North Bristol NHS Trust

South West Regional Transfusion Committee

Haemolytic Disease of the Fetus and Newborn

Janet Birchall

Mothers, babies and blood. 28th January 2015

Case history

- 30 yr old in 2nd pregnancy, EDD 14/1/16
- Booking – no αD
- 27+4 antibody screen + prophylactic 1,500iu αD

  Antibody +ve αD → flow cytometry. 0.4iu/ml

  Report "may be passive or immune. Continue prophylaxis & monitor as immune"
- Pregnancy remained under midwife care
- 33+4 αD 0.3iu/ml. Report 4/12/15 "suggestive of immune origin, continue monitoring"
- 37+3 labour, sample αD
- Following day discharged
- Day 3 post delivery, αD 87iu/ml

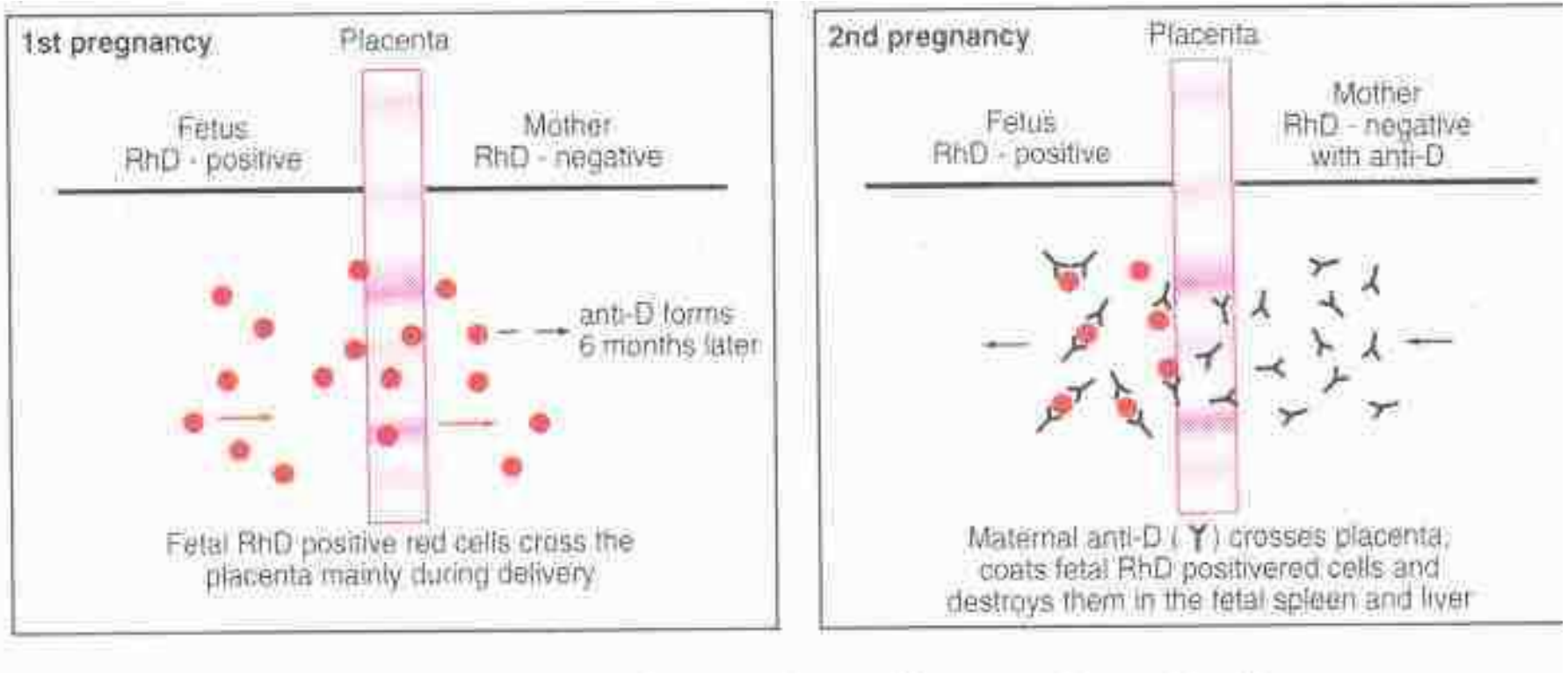
  Baby re-admitted – bilirubin 600

Case history, continued

- Treatment x2 ex tx units
- Now abnormal posture and EEG. MRI shows ↑ signal basal ganglia.
- Likely long term neurological damage

Figure 6.2 Mechanism of RhD Sensitisation during the 1st Pregnancy

ABC of Transfusion, 3rd Edition. Edited by Marcela Contreras

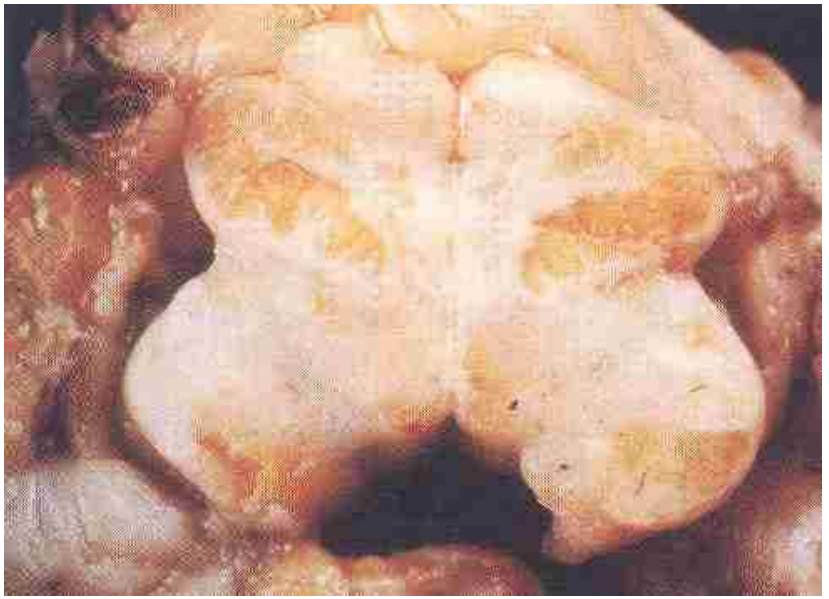


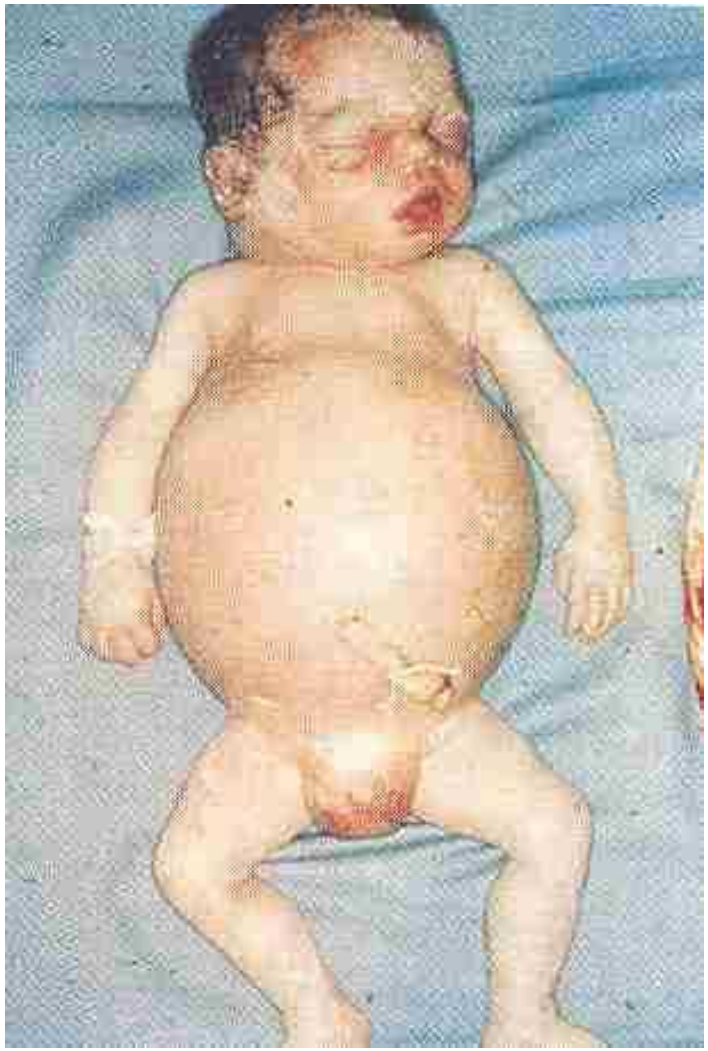
Haemolytic disease of fetus & newborn

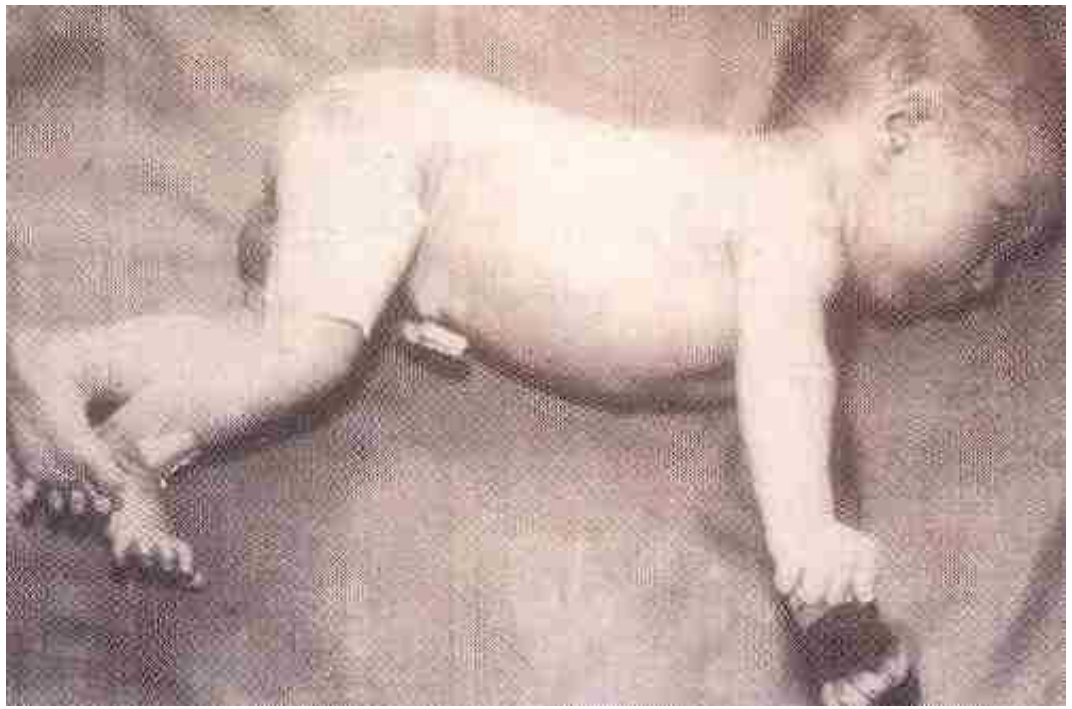
- Range in severity - detectable only in laboratory → infant with anaemia/jaundice → stillborn
- Risk of significant fetal anaemia low in 1st affected fetus
- Severity ↑ with each subsequent pregnancy

ABC of Transfusion, 3rd Edition.

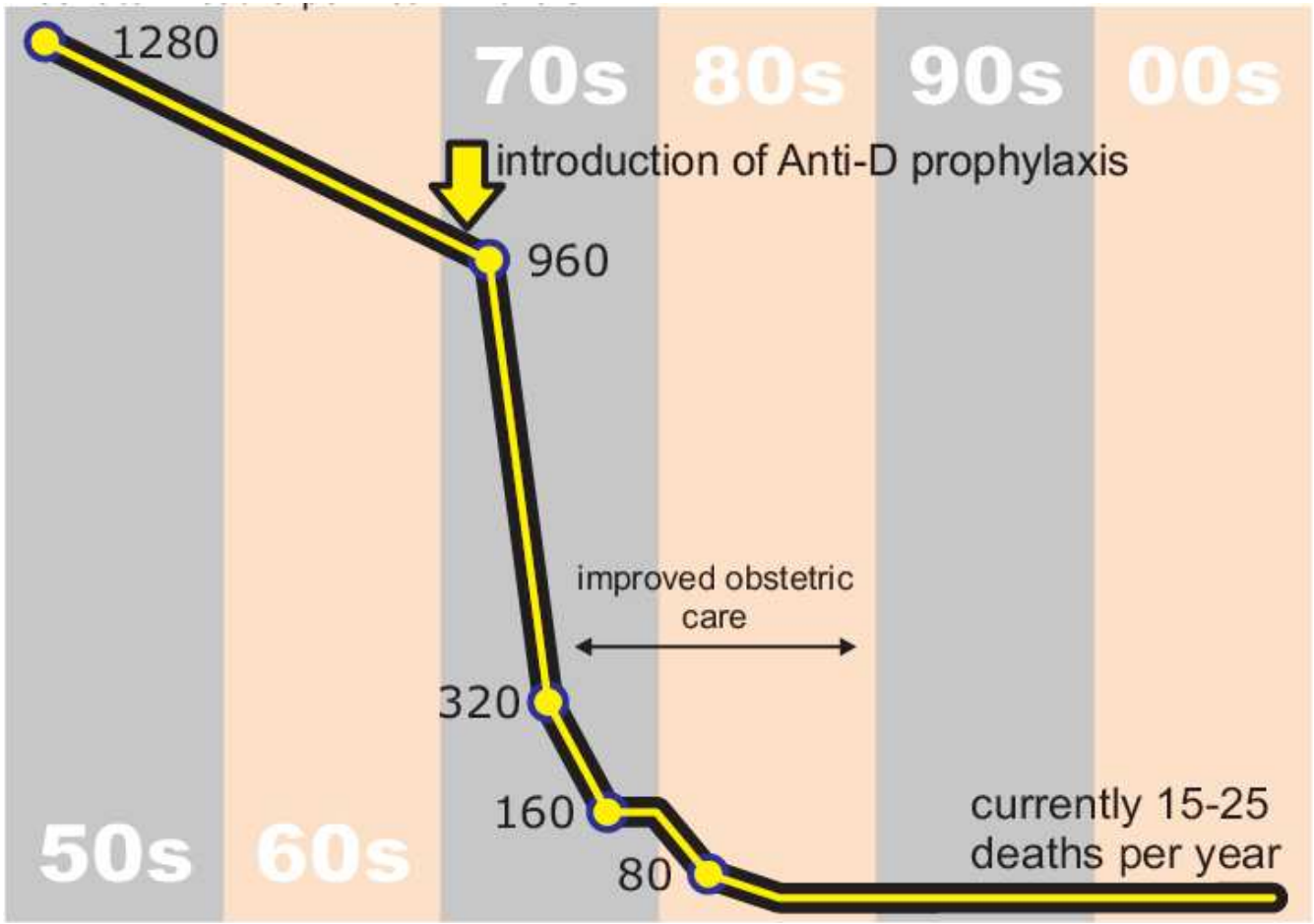
Hydrops Fetalis, Medulla, Infant with Kernicterus







The impact of Anti-D Ig



Mothers, babies and blood. 28th January 2015

Significant RBC antibodies

- What is the antibody
  - many antibodies capable of causing HDFN
  - anti-D,-c,-K cause the most serious disease

- How active is the antibody
  - antibody level/titre
  - past history of HDFN

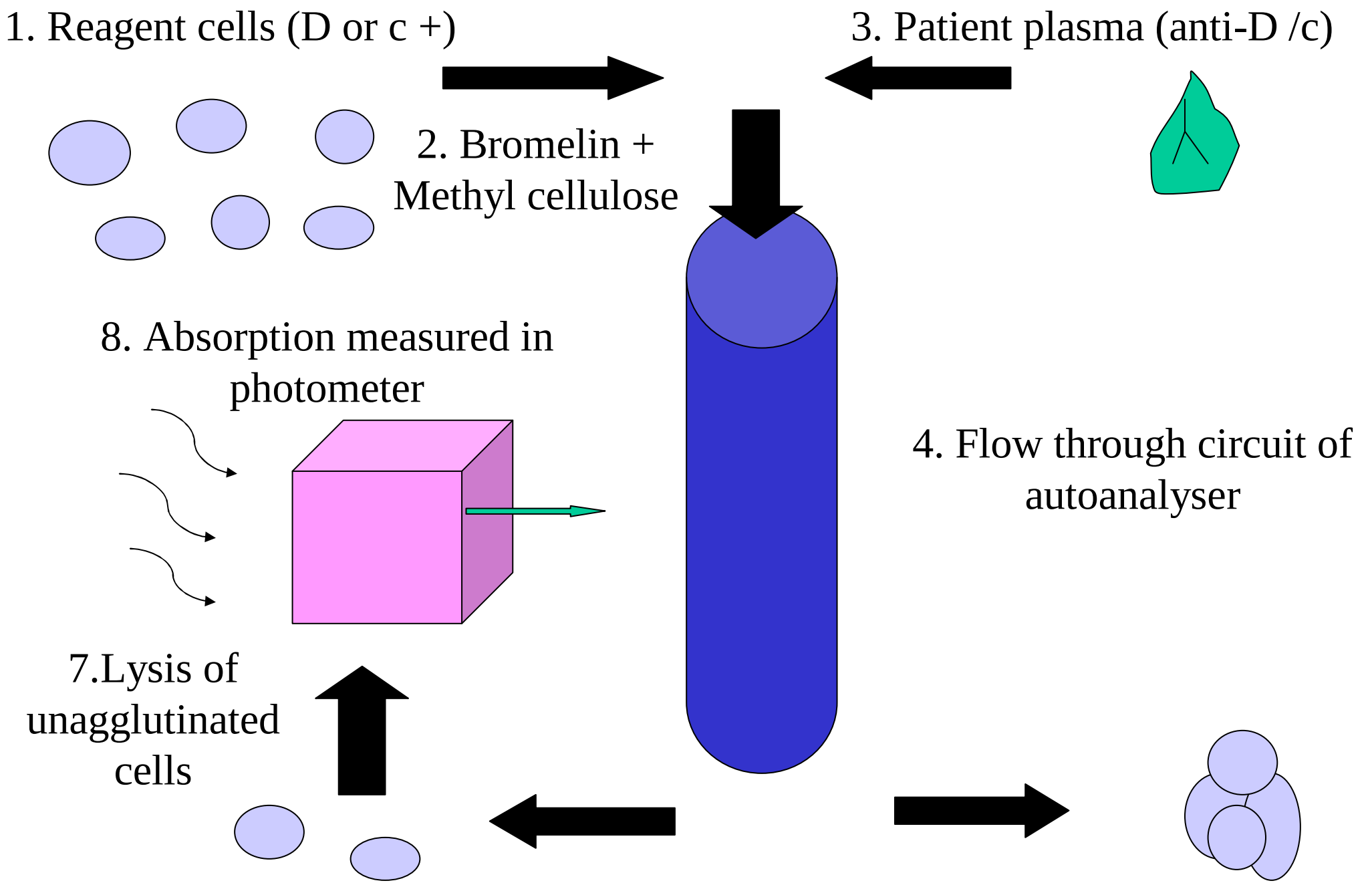
Determination of antibody titre or level

Titration:

- Serial dilution compared in parallel with previous sample
- Titre = reciprocal of the highest dilution which gives agglutination
- Inherently imprecise, reliant on experienced personnel

Quantitation: anti-D and anti-c

- Autoanalyser - more automated, greater reproducibility

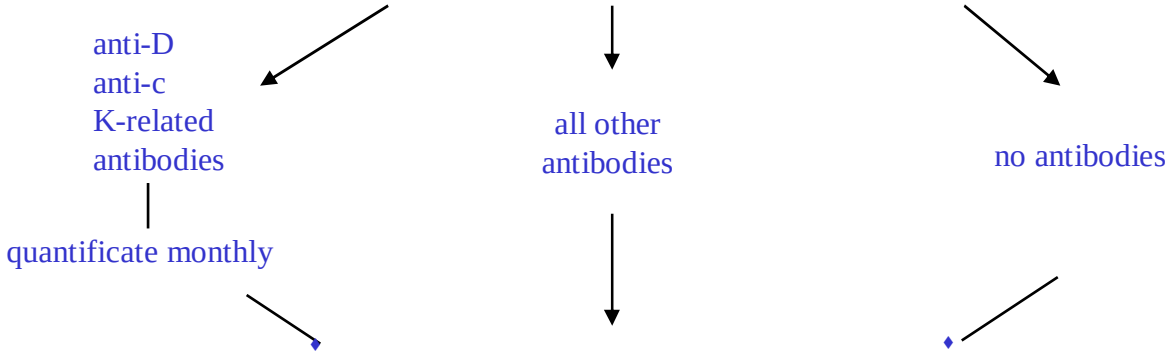

1. Reagent cells (D or c +)
3. Patient plasma (anti-D /c)
2. Bromelin +
Methyl cellulose
8. Absorption measured in
photometer
4. Flow through circuit of
autoanalyser
7.Lysis of
unagglutinated
cells
6. Unagglutinated red cells flow through
5. Agglutinated cells precipitate

SEROLOGICAL TESTING DURING PREGNANCY

12-16 weeks (booking)

ALL PREGNANT WOMEN

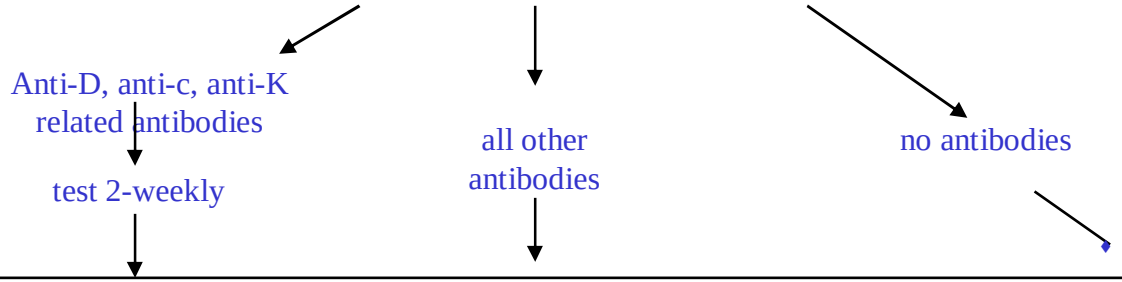
test ABO + RhD blood groups
+ antibody screen



28 weeks

ALL PREGNANT WOMEN

recheck RhD group
+ antibody screen/test



at delivery

Cord red cell DAT. If DAT+, do Hb and serum bilirubin + treat as appropriate.

test cord rbc
D group if
mother D negative.

Haemolytic disease due to anti-c & anti-K

- **Anti-c**
  - c Ag common therefore immunised by transfusion
- **Anti-K**
  - ↓ fetal erythropoiesis →↑anaemia ↓haemolysis
  - often transfusion induced
  - check husband's K type,
    - if Kk or unknown monitor monthly/2 weekly
    - If "confirmed father" K-ve (91% K –ve) ↓ monitoring

Antibody level and risk of HDFN

anti-D iu/ml

<4	-	low
≥ 4	-	mod
>15	-	high

anti-c iu/ml

<7.5	-	low
≥7.5	-	mod
>20	-	high

other abs - HDN unlikely when titre <32

ABO HDFN

- ABO incompatible infants have ↓ Hb, ↑bilirubin
- more common in Asia, ME, S. America
- maternal IgG anti-ABO titre not predictive
- neonatal jaundice is first sign and prompts investigation
- usual O mother and A or B baby
- first incompatible infant is affected in 50% of families

If prev h/o ABO HDN

- consider fetal monitoring in subsequent pregnancy
- hospital delivery
- cord ABO gp, DAT, bilirubin, Hb (baseline)
- do not discharge early
- community midwife to monitor baby

Fetal Medicine Unit

- Refer FMU
  - Level/titre anti-D $\geq$ 4 or c $\geq$ 7.5, other antibody titre $\geq$ 32
  - rising level
  - previous history of HDFN
- Investigation
  - partner homozygous/heterozygous? If heterozygous consider fetal genotyping of maternal blood for D (c,K) Caution father or partner ?
  - ? evidence of fetal anaemia

Tests used by obstetricians to predict fetal anaemia

Ultrasound

- placental thickness
- umbilical vein diameter
- liver length
- spleen perimeter

Doppler

- measure fetal blood flow - middle cerebral artery

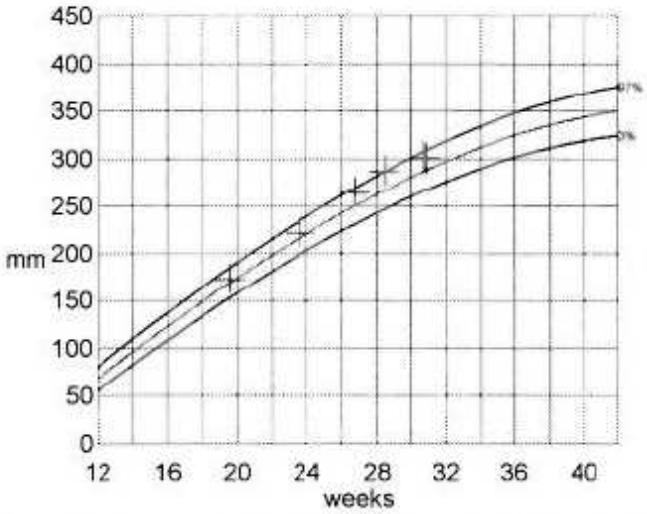
→

- useful to assess fetal maturity
- does not identify early fetal disease - changes visible only once hydrops has occurred
- weak correlation with fetal Hct/Hb

→

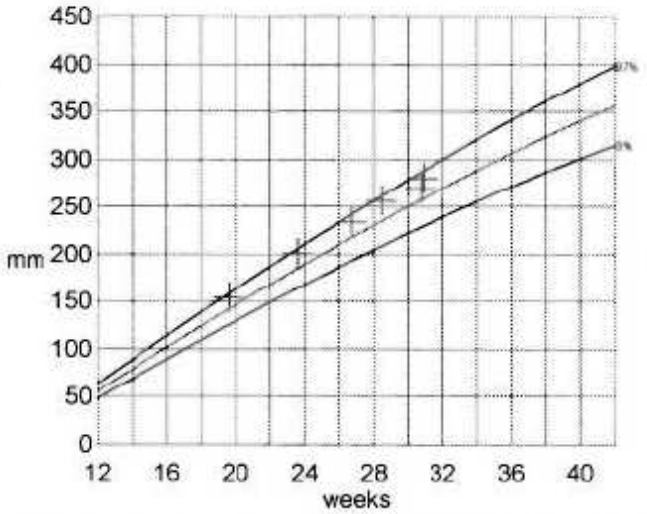
- detects early fetal anaemia

Head circumference



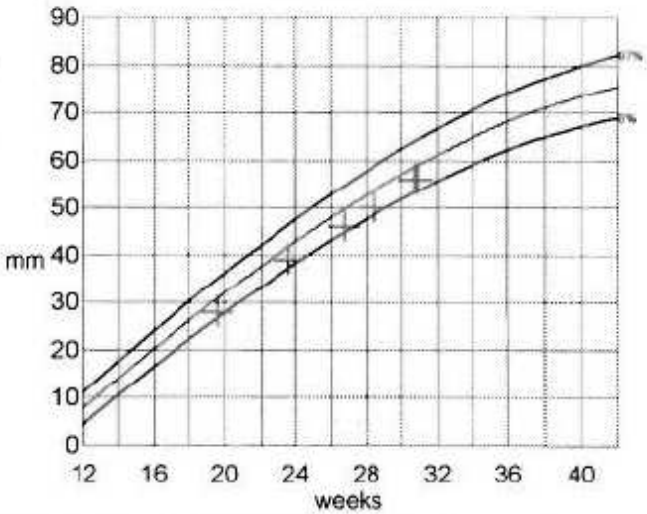
Chitty LS, Altman DG, Henderson A, Campbell S. Charts of fetal size: 2. Head measurements. Br J Obstet Gynaecol 1994; 101: 35-43

Abdominal circumference



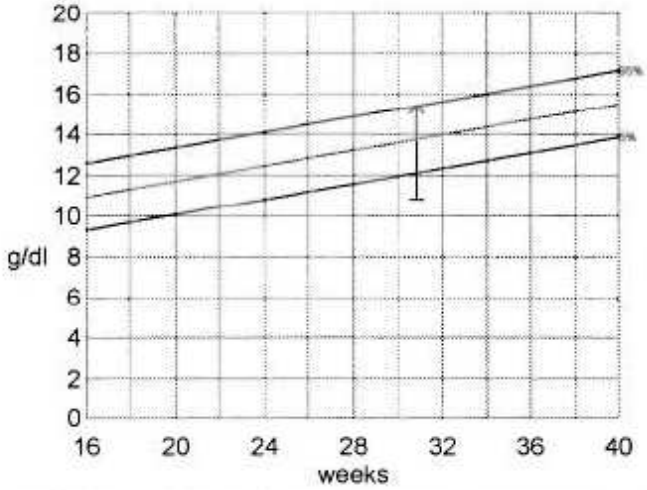
Chitty LS, Altman DG, Henderson A, Campbell S. Charts of fetal size: 3. Abdominal measurements. Br J Obstet Gynaecol 1994; 101: 125-131

Femur length



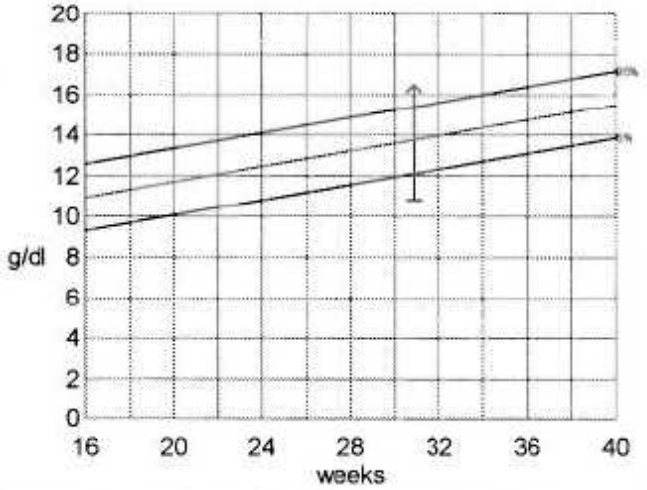
Chitty LS, Altman DG. Charts of fetal size: limb bones. Br J Obstet Gynaecol 2002; 109:919-929

Hb post - calculated



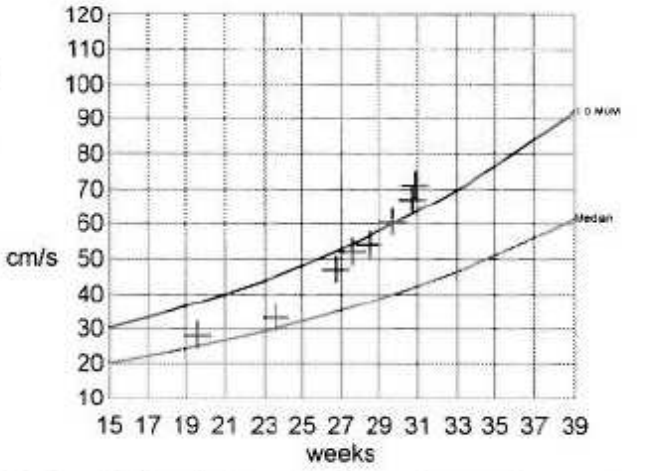
Nicolaides KH, Soothill PW, Clewell WH, Rodeck CH, Mibashan RS, Campbell S. Fetal haemoglobin measurement in the assessment of red cell isoimmunisation. Lancet 1988; 1: 1073-1075

Hb post - measured

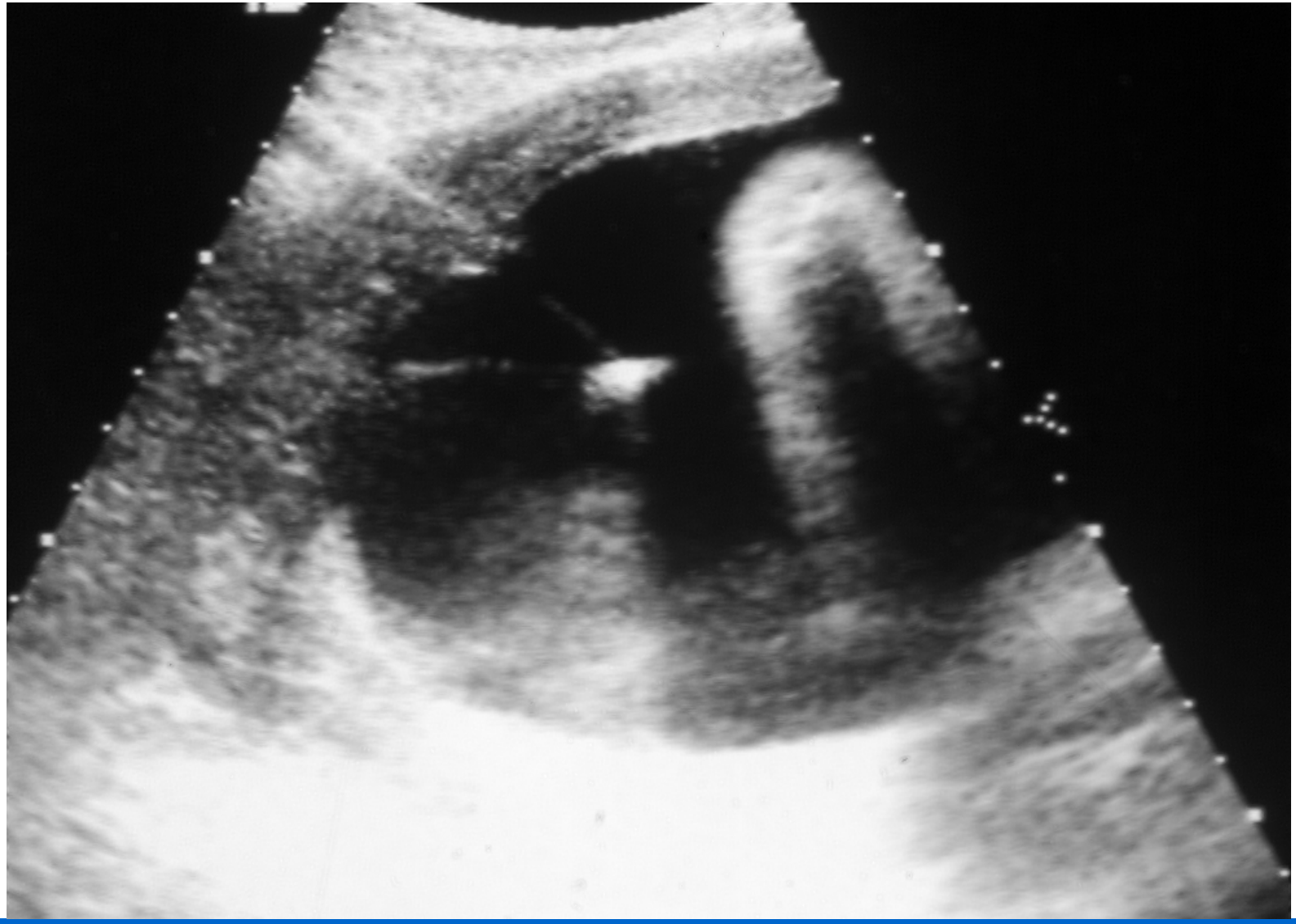


Nicolaides KH, Soothill PW, Clewell WH, Rodeck CH, Mibashan RS, Campbell S. Fetal haemoglobin measurement in the assessment of red cell isoimmunisation. Lancet 1988; 1: 1073-1075

Left Middle Cerebral A. Vmax



Mari G et al. Noninvasive diagnosis by Doppler ultrasonography of fetal anemia due to maternal red-cell alloimmunization. Collaborative Group for Doppler Assessment of the Blood Velocity in Anemic Fetuses. N Engl J Med 2000; 342: 9-14



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At birth if DAT +ve monitor bilirubin & Hb

Consensus-based bilirubin thresholds for the management of babies of 38 weeks or more gestational age with hyperbilirubinaemia

Age (hours)	Bilirubin measurement (micromol/litre)			
0			> 100	> 100
6	> 100	> 112	> 125	> 150
12	> 100	> 125	> 150	> 200
18	> 100	> 137	> 175	> 250
24	> 100	> 150	> 200	> 300
30	> 112	> 162	> 212	> 350
36	> 125	> 175	> 225	> 400
42	> 137	> 187	> 237	> 450
48	> 150	> 200	> 250	> 450
54	> 162	> 212	> 262	> 450
60	> 175	> 225	> 275	> 450
66	> 187	> 237	> 287	> 450
72	> 200	> 250	> 300	> 450
78		> 262	> 312	> 450
84		> 275	> 325	> 450
90		> 287	> 337	> 450
96+		> 300	> 350	> 450
Action	↓	↓	↓	↓
	Repeat bilirubin measurement in 6–12 hours	Consider phototherapy and repeat bilirubin measurement in 6 hours	Start phototherapy	Perform an exchange transfusion unless the bilirubin level falls below threshold while the treatment is being prepared

Exchange transfusion pathway

Offer information to parents and carers about exchange transfusions and intravenous immunoglobulin (IVIG) including:

- why the treatment is being considered
- anticipated duration of treatment
- possible adverse effects
- when it will be possible for parents or carers to see and hold the baby
- the need to admit the baby to intensive care for an exchange transfusion (if needed)

During exchange transfusion do not:

- stop continuous multiple phototherapy
- perform a single-volume exchange
- use albumin priming
- routinely administer intravenous calcium

Prepare for exchange transfusion

- Initiate/maintain continuous multiple phototherapy
- Use IVIG (500 mg/kg over 4 hours) for babies with Rhesus or ABO haemolytic disease if serum bilirubin level rises by more than 8.5 micromol/litre/hour

Serum bilirubin level falls to below threshold for exchange transfusion

Baby has:

- bilirubin level that remains above threshold for exchange transfusion **and/or**
- clinical signs of acute bilirubin encephalopathy

Continue multiple phototherapy and perform exchange transfusion

Continue multiple phototherapy and measure bilirubin level within 2 hours of exchange transfusion and manage according to threshold table and treatment threshold graphs

Go to 'Manage hyperbilirubinaemia' box in 'Investigation pathway' (see pages 10–11)

Summary

- RBC survival ↓ by placental transfer of maternal antibody
- Clinical severity ranges from unaffected to stillborn
- Mortality ↓ since 1950's from detection, prevention, monitoring and antenatal & neonatal intervention
- HDFN from Anti-D, anti-c, anti-K > other antibodies
- Low risk1st affected pregnancy. Risk ↑ future pregnancies
- Serology – detect at risk pregnancy & monitor mild HDFN
- FMU if > mild HDFN or P/H, for further Ix & monitoring
- AN intervention – IUT or delivery
- PN intervention - phototherapy, IVIG, Ex. transfusion