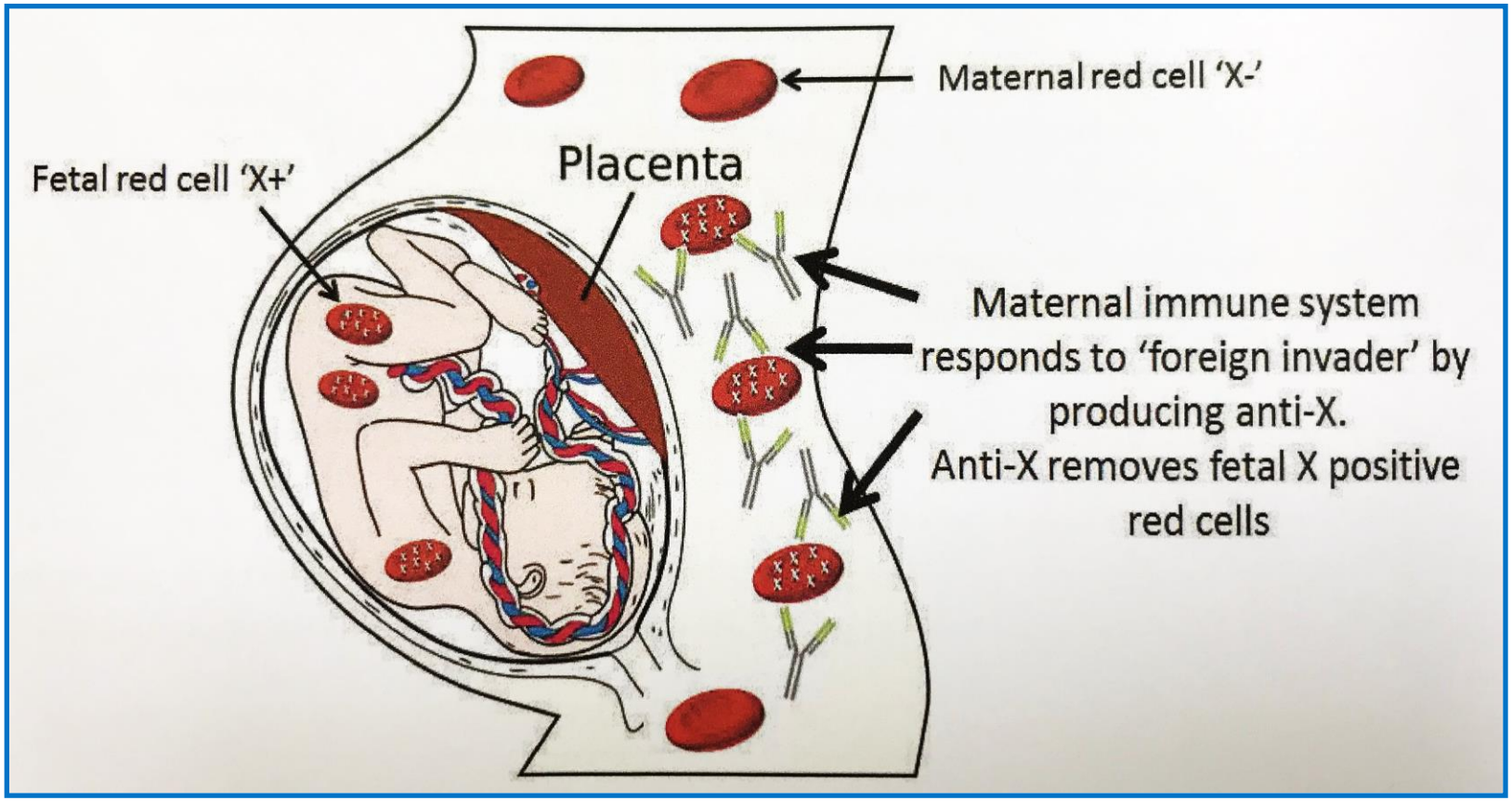


HDFN

NHS Blood and Transplant

- 1st pregnancy usually unaffected - sensitisation
- Subsequent pregnancies - secondary immune response
- Erythroblastosis fetalis
  - Hydrops fetalis
  - Jaundice
  - Kernicterus
  - Haemolytic anaemia
  - Extramedullary erythropoiesis
  - Hepatomegaly
  - Erythroblastosis

There are ways to assess risk for HDFN

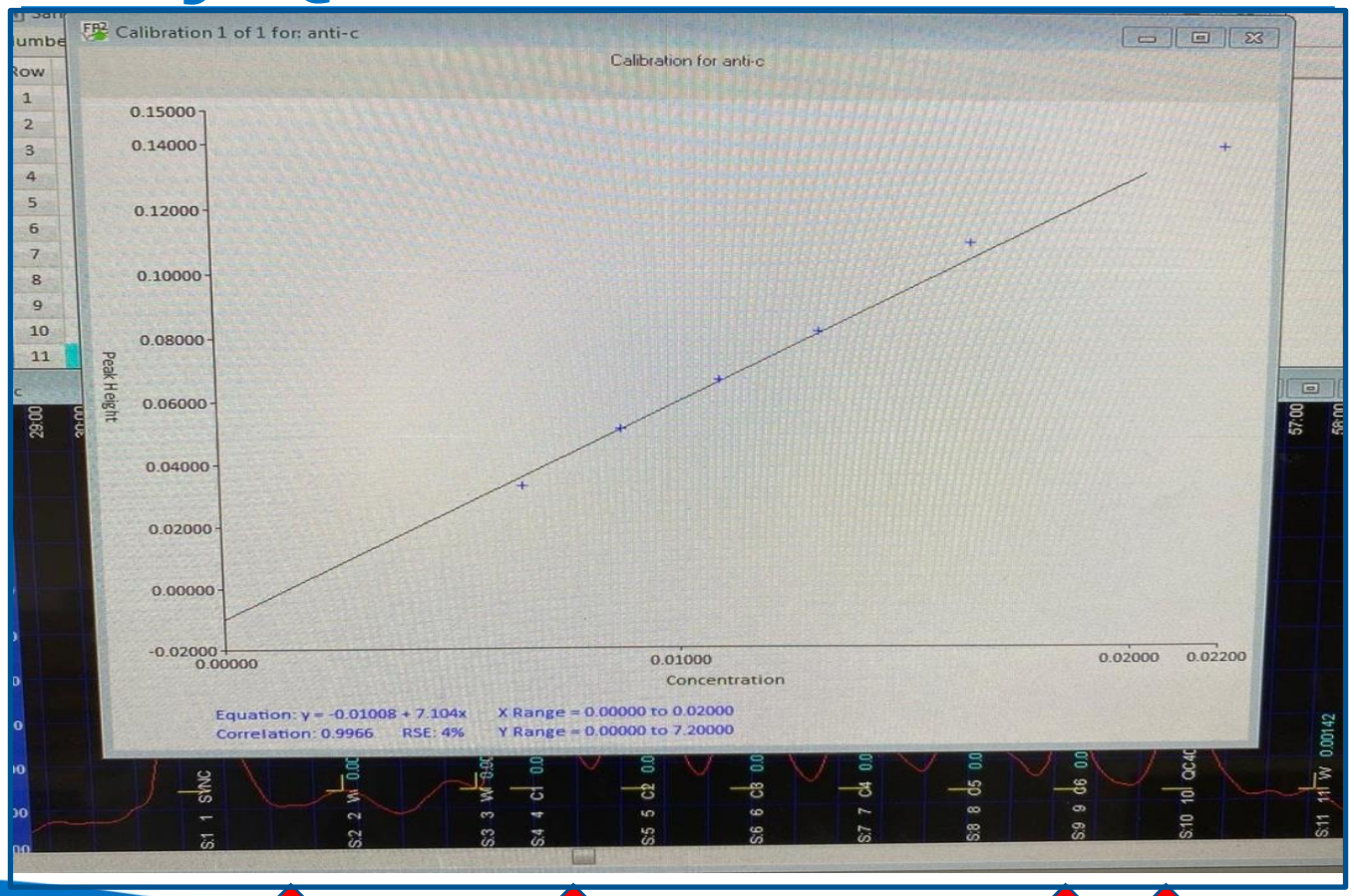
Antibody Quantification

NHS Blood and Transplant

- Continuous Flow Analyser
- Anti-D and anti-c
- Serial dilutions of maternal plasma
- NIBSC Standard
- R1R1 or rr red cell cocktail
- Results given in IU/mL

Antibody Quantification

NHS Blood and Transplant



Antibody Titration

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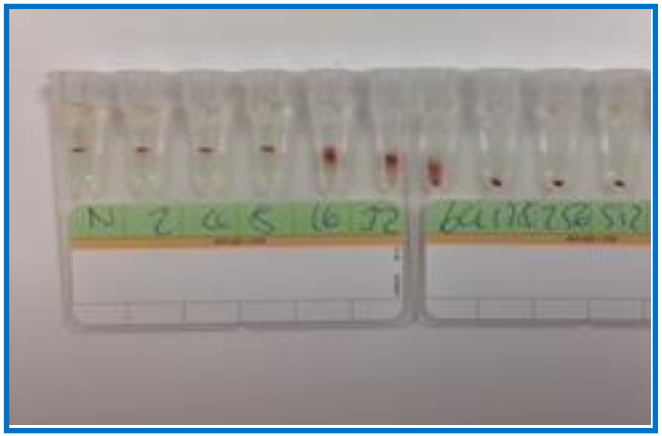
- Doubling dilutions
- Antibodies capable of causing HDFN
- Not anti-D and anti-c
- <32: low risk HDFN
- ≥32: high risk HDFN
- Kell system antibodies- titre not indicative of HDFN



'Heterozygous' expression

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The Patient

- Antenatal referral (December 2017)
- 28 weeks' gestation
- No booking sample
- Historical anti-c and anti-E
- Both clinically significant

BSH Guidelines

NHS Blood and Transplant

The presence of anti-Jka, anti-Jkb, anti-S, anti-s, anti-Fya and anti-Fyb should be excluded using red cells having ‘homozygous’ expression of the relevant antigen

A single example only of each phenotype is sufficient for exclusion

https://b-s-h.org.uk/guidelines/guidelines/pre-transfusion-compatibility-procedures-in-blood-transfusion-laboratories/

ABID Panel 1

Cell	Rh	D	C	E	c	e	M	N	S	s	P1	Lu^a	K	k	Kp^a	Le^a	Le^b	Fy^a	Fy^b	Jk^a	Jk^b	Other	IAT	EIAT
1	$R_1^wR_1$	+	+	0	0	+	+	0	+	+	0	0	0	+	0	0	+	+	0	+	0		0	0
2	R_1R_1	+	+	0	0	+	0	+	0	+	0	0	+	+	0	+	0	0	+	0	+		0	0
3	R_2R_2	+	0	+	+	0	+	0	+	0	0	0	0	+	0	+	0	0	+	+	0		4	5
4	r'r	0	+	0	+	+	0	+	+	0	0	0	0	+	0	0	+	0	+	+	0		3	5
5	r''r	0	0	+	+	+	0	+	0	+	4	0	0	+	0	0	+	+	0	0	+		4	5
6	rr	0	0	0	+	+	+	0	+	0	4	0	+	0	0	0	+	+	0	0	+		4	5
7	rr	0	0	0	+	+	0	+	0	+	2	+	+	+	0	+	0	0	+	+	0		4	5
8	rr	0	0	0	+	+	0	+	0	+	0	0	0	+	+	0	+	0	+	0	+		4	5
9	rr	0	0	0	+	+	+	0	0	+	2	0	0	+	0	+	0	+	0	0	+		4	5
10	rr	0	0	0	+	+	0	+	0	+	3	0	0	+	0	+	0	+	0	+	0		4	5
																						Auto	0	/
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Unable to exclude: anti-E, S, P1, Lua and Kpa

Why can't you exclude anti-S? 'Heterozygous'

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What next?

- Unable to exclude: anti-E, S, P1, Lua and Kpa
- Known anti-c and historic anti-E
- Why do we need to include or exclude additional specificities?
  - Provide antigen negative blood
  - Anti- P1, Lua and Kpa – crossmatch compatible by IAT
- Assess risk for HDFN
  - Antibody quantification and titration

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Reference panel 1 (R1R1 panel)

Cell	Rh	D	C	E	c	e	M	N	S	s	P1	Lu^a	K	k	Kp^a	Le^a	Le^b	Fy^a	Fy^b	Jk^a	Jk^b	Other	IAT
1	**$R_1^wR_1$**	+	+	0	0	+	+	0	+	+	**0**	**0**	**0**	+	**0**	**0**	+	+	**0**	+	**0**		0
2	**R_1R_1**	+	+	0	0	+	0	+	0	+	**0**	**0**	+	+	**0**	+	**0**	**0**	+	**0**	+		0
3	**R1Rz**	+	+	+	0	+	+	0	+	0	**0**	**0**	**0**	+	**0**	+	**0**	**0**	+	+	**0**		4
4	Rzr'	+	+	+	0	+	0	+	+	0	**0**	**0**	**0**	+	**0**	**0**	+	**0**	+	+	**0**		4
5	RoRo	+	0	0	+	+	0	+	0	+	**4**	**0**	**0**	+	**0**	**0**	+	+	**0**	**0**	+		4
6	R1R1	+	+	0	0	+	+	0	+	0	**4**	**0**	+	**0**	**0**	**0**	+	+	**0**	**0**	+		0
7	**R1R1**	+	+	0	0	+	0	+	0	+	**2**	+	+	+	**0**	+	**0**	**0**	+	+	**0**		0
8	R1R1	+	+	0	0	+	0	+	+	0	**0**	**0**	**0**	+	+	**0**	+	**0**	+	**0**	+		0
9	R1R1	+	+	0	0	+	+	0	0	+	**2**	0	**0**	+	**0**	+	**0**	+	**0**	**0**	+		0
10	R1R1	+	+	0	0	+	0	+	0	+	**3**	**0**	**0**	+	**0**	+	**0**	+	**0**	+	**0**		0
																						Auto	**0**
																						K control	**2**

BSH Guidelines Anti-c and E

- Anti-c
  - <7.5 IU/mL: low risk HDFN
  - 7.5-20 IU/mL: moderate risk HDFN
  - > 20 IU/mL: high risk HDFN
- Anti-E
  - Titre <32: low risk HDFN
  - Titre ≥32: high risk HDFN

https://b-s-h.org.uk/guidelines/guidelines/blood-grouping-and-antibody-testing-in-pregnancy/

NHS Blood and Transplant

Patient History

- November 2013: 13/40
- Pan-reactive enzyme antibody
- Repeat requested at 28 weeks
- Blood selection

  ABO compatible RhD+ c- E- K-
- No 28 week sample received

NHS Blood and Transplant

Patient History

- November 2014: TOP
- Anti-c and anti-E detected
- Anti-E titre: 32
- High Risk HDFN

- Anti-c quant: 0.2 IU/mL
- HDFN unlikely when anti-c <7.5 IU/mL

- Antibody card issued
- No repeat needed

Patient History continued..

- March 2016: 14/40
- Twin Pregnancy
- Anti-c: quant 0.1 IU/mL
- Anti-E: titre 8

Low risk HDFN (anti-E titre <32, anti-c quant <7.5 IU/mL)

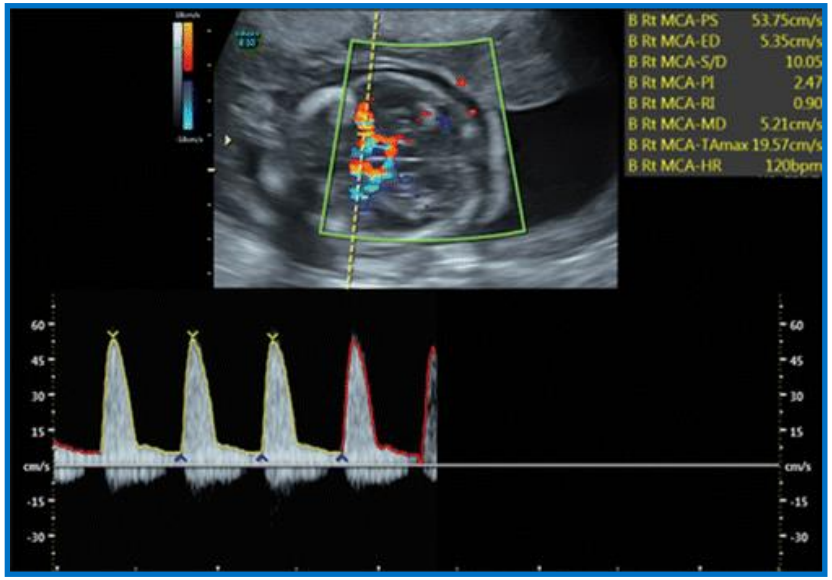
- Follow up samples requested (BSH guidelines)

- June 2016: 27/40
- Anti-c: previously reported
- Anti-E: titre 2

- August 2016: 32/40
- Anti-c: quant 0.5 IU/mL
- Anti-E: titre neat

Current Pregnancy

- 28/40
- Anti-c quant: 37.5 IU/mL
- High Risk HDFN (>20 IU/mL)
- Anti-E: insufficient for titre
- Repeat requested
- Referred to Fetal Medicine Unit
- MCA Doppler

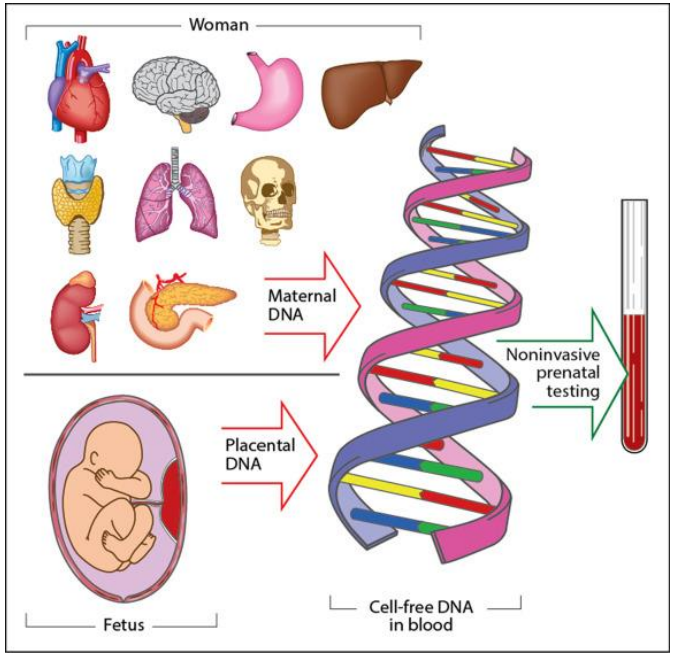


Further samples

- Repeats received 17/01/2018 (pre-IUT)
- 32/40
- c quant: 41.3 IU/mL
- E titre: 512
- High Risk HDFN
- Last sample we received

Fetal Genotype

- International Blood Grouping Laboratory
- Results received 16/01/18
- cff DNA
- Maternal blood
- Non-invasive
- Real time PCR
- ~ 16 weeks' gestation



This fetus is predicted c+ E+

IUT on 17/01/18

- HTL ordered O R1R1 K- IUT from HSD
- No R1R1 K- IUT unit on site
  - Newcastle no longer manufacturing site
- Patient travelled from Carlisle to FMU at RVI
- ~ 6 hours (min) for Manchester
- Had to issue non-IUT
- Best available irradiated adult unit as advised by RCI
- No CPD units

Units for IUT

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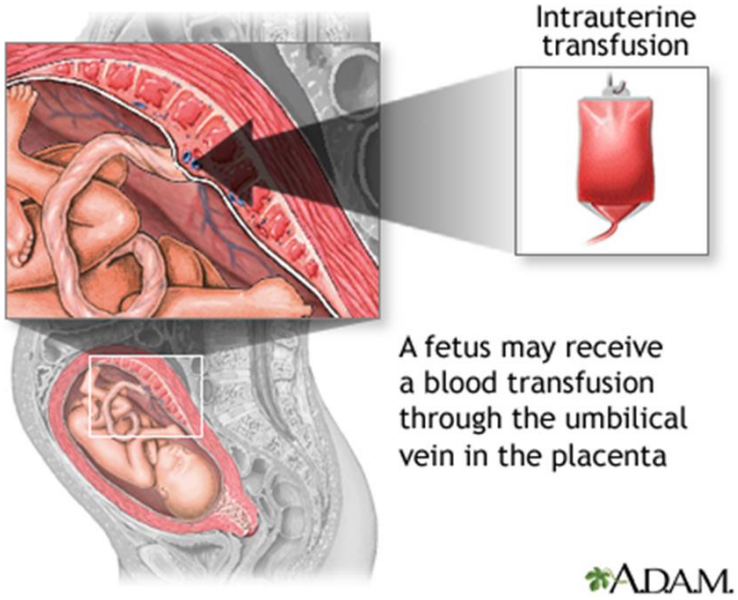
- Less than five days old
- High titre negative (HT-)
- HbS- K-
- Cytomegalovirus (CMV) seronegative
- PANTS-
- Citrate Phosphate Dextrose (CPD)
- HCT 0.70–0.85
- Irradiated – used with 24 hours of irradiation
- Selected phenotyped units
- Antigen negative for maternal antibodies
- O R1R1 K- (RhD+ C+ c- E- e+ K-)
- Crossmatched against maternal plasma

https://www.transfusionguidelines.org/red-book/chapter-7-specifications-for-blood-components/7-22-red-cells-for-intrauterine-transfusion-iut-leucocyte-depleted

Risks for IUT



- Invasive procedures with a risk of fetal death of 1-3% per procedure
- Up to 20% for hydropic fetuses
- Undertaken in specialised fetal medicine units
- Can be performed as early as 16/40
- 34-35/40 increased risk/benefit ratio

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Complications

- Miscarriage/preterm labour
- Fetal bradycardia
- Cord haematoma
- Vessel spasm
- Bleeding from puncture site
- Fetal death

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To transfuse or not to transfuse?

- Exposing fetus to sub-optimal adult product
- Serious clinical problems
- Potentially endangering baby
- Risk/benefit: procedure delayed for 24 hours
- IUT ordered from Manchester

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Quality Incident

"This was definitely a near miss and also reputationally damaging in terms of the Regional Fetal Medicine Department's view of NHSBT and our contingency plans"

Surprise!

NHS Blood and Transplant

- 13/02/18 - Hospital Blood Bank get call to say patient delivered
- EDD 16/03/18
- Unaware as Transfusion Laboratory not informed
  - Planned c-section
- Baby ‘unwell’
- Hb 77g/L (140g/L to 240g/L)
- Two exchange units required
- Only one unit in Newcastle

NHS Blood and Transplant

Provision of suitable blood for mother and baby at delivery

"Please inform the reference laboratory as soon as any woman with alloantibodies other than anti-D or anti-K is admitted for delivery, whether or not a sample has been referred. This will ensure that suitable antigen negative blood will be swiftly available for the mother and the baby"

Emergency Blood?

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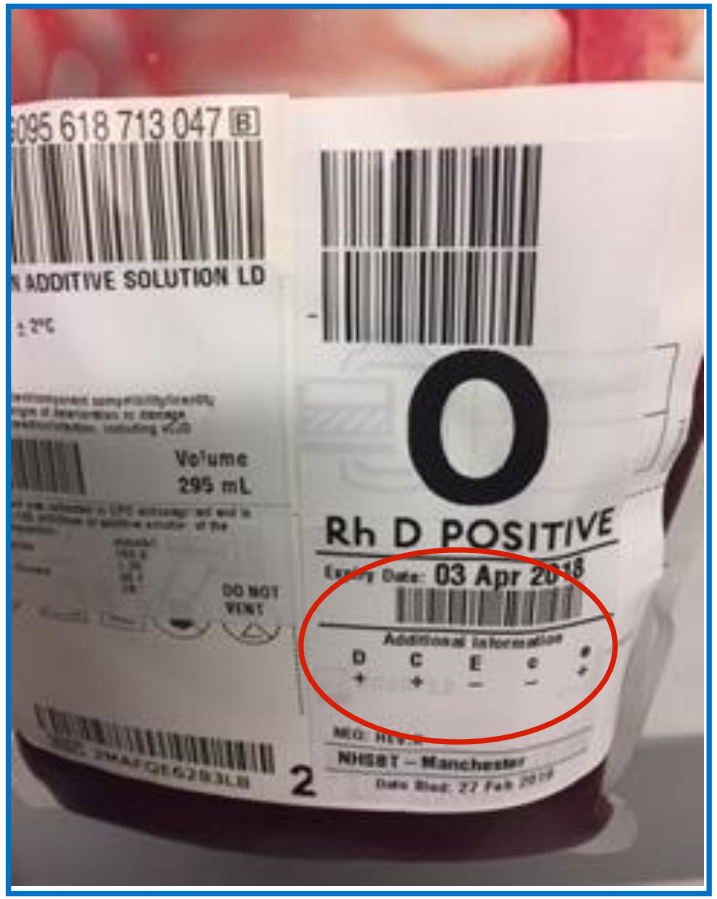


What next

- 2 exchange units requested
- Emergency delivery of exchange unit from Manchester
- ~ 6 hours to arrive
- Had to take 1 exchange and 1 Large Volume Transfusion
- Sent straight to RVI

Lessons Learned

- Need R1R1 IUT and exchange units at SHU
  - BSH guidelines state O+ IUT/exchange should be R1R1
  - O R1R1 K- IUT and exchange units now stocked at Newcastle
- CPD stock of R1R1
  - This was not available
  - Now have R1R1 CPD stock at Newcastle

Changes to Reporting 2021

NHS Blood and Transplant

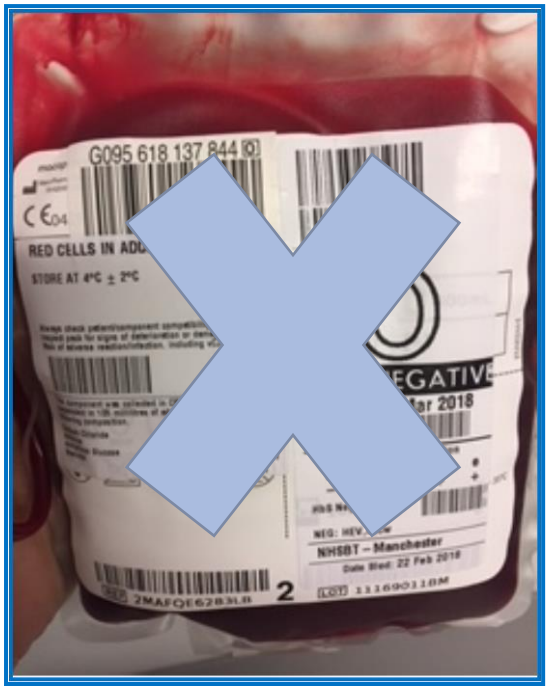
In antenatal cases where anti-E is found in the presence of anti-c, the following comment must be include on the report – ‘Combinations of antibodies may increase the relative risk of HDFN, therefore we recommend MCA Doppler monitoring at 28, 32 and 36 weeks gestation.’

Take Home Message

NHS Blood and Transplant

- Patient at the end of this
- High Risk Pregnancy
- Potential death of baby due to delay
- Already had miscarriage
- Stressful on patient and staff
- Communication is key
  - Between all departments

- O neg is not always the answer!



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Thank you for listening
Any questions?

c-riously?