Haemolytic diseases of the fetus &newborn

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- Haemolytic diseases are those conditions in which the red cells of the individual do not survive normally *in vivo.*
- Haemolysis lead to red cell destruction and may be associated with anaemia.
- If red cell destruction occur inside the blood vessels it is called **intravascular haemolysis**.
- Intravascular haemolysis is **mediated by compliment** activation and results in free Hb in circulation (not good for the kidney) and DIC.
- Red cell destruction in the RES (e.g. Liver and spleen) is known as **extravascular haemolysis** (e.g. aged red cells).
- Extravascular haemolysis is **macrophage mediated** red cell destruction.
- The liver is vital for the removal of toxic metabolites which are produced following red cell haemolysis.

Role of the liver in RBC haemolysis

1) Intravascular haemolysis:

- Releases free hemoglobin which is toxic to the kidney.
- Hb is immediately bound by haptoglobin in the plasma.
- Hb-haptoglobin complex is removed by hepatic RE cells.

- **2) Extravascular haemolysis:**
- Free Hb➔ haem molecules ➔ bilirubin.
- Free unconjugated bilirubin is transported to the liver where it is conjugated to glucuronic acid and eventually removed (in faeces).

Fetal liver

- Foetus liver cannot metabolise bilirubin which is toxic (cannot be filtered by kidney and can damage the brain tissues).
- Bilirubin in fetal circulation is transferred to the mother circulation for its excretion.
- Newborn baby liver enzymes are not functioning before day 10 post-delivery.

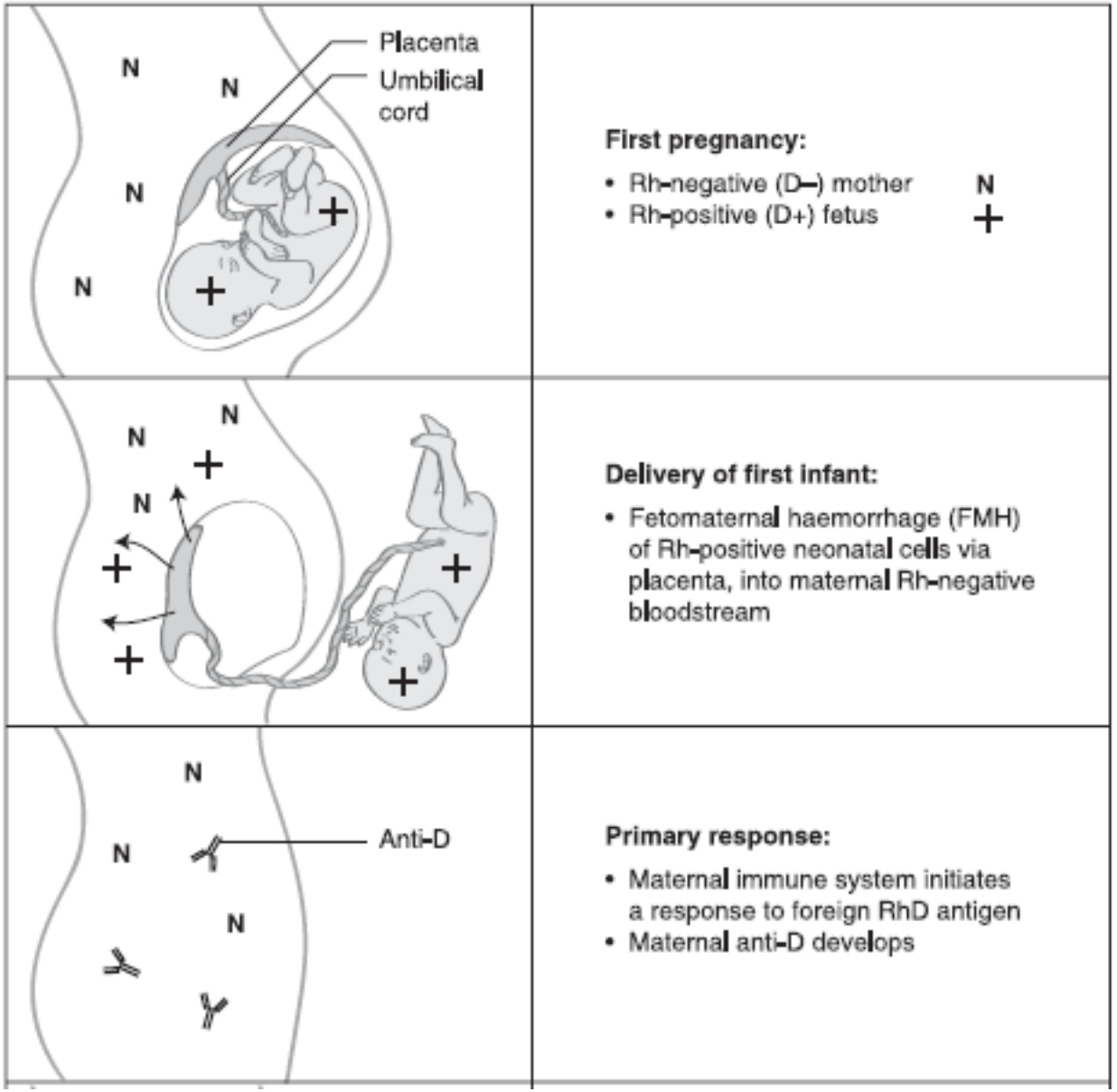
Haemolytic disease of the fetus and newborn (HDFN)

- HDFN is triggered by maternal antibodies to paternally inherited antigens in the fetus.
- The most frequently described antibody in HDFN is the RhD antibody.
- If the mother is RhD negative and the father is RhD positive the baby may inherit the D antigen and express it on fetal RBC.
- Fetal red cells (RhD +) enter the maternal circulation as a result of fetomaternal haemorrhage (FMH) **at the time of delivery.**
- The mother immune system reacts and form anti-D antibodies for many years.
- **Second pregnancy:** Maternal IgG anti-D crosses the placenta and sensitizes the D+ fetal cells.

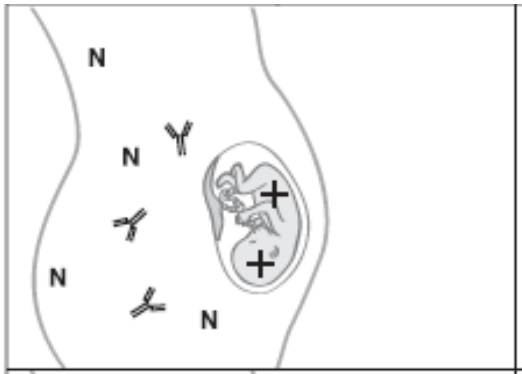
Haemolytic disease of the fetus and newborn (HDFN)

- Synthesised fetal RBCs are removed from fetal circulation and destroyed by macrophages in the RES.
- This cause severe anaemia and referred to as ***erythroblastosis fetalis.***
- ***During pregnancy, excess free bilirubin is transported to mother for metabolism and excretion.***
- Severe fetal anaemia causes oedema of the fetal liver and spleen, which are the organs for both erythropoiesis and cell destruction.
- In the most severe cases of HDFN, ***Hydrops fetalis*** (severe oedema) may result in intrauterine death and stillbirth.
- At delevery the maternal system is no longer available to remove and excrete bilirubin & neonatal liver is not fully functioning ➔ free toxic bilirubin can damage the brain (*kernicterus).*

HDFN (first pregnancy)

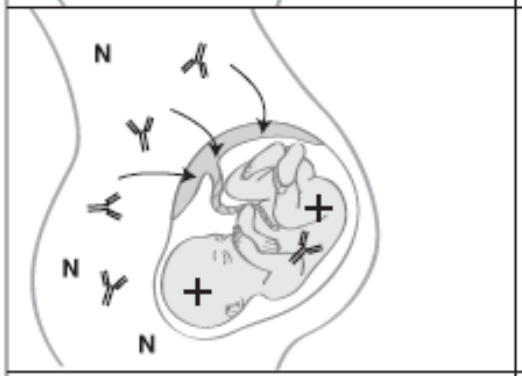


HDFN (first pregnancy)



Second pregnancy:

- Rh-negative mother with anti-D N
- Rh-positive fetus +

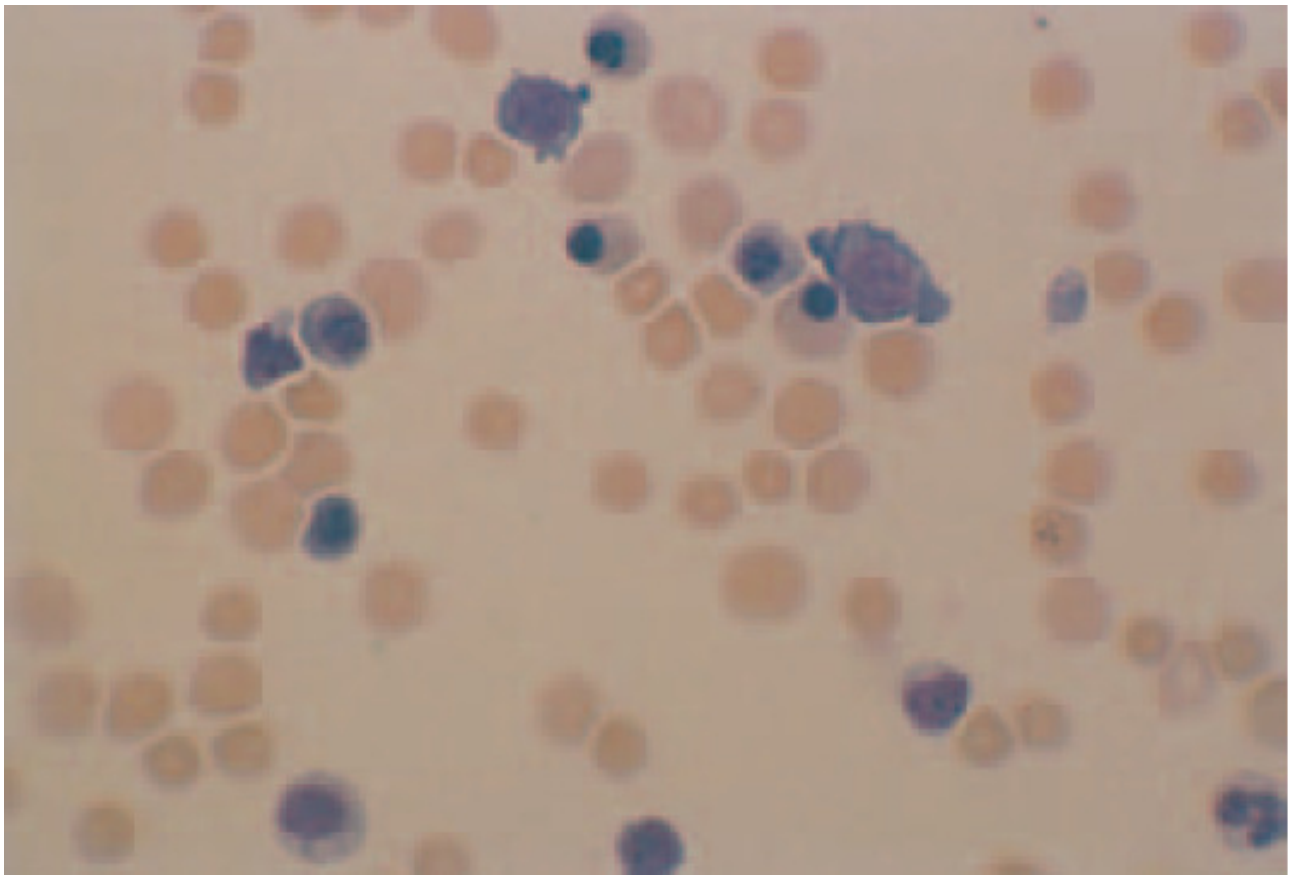


Transfer of antibody:

- Placental transfer of IgG anti-D from mother to Rh-positive fetus during pregnancy
- Fetus becomes increasingly anaemic trying to compensate for red cell destruction by maternal anti-D

Delivery of second infant: born suffering from HDN

- FMH at delivery boosts maternal antibody
- Neonate is anaemic
- Bilirubin is raised and keeps rising
- Exchange transfusion may be needed



Blood film of a fetus affected by HDN, showing polychromasia and increased numbers of normoblasts

HFDN caused by ABO blood group incompatibility

- HDFN occurs very frequently due to ABO incompatibility between the mother and the fetus.
- The ABO antibodies in the maternal blood are IgG anti-A,B in a group O mother carrying a group A or B fetus.
- Bombay $O_h$mothers can cause HDFN similar to ABO HDFN.
- This type of HFDN does not cause problem to the fetus in the uterus but may cause jaundice and mild anaemia post-delivery.
- The disease usually requires conservative treatment such as phototherapy and/ or the administration of immunoglobulin.

Feature	ABO HDFN	Rh HDFN
Frequency	Most common form of HDFN	Most severe form of HDFN
Pregnancy that may be affected	First and subsequent pregnancies, if the fetus inherits the corresponding paternal antigen	Usually from the second pregnancy onwards, if the fetus inherits the corresponding paternal antigen
Neonatal direct antiglobulin test	Negative or weakly positive – a poor diagnostic test	Strongly positive – a good diagnostic test
Antenatal impact	No clinical effect antenatally, therefore no antenatal intervention required	May require antenatal intervention such as premature induction of labour or intrauterine transfusion in severe cases
Postnatal impact	Many cases are self-resolving	Some degree of morbidity, and in severe cases, brain damage or death
Treatment	Neonate may be given intravenous immunoglobulin, may require phototherapy, and occasionally exchange transfusion	Besides phototherapy, and administration of intravenous immunoglobulin, neonate may need exchange transfusion and repeated 'top up' transfusions to correct ongoing anaemia in neonatal period
Prophylaxis	None available as ABO antibodies are naturally occurring	Rh immunoglobulin prevents formation of anti-D in unimmunized Rh-negative mothers

HDFN caused by Rh blood group incompatibility

- Maternal anti-D is the most frequent cause of Rh HDFN and causes the most severe cases of Rh HDFN, followed by anti-c.

- The other antibodies within the Rh system may also be implicated, in addition to combinations of antibodies, e.g. anti-C plus anti-D, anti-C plus anti-e, or anti-c plus anti-E.

HDFN caused by other blood group incompatibility

- HDFN may be caused by anti-K, -Fy^a or other IgG antibodies.
- After anti-D and anti-c of the Rh system, anti-K is most likely to cause severe HDFN.
- Maternal anti-K suppress fetal erythropoiesis causing severe and often fatal anaemia.

Antenatal testing

- Pregnant woman blood should be sent to the lab for antenatal screening tests:

1- ABO grouping.

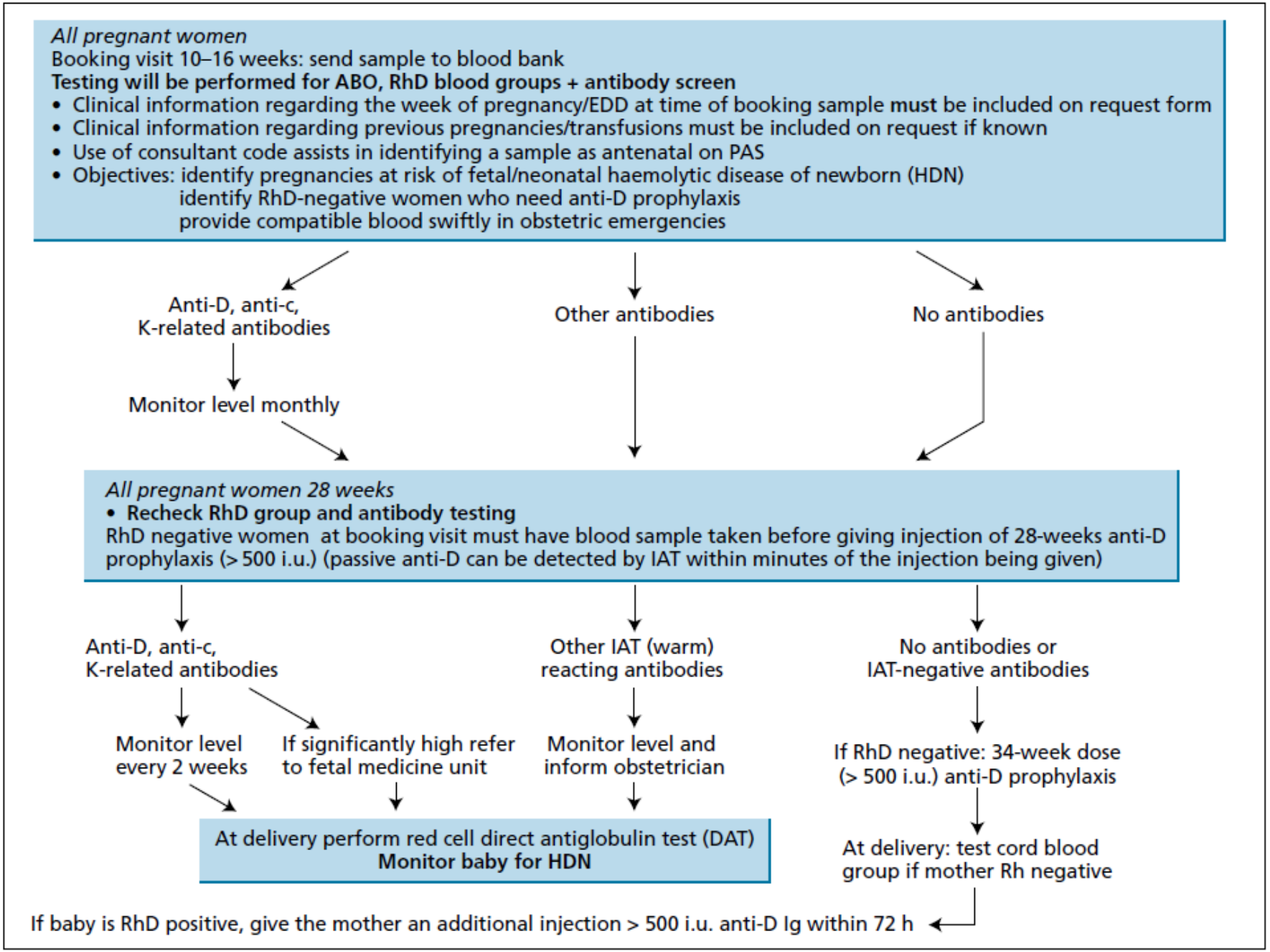
2-Rh typing.

3- antibody screening.

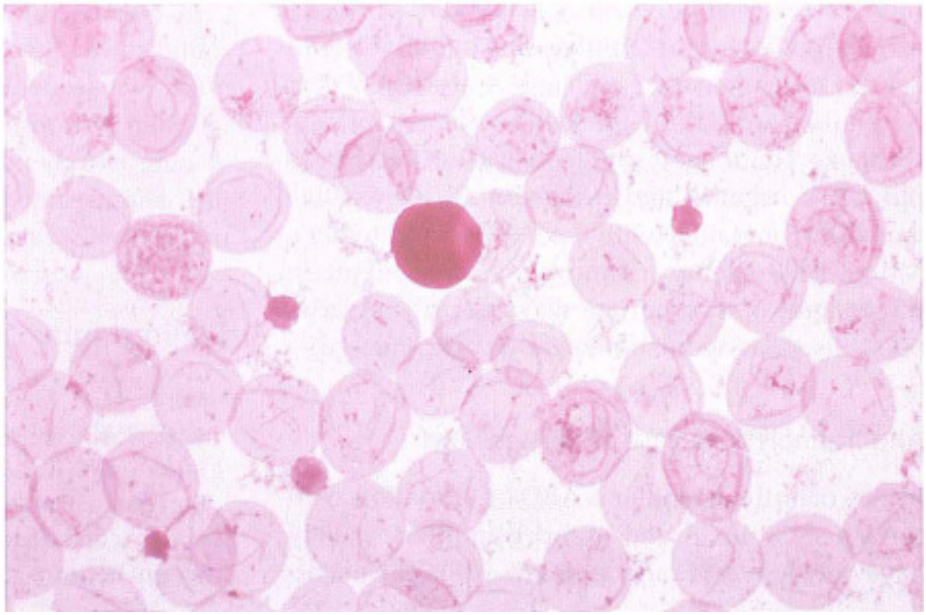
4- antibody identfication.

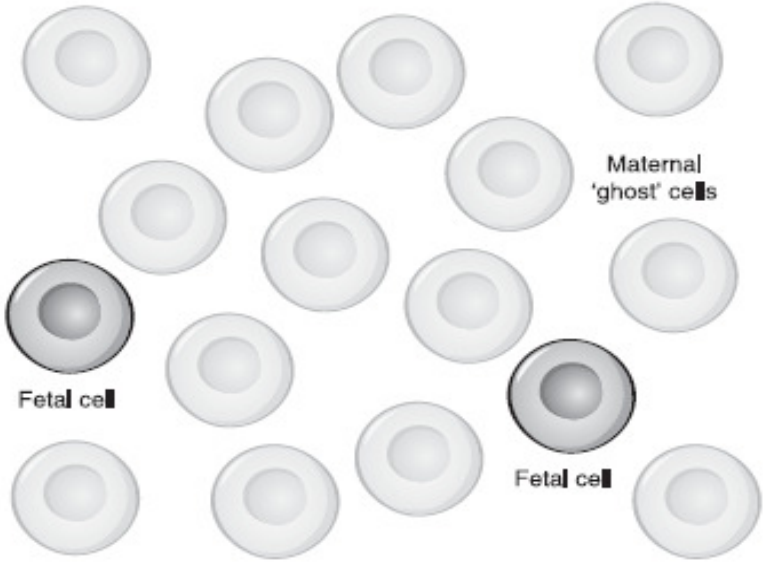
5- titration of significant red cell antibodies.

- **Parental red cell typing**
- **Fetal amniocentesis & Doppler technique**


All pregnant women
Booking visit 10–16 weeks: send sample to blood bank
Testing will be performed for ABO, RhD blood groups + antibody screen
• Clinical information regarding the week of pregnancy/EDD at time of booking sample must be included on request form
• Clinical information regarding previous pregnancies/transfusions must be included on request if known
• Use of consultant code assists in identifying a sample as antenatal on PAS
• Objectives: identify pregnancies at risk of fetal/neonatal haemolytic disease of newborn (HDN)
identify RhD-negative women who need anti-D prophylaxis
provide compatible blood swiftly in obstetric emergencies
Anti-D, anti-c, K-related antibodies
Monitor level monthly
Other antibodies
No antibodies
All pregnant women 28 weeks
• Recheck RhD group and antibody testing
RhD negative women at booking visit must have blood sample taken before giving injection of 28-weeks anti-D prophylaxis (> 500 i.u.) (passive anti-D can be detected by IAT within minutes of the injection being given)
Anti-D, anti-c, K-related antibodies
Monitor level every 2 weeks
If significantly high refer to fetal medicine unit
Other IAT (warm) reacting antibodies
Monitor level and inform obstetrician
No antibodies or IAT-negative antibodies
If RhD negative: 34-week dose (> 500 i.u.) anti-D prophylaxis
At delivery: test cord blood group if mother Rh negative
At delivery perform red cell direct antiglobulin test (DAT)
Monitor baby for HDN
If baby is RhD positive, give the mother an additional injection > 500 i.u. anti-D Ig within 72 h

Kleihauer test for fetal red cells





-Acid elution method. Adult Hb is eluted by acidic PH and appears as ghost cells whereas fetal Hb resist acidic PH and stain red.

- Other methods include flow cytometry.

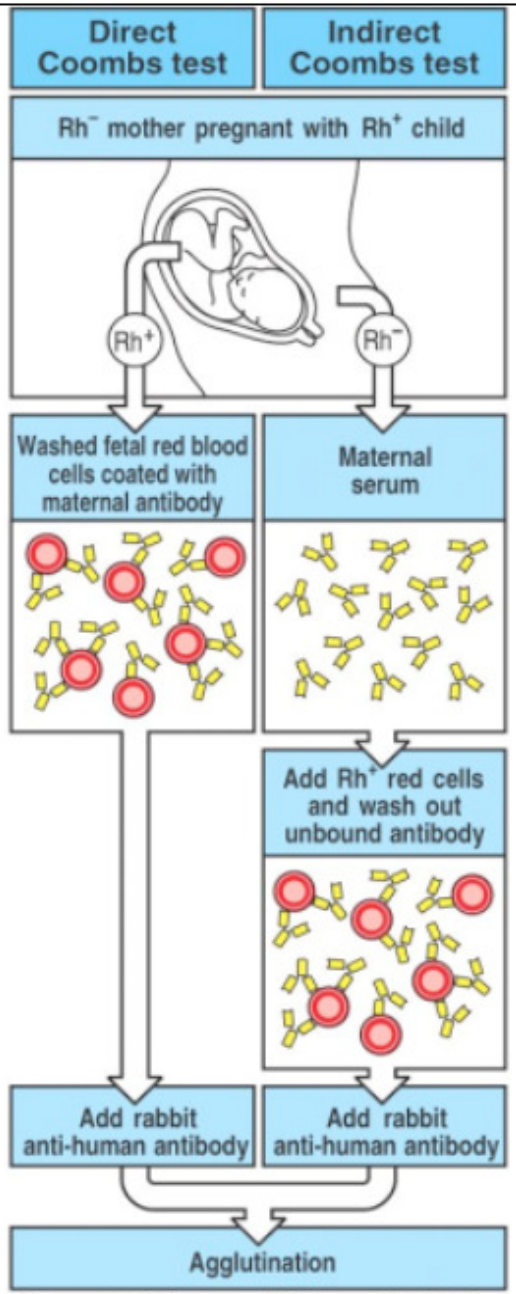


Figure A-13 Immunobiology, 6/e. (© Garland Science 2005)

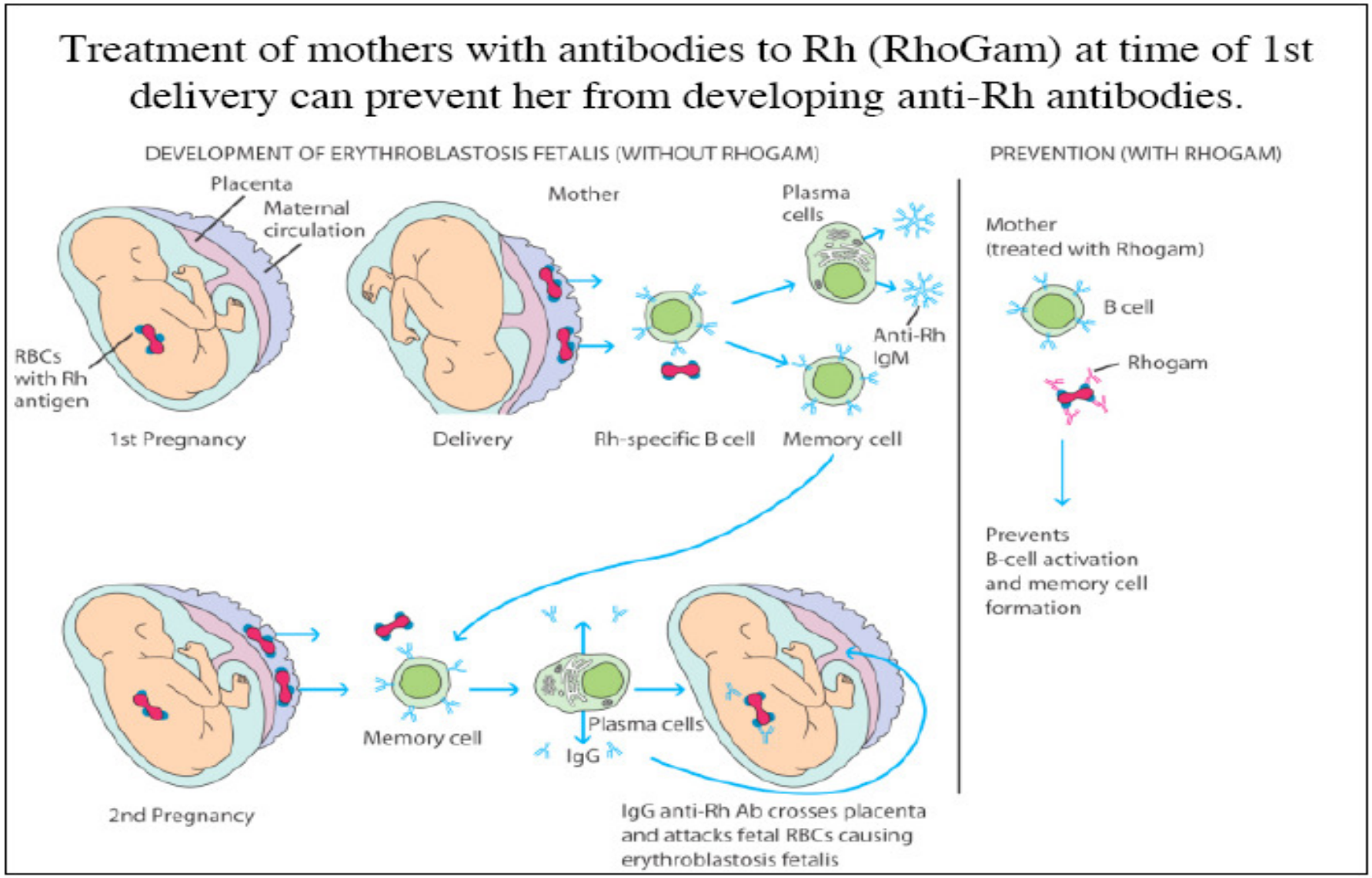
Agglutination as a clinical assay-- Testing for Rh incompatibility

Disease:
Erythroblastosis fetalis

Cause:
Mother produces IgG that bind to an antigen (Rh) on RBC of fetus

Detection:
Expose RBC to anti-human Ab and look for agglutination

Prevention of Rh disease by anti-D



Postnatal tests for HDFN

Test description	Comments
Rh typing	To identify Rh-negative pregnant women
Antibody screening	To detect irregular red cell antibodies
Antibody identification	To identify irregular red cell antibodies detected on screening, to ascertain whether or not they are of obstetric significance
Antibody titration/quantification	To determine titre or strength of obstetrically significant red cell antibodies
Paternal red cell typing/phenotyping	To determine whether or not the father carries the corresponding antigen, and the chances of the fetus inheriting it
Amniocentesis	When HDFN is strongly suspected, amniocentesis may be performed to determine bilirubin level, to assess whether intrauterine transfusion is needed. This is an invasive measure and therefore carries risks
Obstetric ultrasonography	Non-invasive technique to examine the fetus for possible hydrops fetalis
Doppler technique	Non-invasive technique to measure speed of blood flow in fetal vessels, as increased flow rate suggests severe anaemia
Cordocentesis	PUBS is an invasive procedure performed only when HDFN is suspected, to provide a blood sample for the laboratory determination of fetal Hb and blood type, and for DAT to detect *in vivo* red cell sensitization.

Haemolytic anaemias

alloimmune hemolysis

- **Hemolytic disease of the newborn** (also known as HDN or erythroblastosis fetalis)
  - Rh D hemolytic disease of the newborn (also known as Rh disease)
  - ABO hemolytic disease of the newborn (the indirect Coombs test may only be weakly positive)
  - Anti-Kell hemolytic disease of the newborn
  - Rh c hemolytic disease of the newborn
  - Rh E hemolytic disease of the newborn
  - Other blood group incompatibility (RhC, Rhe, Kidd, Duffy, MN, P and others)
- **Alloimmune hemolytic transfusion reactions**

Examples of autoimmune hemolysis

- **Warm antibody autoimmune hemolytic anemia**
  - Idiopathic
  - Systemic lupus erythematosus
  - Evans' syndrome (antiplatelet antibodies and hemolytic antibodies)
- **Cold antibody autoimmune hemolytic anemia**
  - Idiopathic cold hemagglutinin syndrome
  - Infectious mononucleosis
  - Paroxysmal cold hemoglobinuria

Autoimmune & alloimmune haemolytic anaemia

Table 5.5 Immune haemolytic anaemias: classification.

Warm type	Cold type
Autoimmune	
Idiopathic	*Idiopathic*
Secondary	*Secondary*
SLE, other 'autoimmune' diseases	Infections—*Mycoplasma* pneumonia, infectious mononucleosis
CLL, lymphomas	Lymphoma
Drugs (e.g. methyldopa)	Paroxysmal cold haemoglobinuria (rare, sometimes associated with infections, e.g. syphilis)
Alloimmune	
Induced by red cell antigens	
Haemolytic transfusion reactions	
Haemolytic disease of the newborn post stem cell grafts	
Drug induced	
Drug–red cell membrane complex	
Immune complex	

Drug-induced immune-mediated hemolysis

- Methyldopa (IgG mediated type II hypersensitivity)
- Penicillin (high dose)
- Quinidine (IgM mediated activation of classical complement pathway and Membrane attack complex, MAC)

Drug-induced immune-mediated hemolysis

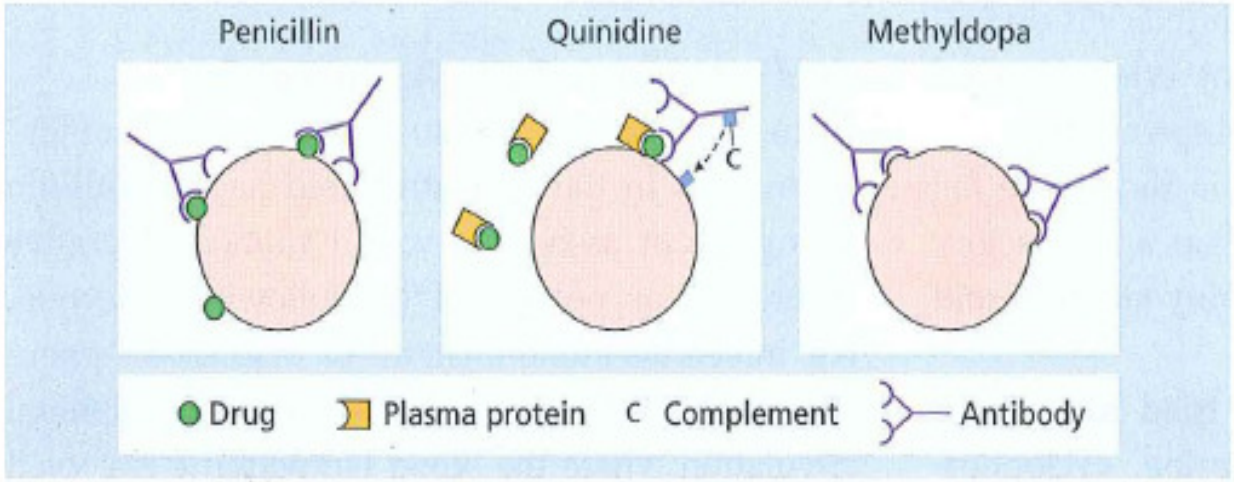


Fig. 5.10 Three different mechanisms of drug-induced immune haemolytic anaemia. In each case the coated (opsonized) cells are destroyed in the reticuloendothelial system.

Infections agents reported to have been transmitted by blood transfusion

Bacteria	
Endogenous	*Treponema pallidum* (syphilis)
	Borrelia burgdorferi (Lyme disease)
	Brucella melitensis (brucellosis)
	Yersinia enterocolitical/Salmonella spp.
Exogenous	Environmental species—staphyloccocal spp./pseudomonas/*Serratia* spp.
Rickettsiae	*Rickettsia rickettsii* (Rocky Mountain spotted fever)
	Coxiella burnettii (Q fever)
Protozoa	
	Plasmodium spp. (malaria)
	Trypanosoma cruzi (Chagas' disease)
	Toxoplasma gondii (toxoplasmosis)
	Babesia microti/divergens (babesiosis)
	Leishmania spp. (leishmaniasis)
Prions	
	New variant Creuzfeldt–Jacob disease (nvCJD)

Viruses	
Hepatitis viruses	Hepatitis A virus (HAV)
	Hepatitis B virus (HBV)
	Hepatitis C virus (HCV)
	Hepatitis D virus (HDV) (requires coinfection with HBV)
Retroviruses	Human immunodeficiency virus (HIV) 1 + 2 (+ other subtypes)
	Human T-cell leukaemia virus (HTLV) I + II
Herpes viruses	Human cytomegalovirus (CMV)
	Epstein–Barr virus (EBV)
	Human herpesvirus 8 (HHV-8)
Parvoviruses	Parvovirus B19
Miscellaneous viruses	GBV-C—previously referred to as hepatitis G virus (HGV)
	Transfusion transmitted virus (TTV)
	West Nile virus