North Bristol NHS Trust

South West Regional Transfusion Committee

Characteristics and Management of Haemolytic Disease of the Fetus and Newborn

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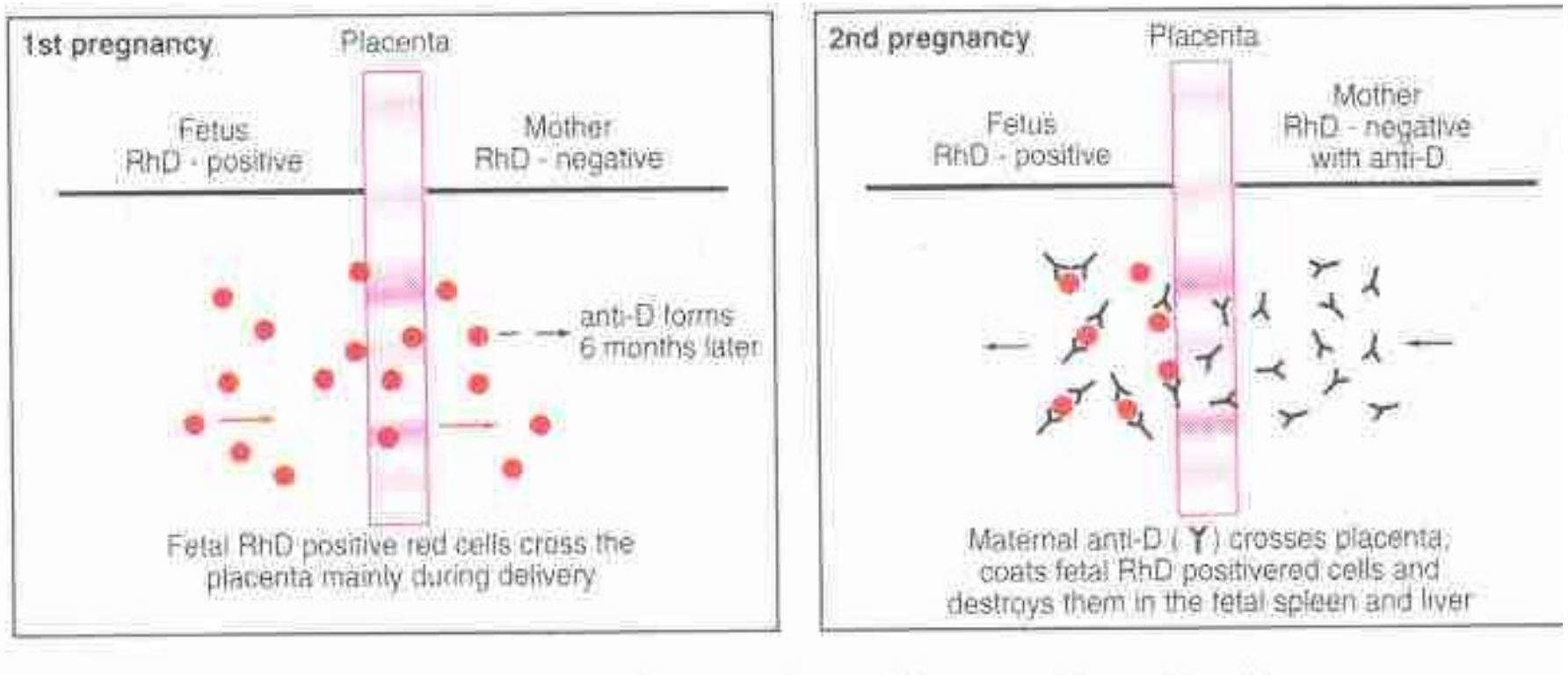
Mothers, babies and blood. 8th March 2012

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

- ***Definition*** - fetal/neonatal rbc lifespan ↓ by placental transfer of antibodies from mother
  - a positive DAT only denotes rbc coated with antibody
  - must have a ↓Hb +/- ↑bilirubin

- HDFN can range in severity from detectable only in laboratory tests, to birth of infants with anaemia and jaundice to stillborn

Stillbirth with Hydrops Fetalis

Figure 6.5, ABC of Transfusion, 3rd Edition. Edited by Marcela Contreras

Section of Medulla *Figure 6.4.*

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

Infant with Kernicterus *Figure 6.3*

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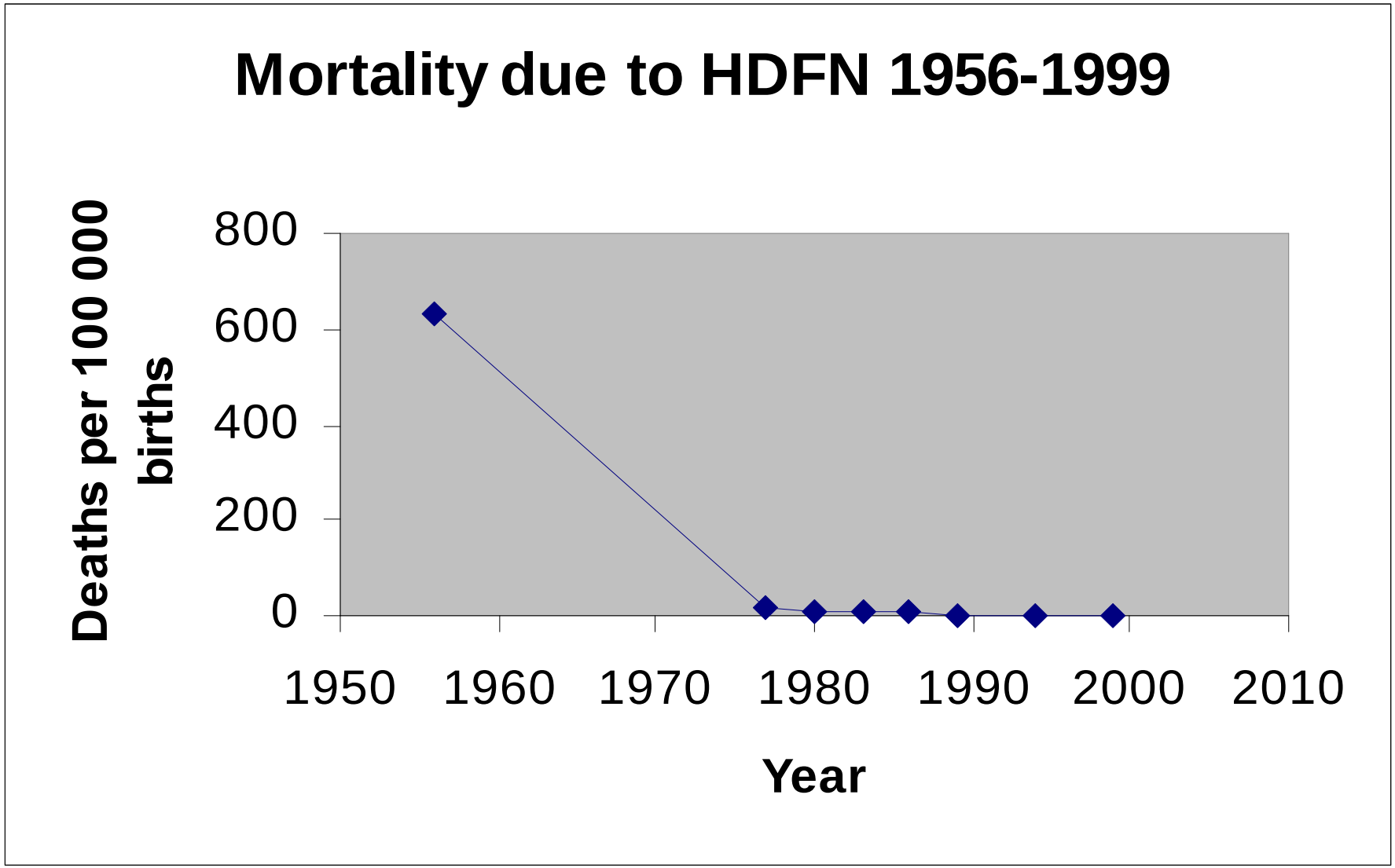
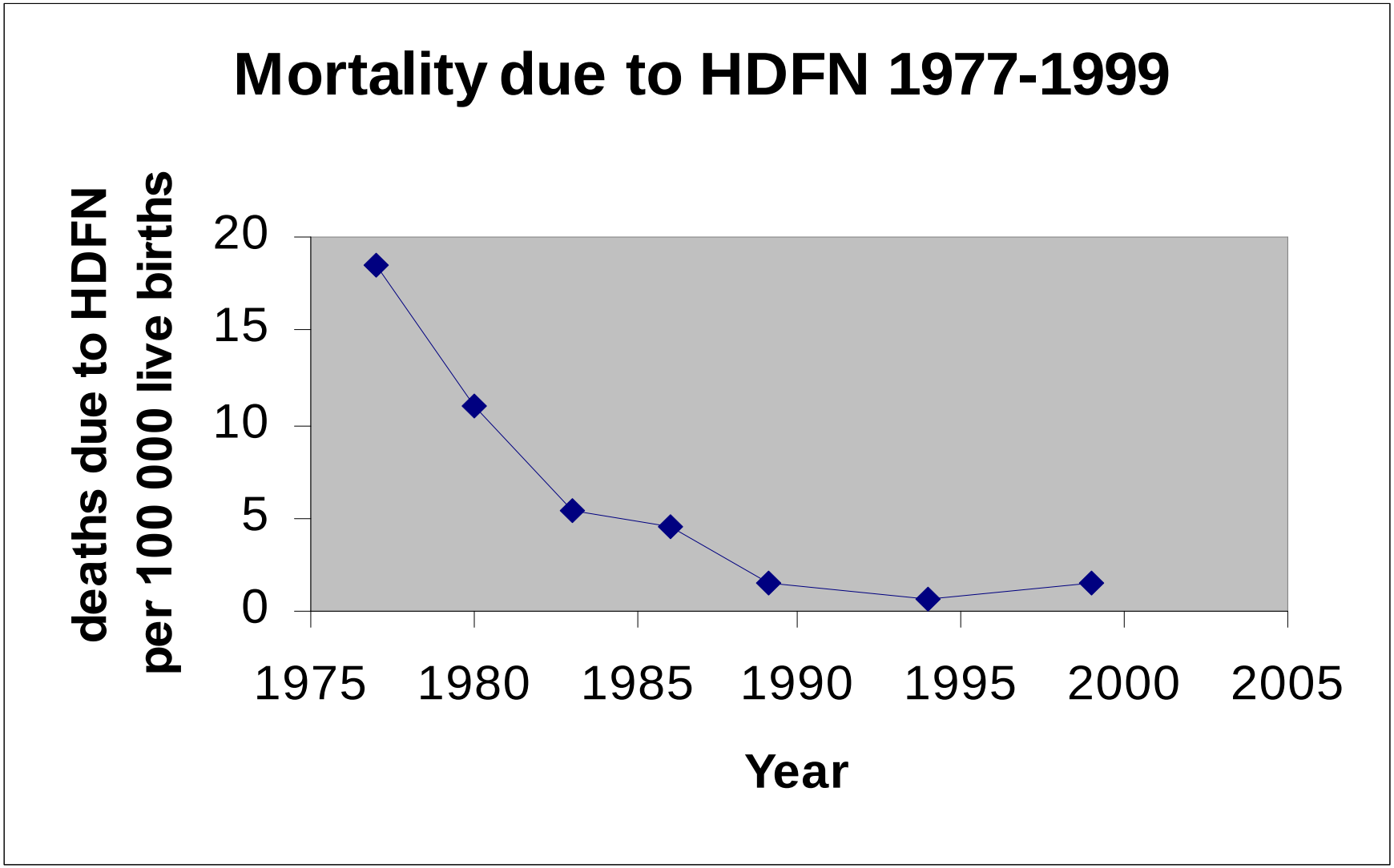


JO&G Brit Emp 44:573. 1957. *JRCP* 23; 181-4, 1989, *BM J* 303; 444. 1992

BJO&G 105 Suppl 18 p23 1998, www.statistics.gov.uk 1999



JRCP 23; 181-4, 1989, *BM J* 303; 444. 1992, *BJO&G* 105 Suppl 18 p23 1998, www.statistics.gov.uk 1999

Risk of morbidity & mortality if Mum D- with anti-D and baby D+

NICE estimate of problem for 2005

- UK - 65,000 D+ babies with D- mothers, 1% sensitised (650)
- In England & Wales (taking account of subsequent pregnancies) estimated 520 require close monitoring. Of these -
  - 10-12% require IUT
  - 37 fetal/neonatal deaths
  - 21 children minor developmental problems
  - 8 children major developmental problems

Prediction of Severity

- Risk of significant fetal anaemia low in 1st affected fetus
- Severity ↑ with each subsequent pregnancy
- If previous hydrops/stillbirth, 90% chance next D+ fetus, if untreated, will die in utero
- After one previous stillbirth at term subsequent stillbirths occur < 35 weeks and < 32 weeks if > one stillbirth
- Aim to intervene ~ 10 weeks before previous IUT, death or birth of severely affected baby

Aim of blood group & antibody screen at booking

- **identify ‘at risk’ pregnancies**
- prevent sensitisation with anti-D prophylaxis
- supply compatible blood to mum

Significant RBC antibodies

- What is the antibody
  - many antibodies capable of causing HDFN
  - anti-D,-c,-K cause the most serious disease
  - card issued
- Care of obstetrician
- Previous transfusion
- Paternal sample
- Fetal genotyping from maternal blood
- How active is the antibody
  - antibody level/titre
  - past history of HDFN

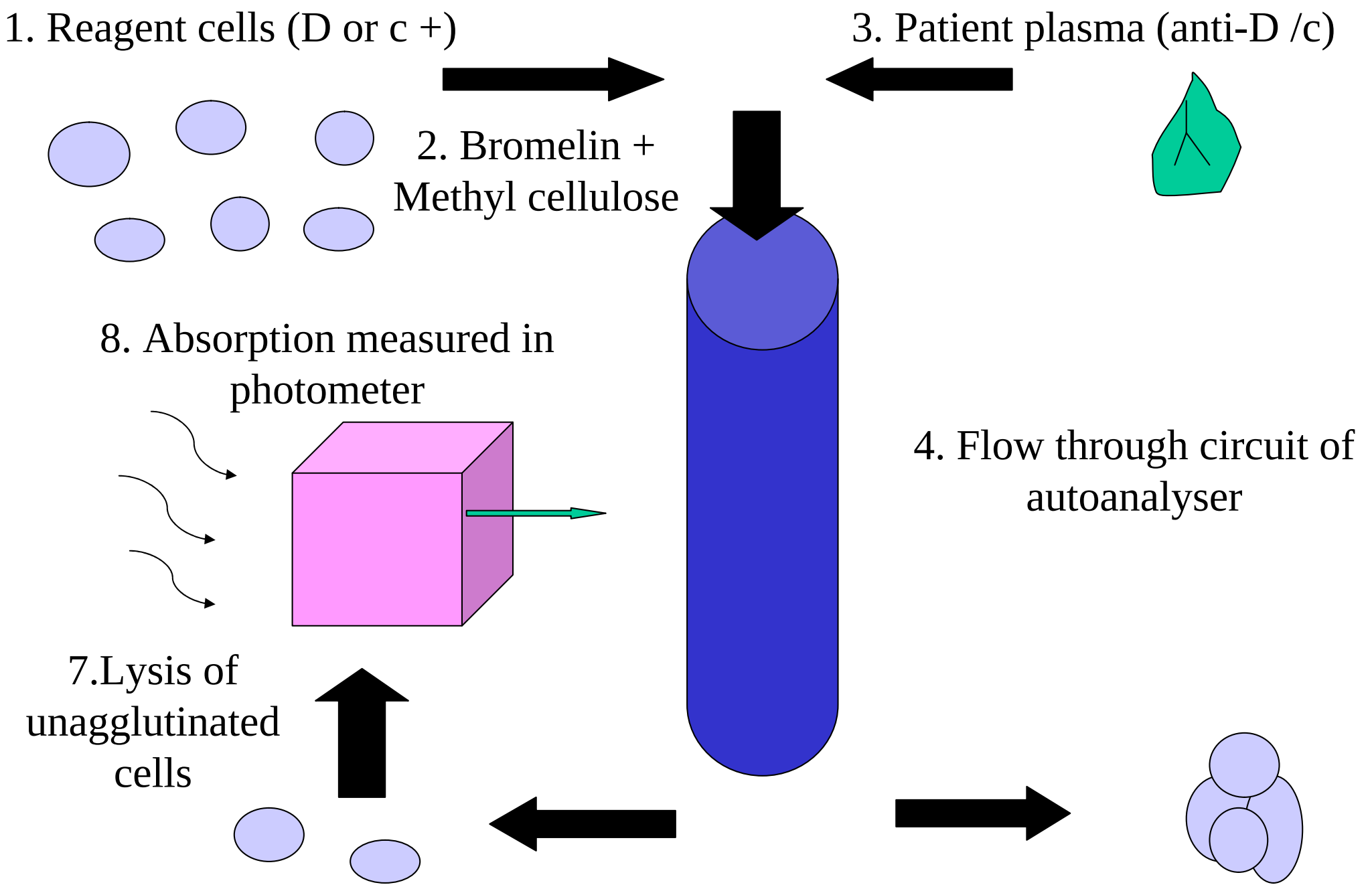
Determination of antibody titre or level

Titration:

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

Quantitation: anti-D and anti-c

- Autoanalyser - more automated, greater reproducibility
- Enzyme treated antigen +ve reagent cells + patient plasma passed through a circuit. Agglutinates precipitate and remaining cells lysed and the optical density measured. Again sample compared in parallel with previous.


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

anti-D
anti-c
K-related
antibodies

quantificate monthly

all other
antibodies

no antibodies

28 weeks

ALL PREGNANT WOMEN

recheck RhD group
+ antibody screen/test

Anti-D, anti-c, anti-K
related antibodies

test 2-weekly

all other
antibodies

no antibodies

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**
  - 2nd most common cause of HDFN
  - 40-50% immunised by transfusion
- **Anti-K**
  - ↓ fetal erythropoiesis →↑anaemia ↓haemolysis
  - usually transfusion induced - > 80%
  - 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

Value and limitation of antibody measurement

- An increase of > 50% over previous level indicates a significant increase
- Most useful in only mildly affected previous pregnancies
- If level/titre indicates > mildly affected refer fetal medicine specialist
- If previous HDFN refer fetal medicine specialist < 20/40

ABO HDFN

- 15% of caucasian group O mothers will carry group A or B fetus
- Difficulty in defining HDFN but approximately 15-30% are DAT positive
- ABO incompatible infants particularly if DAT+ have a lower Hb, higher bilirubin and reticulocyte count
- More common in Asia, ME, S. America
- The first incompatible infant is affected in 50% of families. Severe disease is likely to recur.
- neonatal jaundice is first sign and prompts investigation
- usual O mother and A/B baby
- maternal IgG anti-ABO titre not predictive

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

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

Doppler

- measure fetal blood flow - middle cerebral artery

→
- detects early fetal anaemia

Antenatal therapy for HDN

- Intrauterine blood transfusion
  - intravenous via umbilical cord
    - interval of 2-3 weeks up to 35 weeks
    - survival 92% non hydropic, 70% hydropic
    - Associated with 2% fetal loss (↑ if < 20 wks)
  - intraperitoneal if no intravenous access
- Neonatal anaemia after IUT
    - 50% require top up transfusion at ~ 1 month

Mothers, babies and blood. 8th March 2012

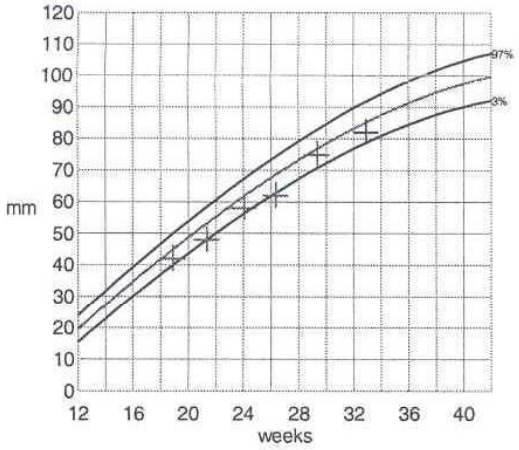
Doppler:

Middle Cerebral Artery: Vmax 53.0

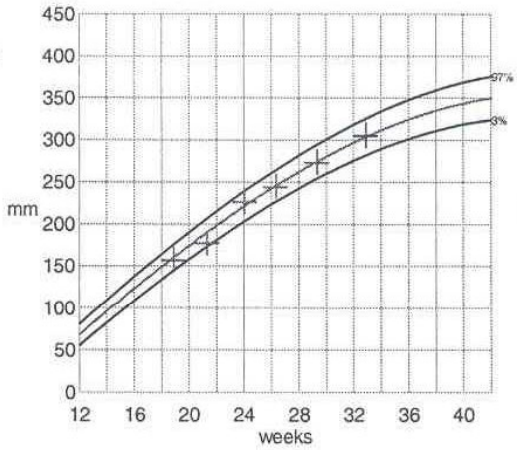
Procedure:

Intrauterine blood transfusion: An intravenous fetal blood transfusion was performed. The indication was anaemia - rhesus. The provisional measurement of haemoglobin after transfusion was 18.0 g/dl.

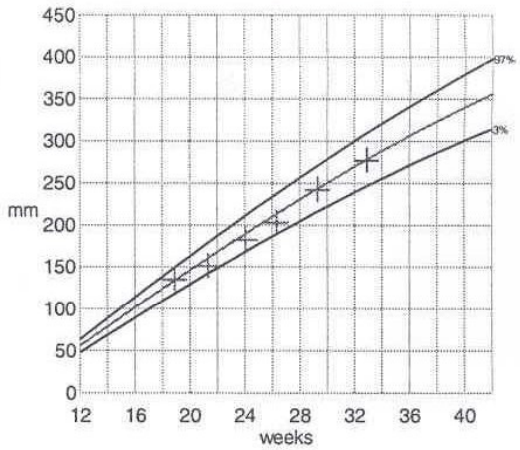
Biparietal diameter (outer-outer)



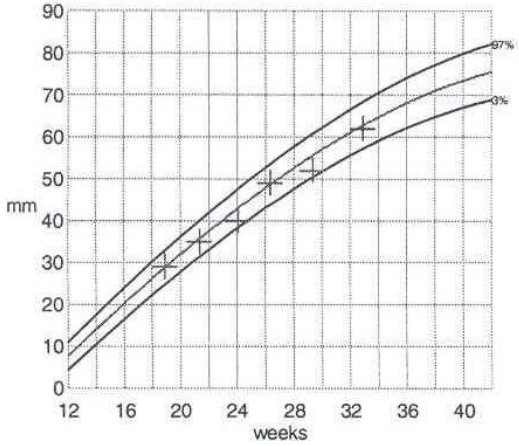
Head circumference



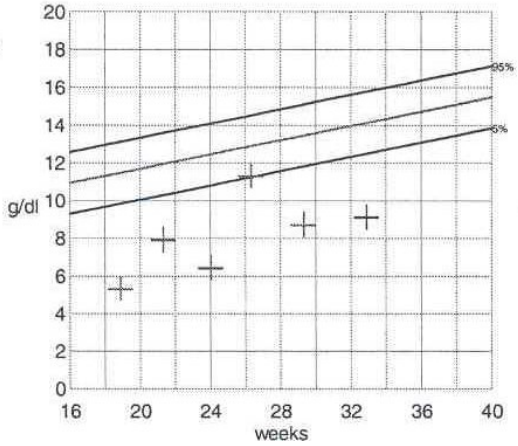
Abdominal circumference



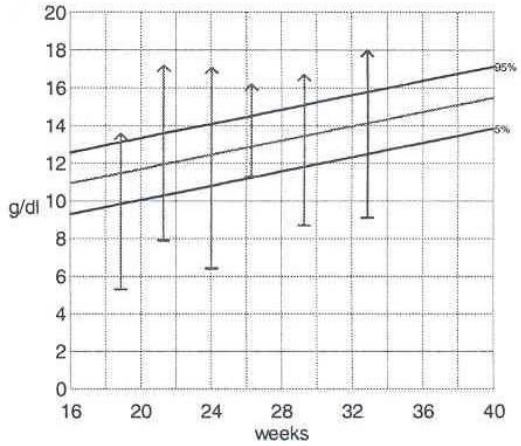
Femur length



Hb pre



Hb post - measured



Action at time of delivery

- Mothers with red cell antibodies
  - Cord Blood DAT
  - If positive check Hb and bilirubin observe for HDN for 48-72h
- D negative with no immune anti-D
  - Cord D group (not including DVI)
  - DAT will be positive if RAADP has been given and is therefore not performed

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)

Intravenous immunoglobulin

Intravenous immunoglobulin (IVIG) acts by preventing the destruction of sensitised erythrocytes. IVIG contains pooled IgG immunoglobulins extracted from the plasma of over 1000 blood donors. The Department of Health has recently updated their guidance on the use of IVIG (www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_085235).

Use intravenous immunoglobulin (IVIG) (500 mg/kg over 4 hours) as an adjunct to continuous multiple phototherapy in cases of Rhesus haemolytic disease or ABO haemolytic disease when the serum bilirubin continues to rise by more than 8.5 micromol/litre per hour.

May 2008

Clinical guidelines for IMMUNOGLOBULIN USE

SECOND EDITION

IVIG may be used in selected cases of HDN with worsening Hyperbilirubinaemia (grade B, level III evidence)

Blood for Exch/IUT

- Compatible with maternal sample
- repeat donor
- group -antigen negative
- K negative
- HbS negative
- plasma reduced
- no IAT reactive rbc antibodies/ no HT anti-A or B
- < 5 days old
- irradiated therefore use within 24 hrs
- CMV negative

Exch: hct 50 -55% IUT: hct > 70%

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
- Antenatal intervention – IUT or delivery
- Post natal intervention - phototherapy, IVIG, Ex. transfusion