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يونيرسيتي إسلام انتارابغسا ملسيا
Garden of Knowledge and Virtue

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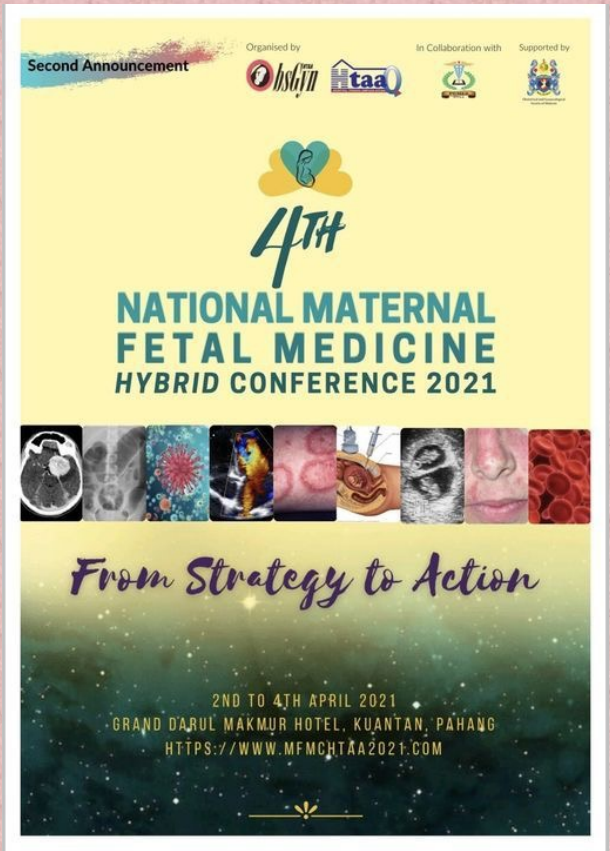

The fetus at risk for anaemia : Diagnosis and Management

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- Definition on Severity of Fetal Anaemia
- Advancement in Management of Fetal Anaemia
  - Investigation
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- Management on Specific Causes of Fetal Anaemia
  - Haemolytic Diseases of Fetus and Newborn
  - Parpovirus B19

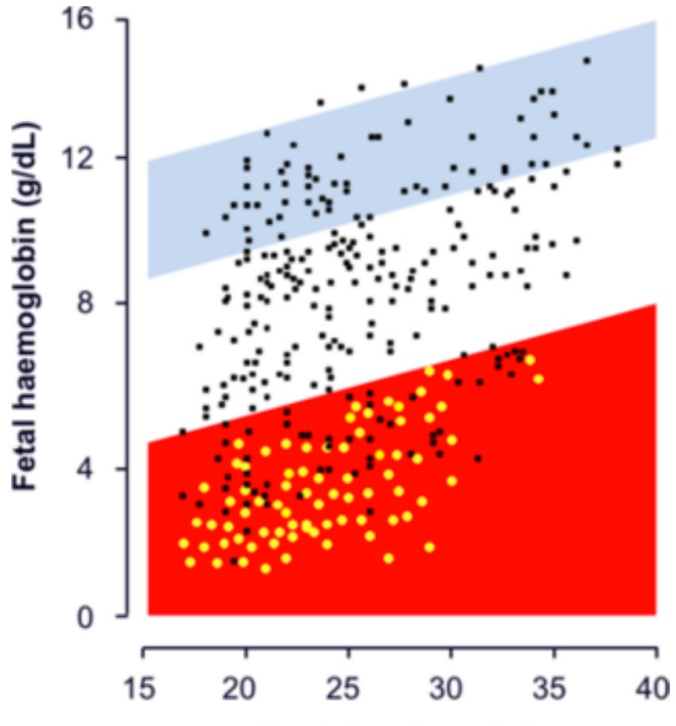
Introduction

- Rare, serious and dangerous complication of pregnancy with high fetal mortality
- Most common causes
  - Immune Hydrops Fetalis - Rhesus D alloimmunization
  - Non-Immune Hydrops Fetalis - Parvovirus B19 (8-10%)
- Over the last decade the incidence, morbidity and mortality reduced
  - Anti- D : postpartum and antepartum prophylaxis
  - Method of surveillance from invasive to non-invasive technique
  - Improvement in technique of intrauterine blood transfusion

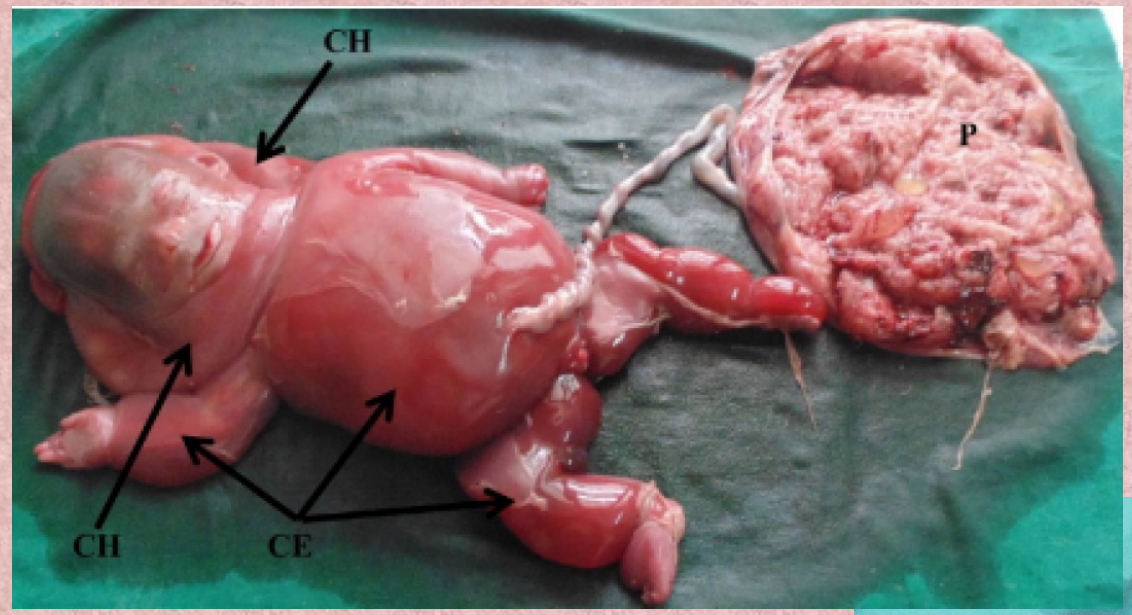
Table 1. Definitions of fetal anemia

Definition	Reference	Severity		
		Mild	Moderate	Severe
Hemoglobin deviation from GA mean	Nicolaides *et al*.5	< 20 g/L	20–70 g/L	> 70 g/L
Hemoglobin values expressed as MoM	Mari *et al*.1; Goodwin and Breen96	0.84–0.65	0.64–0.55	≤ 0.54
Hematocrit	Moise Jr and Argoti10	< 30%		

GA, gestational age; MoM, multiples of the median.



Clinical Manifestation of Severe Anaemia – Fetal Hydrops



Severely affected fetus

↓

Subcutaneous oedema and effusion into the serous cavities

↓

The placenta is also markedly oedematous, boggy and enlarged

Excessive Haemolysis

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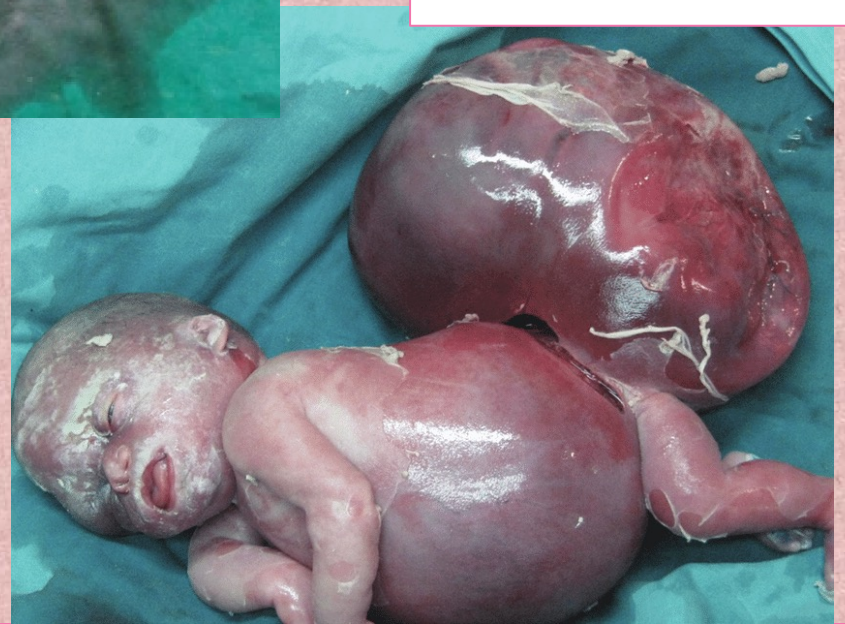
Marked erythroid hyperplasia of the bone marrow and extramedullary haematopoiesis

↓

Hepatosplenomegaly causes hepatic dysfunction

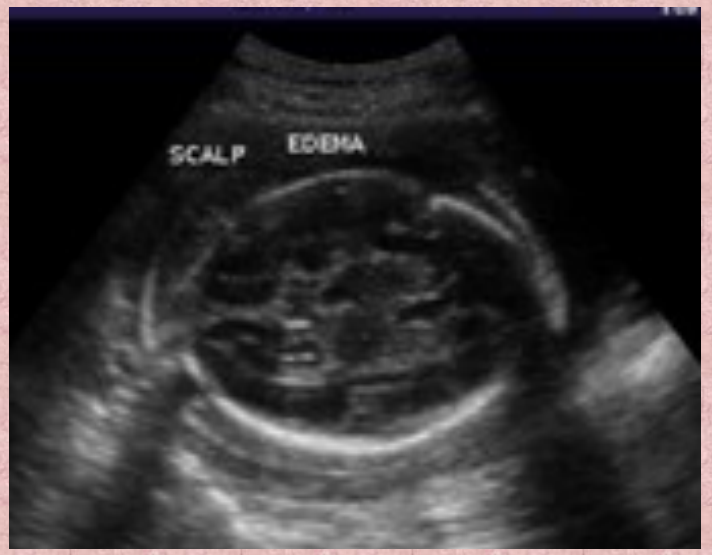


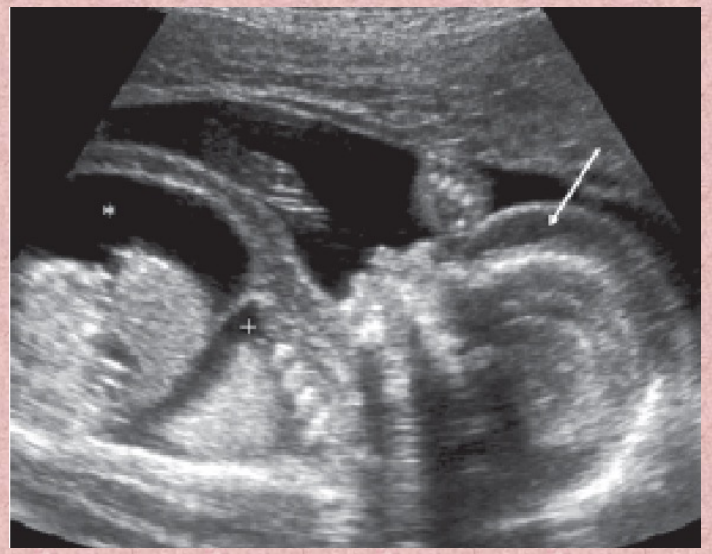
Hydrothorax and Ascites

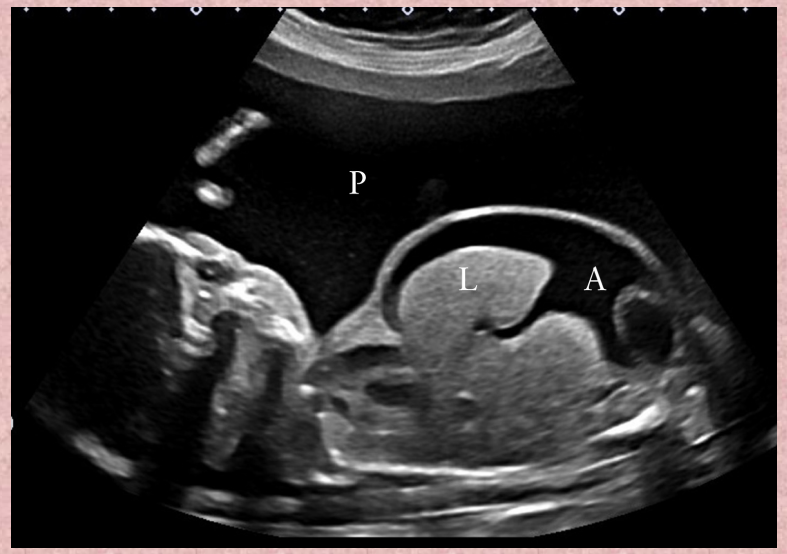
↓

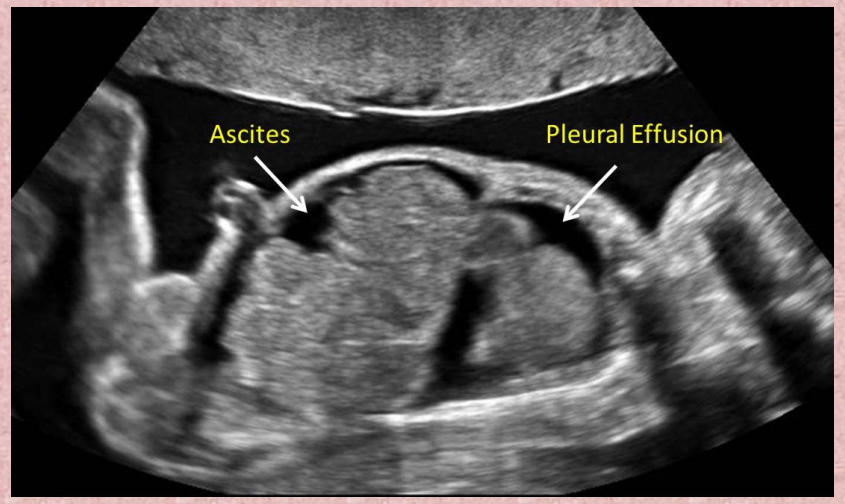
Compromise respiration after birth or lead to severe dystocia as consequence of the greatly enlarged abdomen

Ultrasound Manifestation of Severe Anaemia – Fetal Hydrops









Abnormal fluid collection in at least two different fetal compartments

- Pericardial effusion
- Pleural effusion
- Ascites
- Skin oedema (>5 mm)
- Polyhydramnios
- Thickened placenta (>6 cm)
- Cardiac failure
- IUD

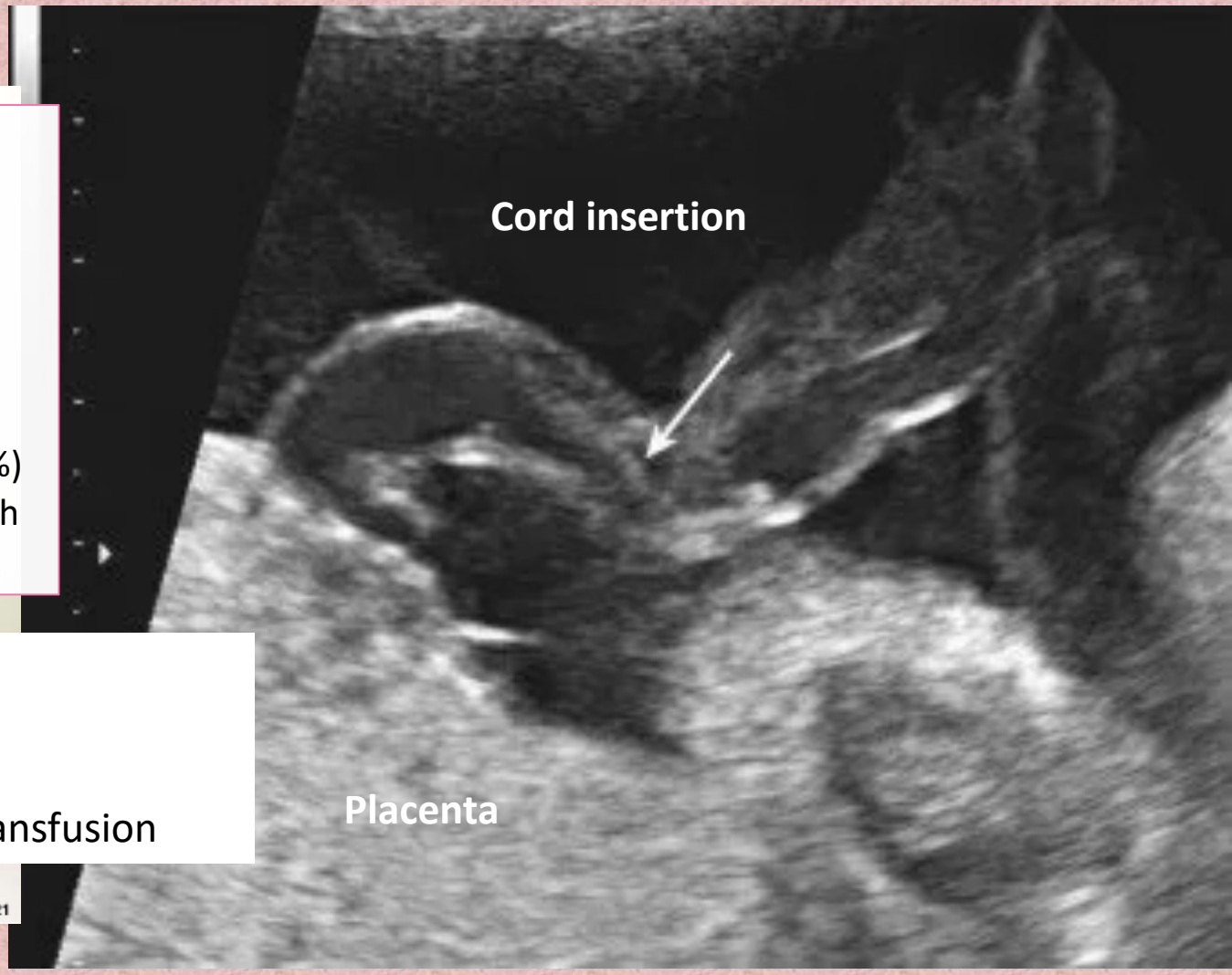
Investigation for Severity of Fetal Anaemia - Cordocentesis

Fetal Loss 2%

- PPROM / Preterm labor
- Maternal-fetal haemorrhage
- Placental Abruption
- Alloimmunization
- Transient Fetal Bradycardia 5 %
- Streaming from needle insertion 20-30%
- Fetal Exsanquination (less if take from intrahepatic vein (9%)
- Emergency caesarean for prolonged bradycardia (2.4 % with birth asphyxia 73% / neonatal demise 33%)

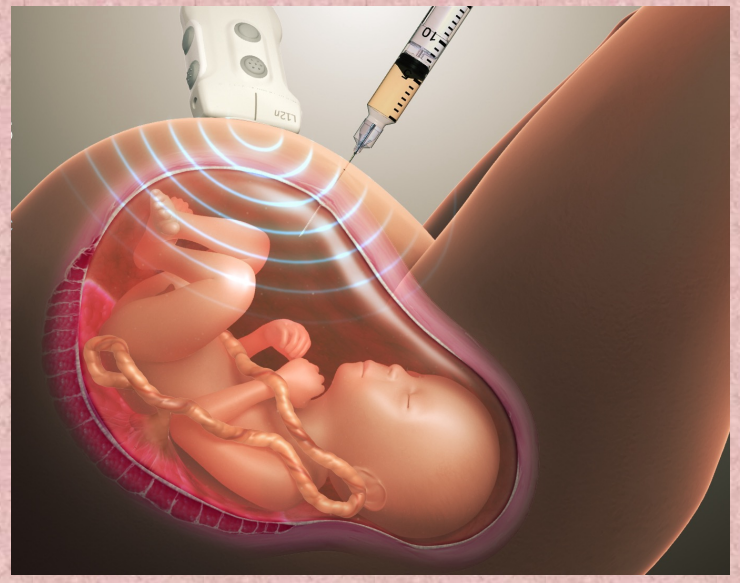
Trend for Cordocentesis:
26.4 % (1982-1985 → 2.2 % (2000-2004)

Limited to assessing Anaemia at Pre and Post Intrauterine Transfusion



Investigation for Severity of Fetal Anaemia - Amniocentesis

Previously Used:
Optical Density -Δ 450 nm of bilirubin in amniotic fluid



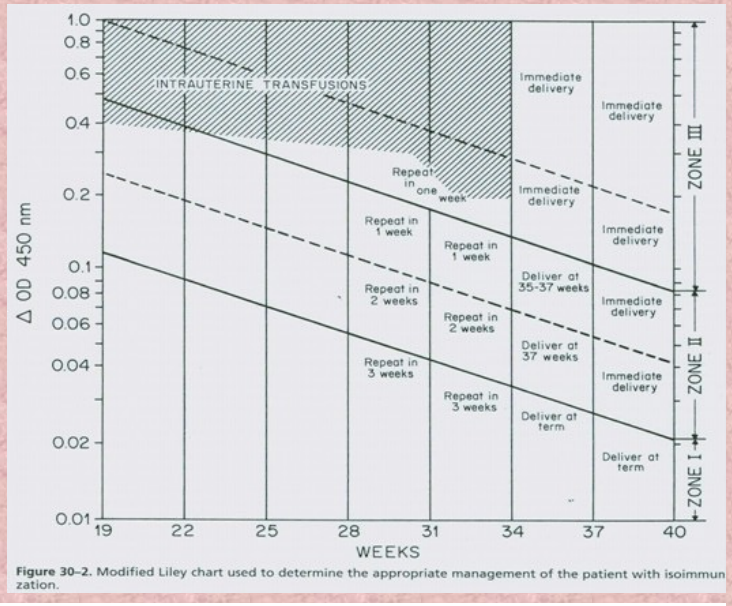
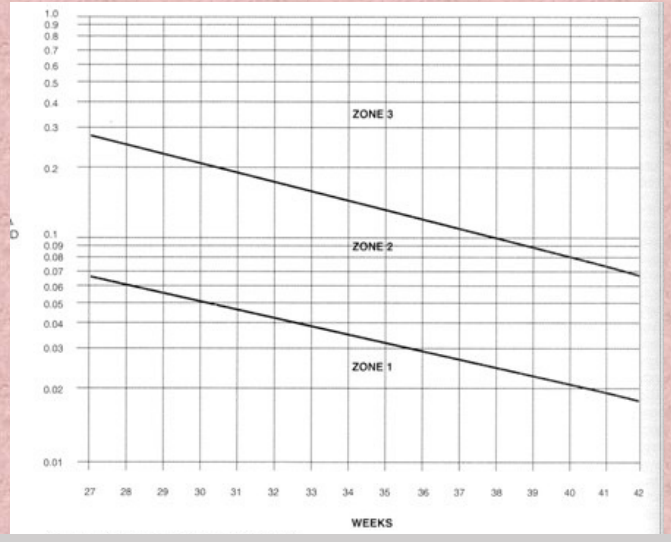
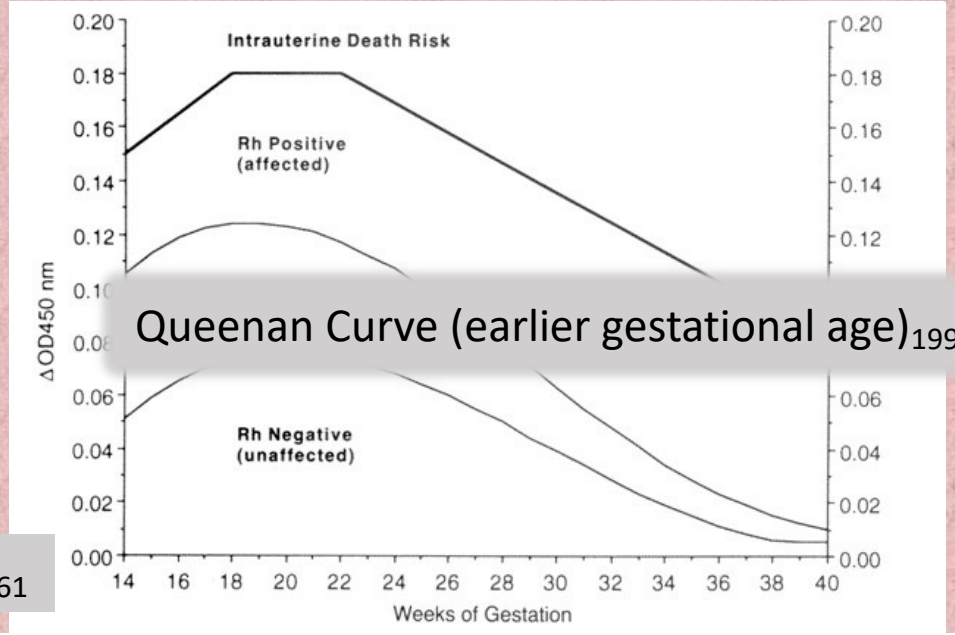


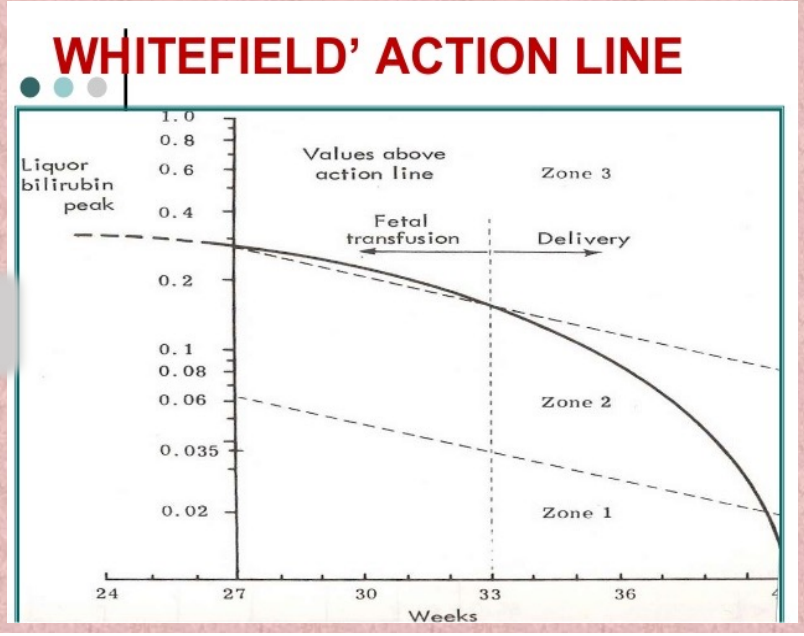
Figure 30–2. Modified Liley chart used to determine the appropriate management of the patient with isoimmunization.



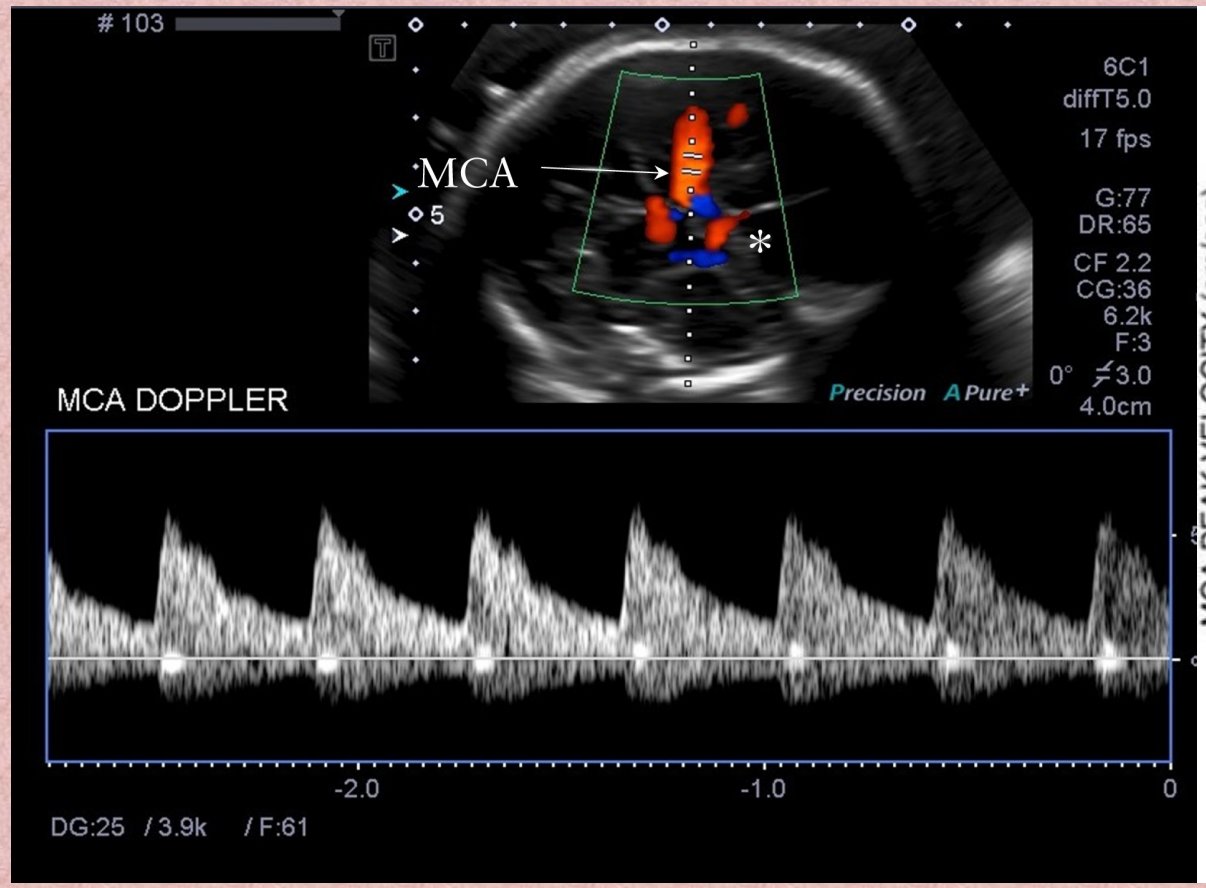
Liley Curve (27-41 weeks gestation)$_{1961}$

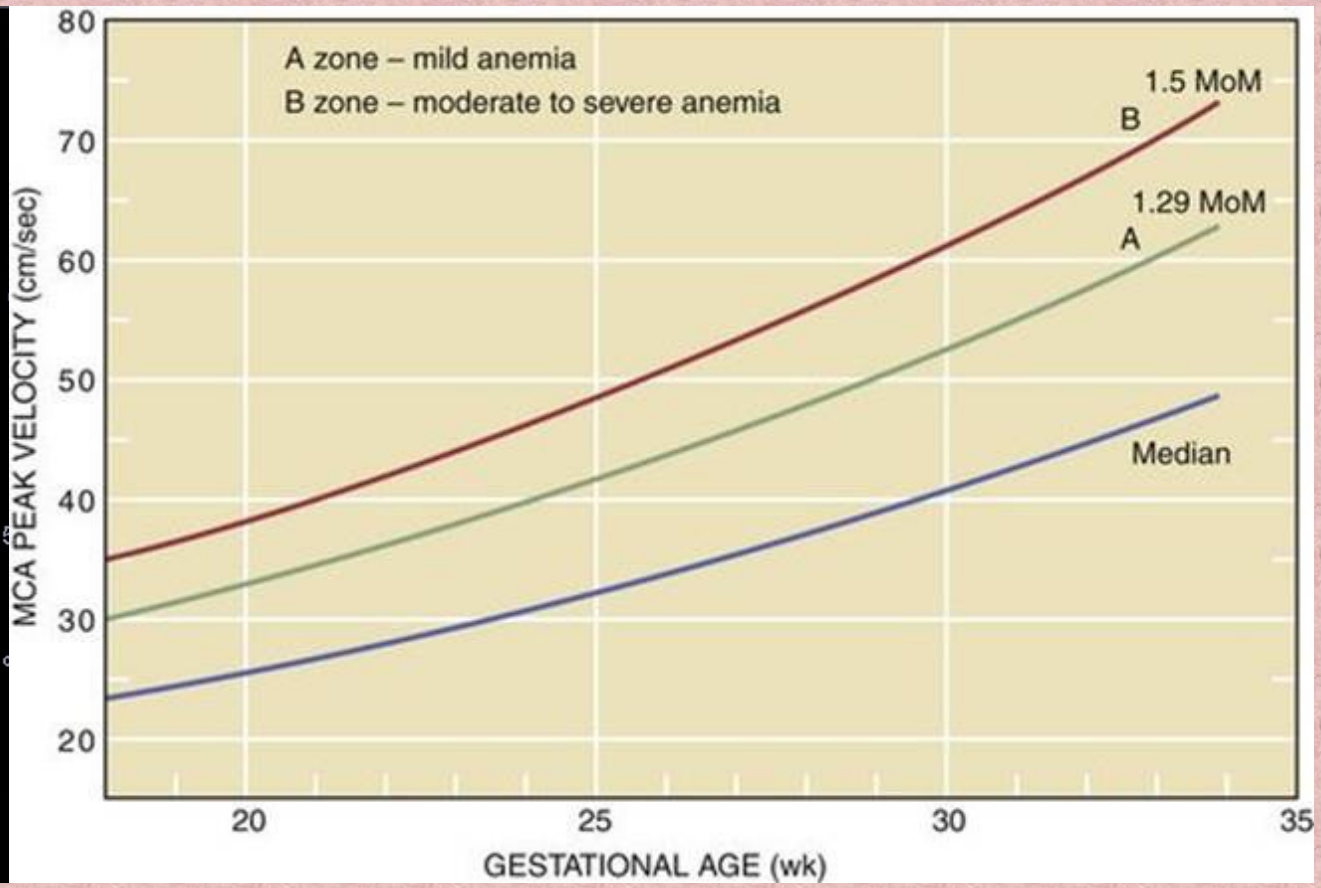


Queenan Curve (earlier gestational age)$_{1993}$



Investigation for Severity of Fetal Anaemia – Middle Cerebral Artery-Peak Systolic Velocity (MCA-PSV)





MCA-PSV > 1.5 MoM detect almost all (75-95%) severe anaemia with 15 % false positive

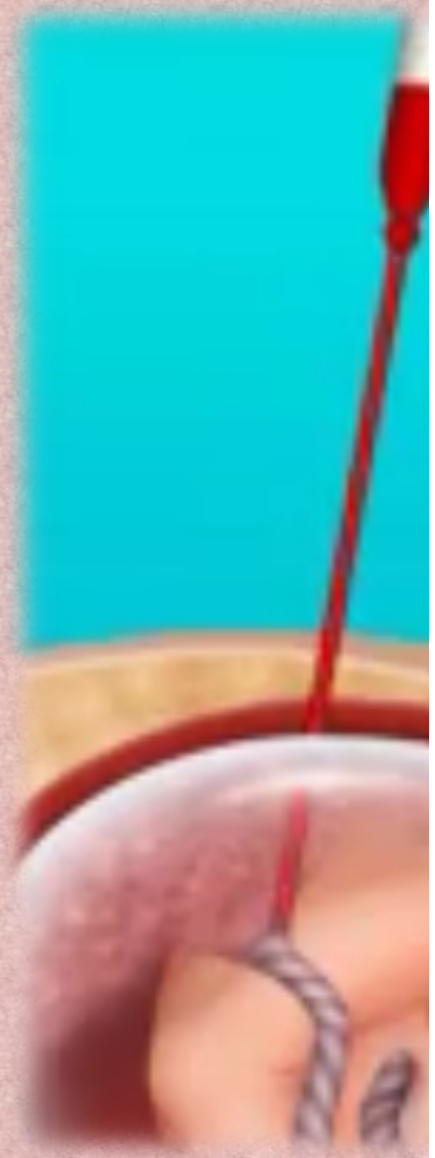
Middle Cerebral Artery – Peak Systolic Velocity and Fetal Haemoglobin Level

Gestation (wks)	Fetal Hb (g/dl)		MCA PSV (cm/s)	
	Mean	-6 SD's	Mean	1.5 SD's
18	11.0	5.3	23.1	30.8
20	11.3	5.6	25.6	34.2
22	11.6	5.9	28.4	37.9
24	11.9	6.3	31.5	41.9
26	12.2	6.6	34.9	46.5
28	12.5	6.9	38.6	51.5
30	12.8	7.2	42.8	57.1
32	13.1	7.5	47.4	63.3
34	13.5	7.8	52.6	70.1
36	13.8	8.1	58.3	77.7
38	14.1	8.4	64.6	86.1
40	14.4	8.8	71.5	95.4

Management : Intrauterine Blood Transfusion

- First successful fetal intraperitoneal transfusion with fluroscopy Liley 1963
- Cannulate fetal blood → preterm birth and death
- Direct intravascular transfusion – needling chorionic plate vessels under fetoscopic visualization Rodeck et al 1981
- Intra-abdominal umbilical vein under real-time ultrasound Bang et al 1982
- Refinement in blood transfusion techniques Zwiers 2017
  - Umbilical vein at cord insertion site of placenta / intrahepatic vein/ intracardiac
  - Blood products preparation

Treatment for Fetal Anaemia : Intrauterine Blood Transfusion



- Outpatient Procedure
- Consent : 1-2 % related loss (PPROM/Fetal Bradycardia)
- Iv antibiotic prophylaxis
- Aseptic Technique
- Local anaesthetic to mother abdomen
- Ultrasound guidance
- Pancuronium to fetal thigh
- 17 gauge needle into the Umbilical Vein – at its insertion to Placenta
- 1 ml pre-transfusion –immediate result -Haemoglobin, Haemtocrit, Platelet
- Blood Transfusion :

  GpO Rh negative, packed cells (HCT>85%, CMV negative and Kell negative)
  Rate 10 to 15 ml/ min
  Monitor Fetal Heart
  Volume depend on HCT and fetal Hb
  - 16-18 weeks 5 ml
  - 20 weeks 20 ml
  - >20 weeks 20 ml + 10 ml/week of gestation (max 100 ml)

Procedure time periods upto 50 minutes
Post-transfusion Hb, HCT :

- Flush needle with saline solution 0.5 ml
- After 60 sec aspirate blood for lab test

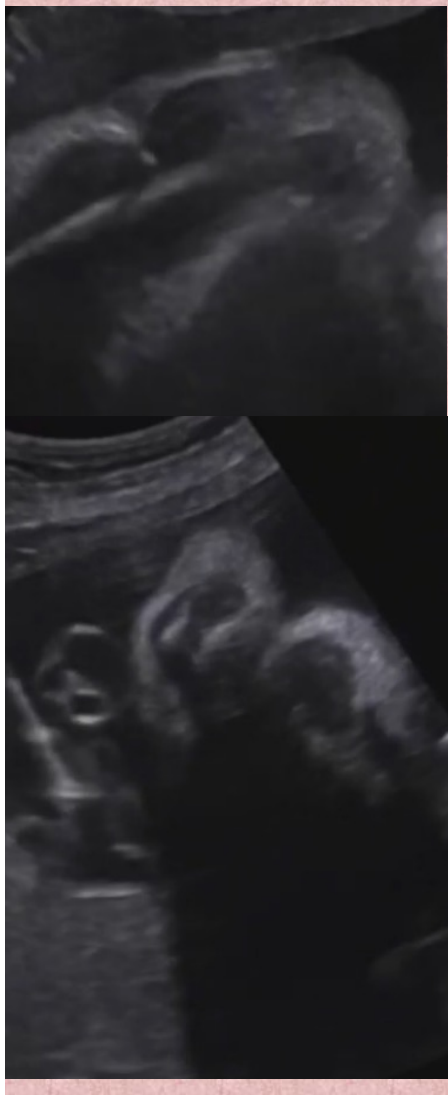


Table 3
Formulas for calculating the volume of transfusion.

Rodeck et al. [65]

$$\text{Intravascular transfusion volume (mL)} = \frac{(\textit{target Hb} - \textit{fetal Hb}) \times \textit{fetoplacental blood volume}}{(\textit{donor Hb} - \textit{target Hb})}$$ [a]

The fetoplacental blood volume is estimated by one of the following:

- 0.1 mL/g of estimated fetal weight [66]
- 1.046 + (fetal weight in g) × 0.14 [67]
- 0.15 mL/g of estimated fetal weight [68]

Giannina et al. [66]

Intravascular transfusion volume (mL) = 0.02 × target increase in fetal Ht per 10% × g of estimated fetal weight[b]

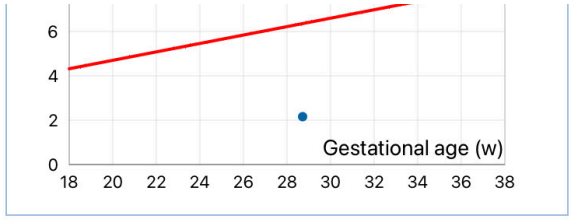
Intraperitoneal transfusion [7]

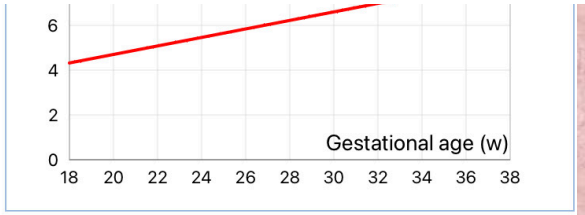
Intraperitoneal transfusion volume (mL) = (gestational age in weeks − 20) × 10

Hb: hemoglobin concentration; Ht: hematocrit.

[a] Can also be used for hematocrit.

[b] Can only be used for hematocrit; assumes donor hematocrit of 75%.



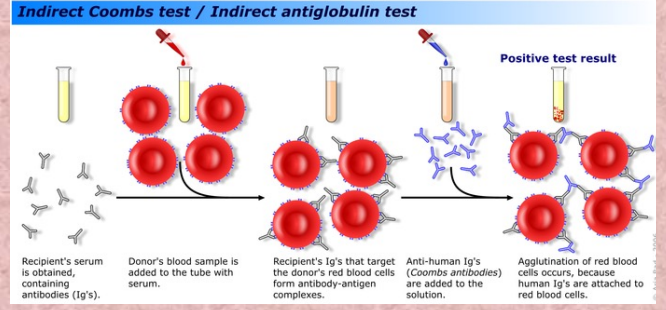


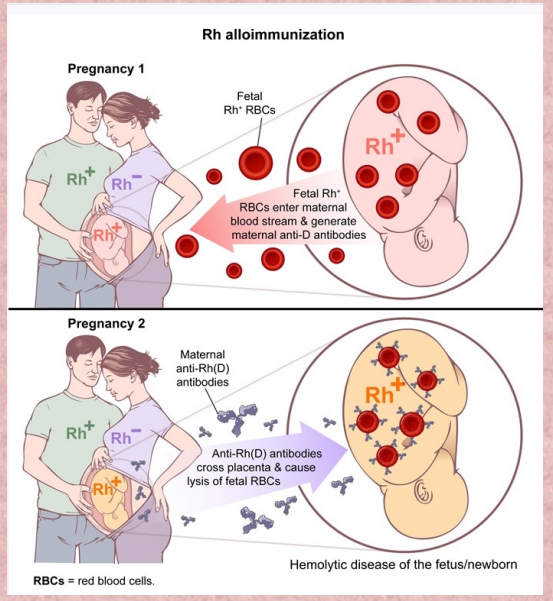
Causes of Fetal Anaemia

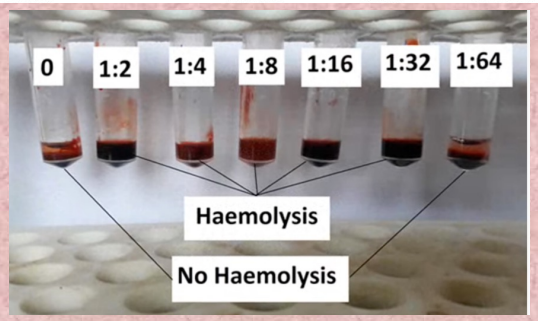
Table 2 Etiology of fetal anemia

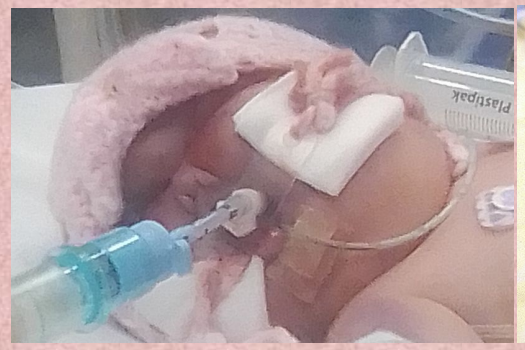
Classification	*Causes*
Immune	
RBC alloimmunization*	Rh blood group (D, c, C, e, E)*, Kell*, Duffy (Fy^a)*, Kidd (Jk^a, Jk^b)*or any IgM RBC antibody*
Non-immune	
Congenital infection*	Parvovirus B19*, CMV, toxoplasmosis, syphilis
Inherited anemias*	Hemoglobinopathies (e.g. α-thalassemia major*), RBC membrane or enzyme disorders (e.g. G6PD deficiency, pyruvate kinase deficiency)
Bone-marrow disorders	Fanconi anemia, Diamond–Blackfan anemia
Hematopoietic malignancies	Congenital leukemia, transient myeloproliferative disorder
Fetal or placental tumors, vascular malformations, other placental pathology*	Sacrococcygeal teratoma*, liver hemangioma, hepatoblastoma, diffuse neonatal hemangiomatosis, placental chorangioma*, fetal or placental arteriovenous malformations, placental mesenchymal dysplasia
Fetomaternal hemorrhage*	Placental abruption*, trauma*
Rare genetic disorders	Lysosomal storage disorders (e.g. Niemann–Pick, Gaucher disease, mucopolysaccharidosis), neonatal hemochromatosis
Complications of monochorionic placentation*	TAPS*, cotwin demise*

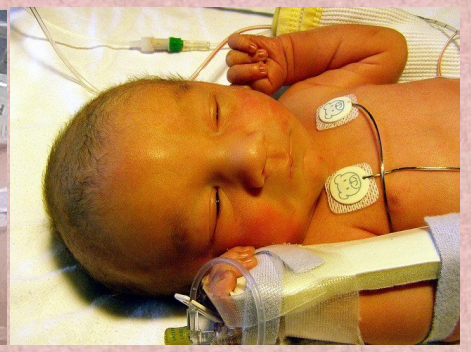
*Potential candidates for intrauterine transfusion (IUT). CMV, cytomegalovirus; G6PD, glucose-6 phosphate dehydrogenase; IgM, immunoglobulin; RBC, red blood cell; Rh, Rhesus; TAPS, twin anemia–polycythemia sequence.









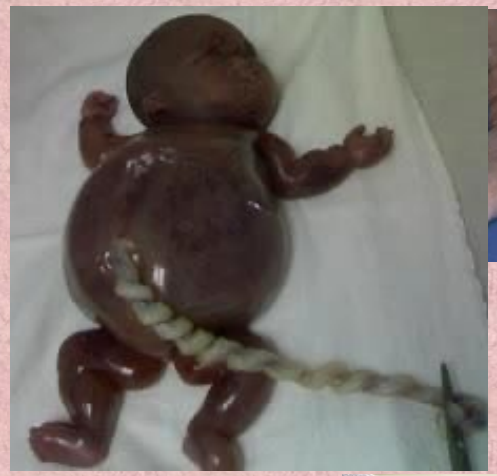


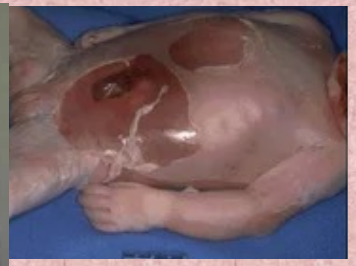
24 % die in neonatal period (Hydrops fetalis or kernicterus)

29 % severe hyperbilirubinaemia with potential irreversible neurological damage

14 % develop antibodies during first 6 months postpartum or during the next Rh tve pregnancy

Rhesus Negative – Rhesus Positive

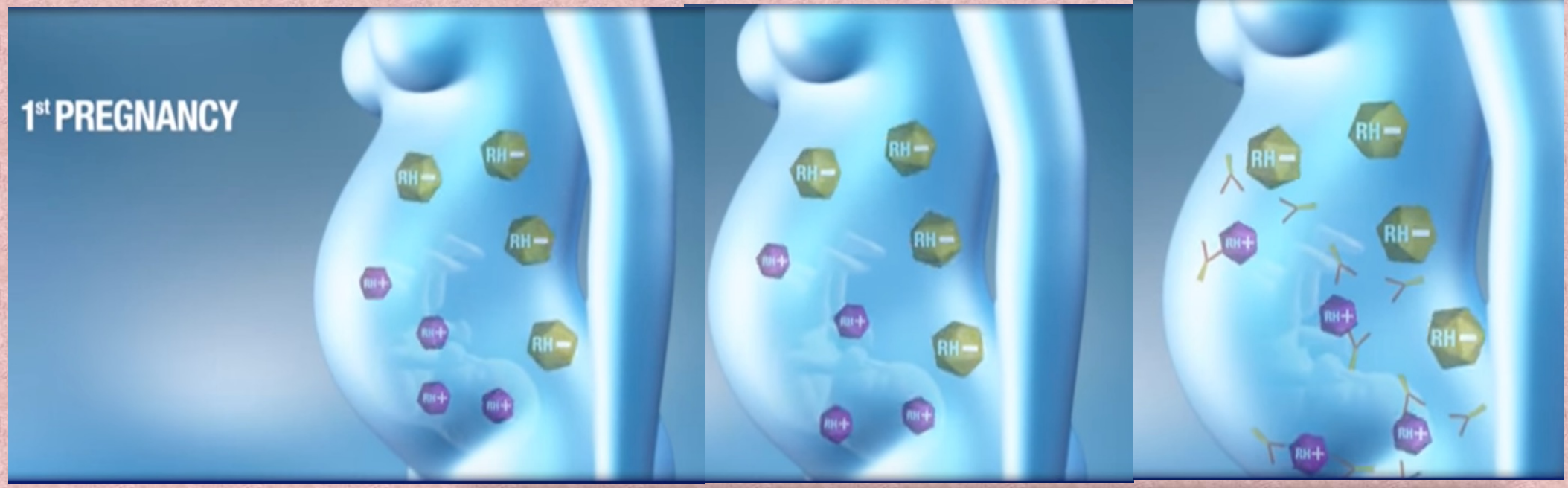


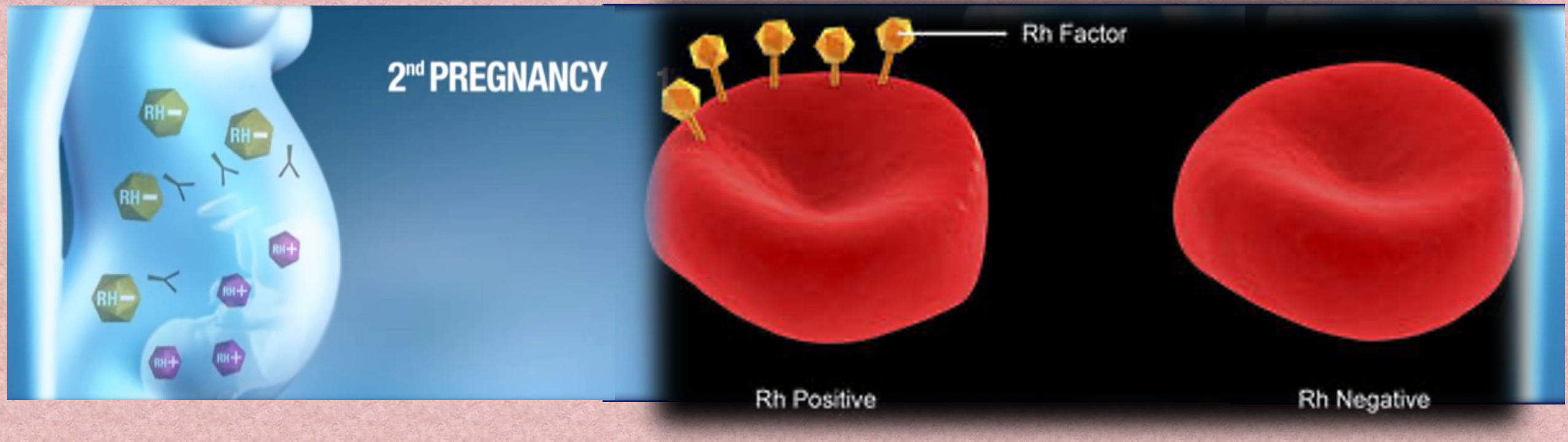


14 % IUD

33 % will not need treatment

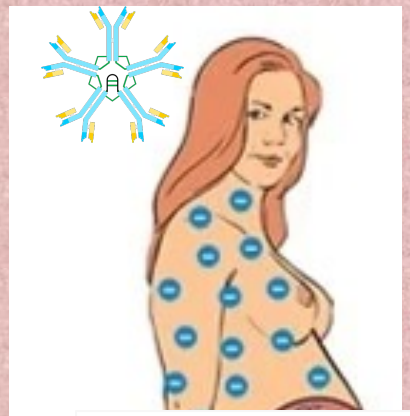
Rodrquez 2018

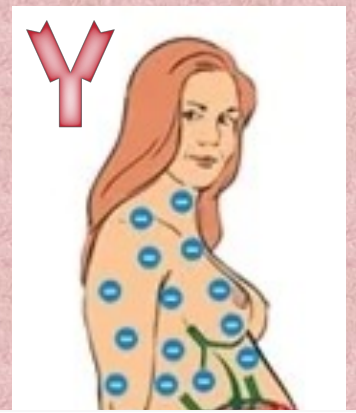

1st PREGNANCY
RH−
RH+

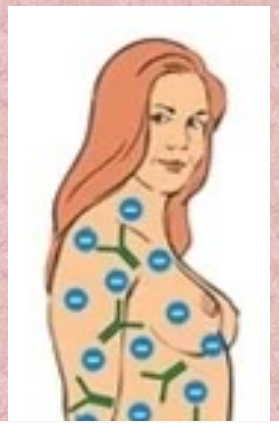

2nd PREGNANCY
RH−
RH+
Rh Factor
Rh Positive
Rh Negative

Anti-D & INCIDENCE OF ALLOIMMUNISATION

ABO
Rhesus
Phenotype
DD or Dd







ROUTINE ANTI-D

46/100,000 → 1.6 / 100,000 births

- Reduction in mortality associated with Haemolytic Disease of Newborn Pilgrim et al 2009

D deliveries of D positive, ABO compatible infants	**16 %**	**administration of anti-D, within 72 hours of labour**	**2 %**	**prophylaxis during third trimester at 28 weeks and 32 weeks gestation**	**0.17 – 0.28 %**

ROUTINE ANTI-D

- 40 % of D negative women who are carrying an D-negative fetus will received anti-D
- 40,000 women in UK received unnecessarily

Cell free fetal DNA (cffDNA) test - taking maternal blood to check for Fetal Blood

→ Blood Group

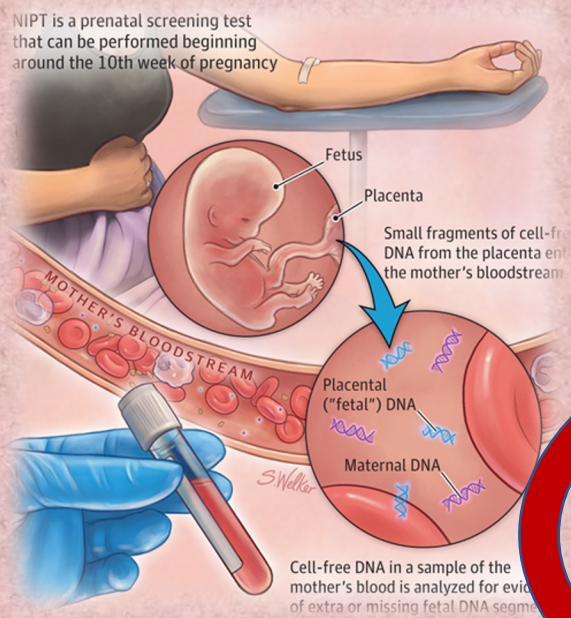
→ Rh D Genotype

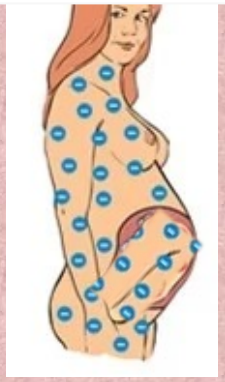
→ Other Rh Genotype (C,c,E ad Kell(K) status

16-20 week gestation

Diagnostic accuracy 96%Geifman-Holzman 2006, Finning 2008, Daniels 2009)

False negative 0.08 – 0.16 %Finning 2008, Clausen 2012





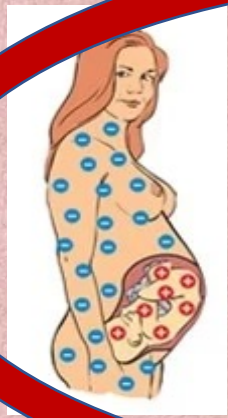
35-40 % Rhesus negative women

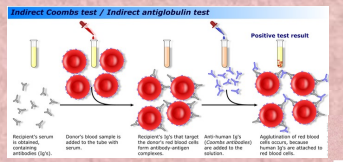
→ Not require anti D (RhOGm/RhOD)

→ Not require Lab monitoring

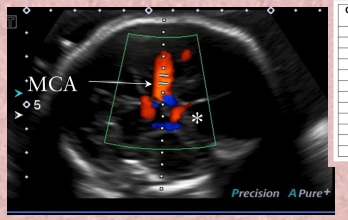
→ Not require ultrasound monitoring for MCA-PSV / hydrops

→ NO unnecessary anxiety for both [illegible] personnels

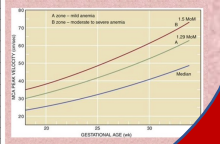


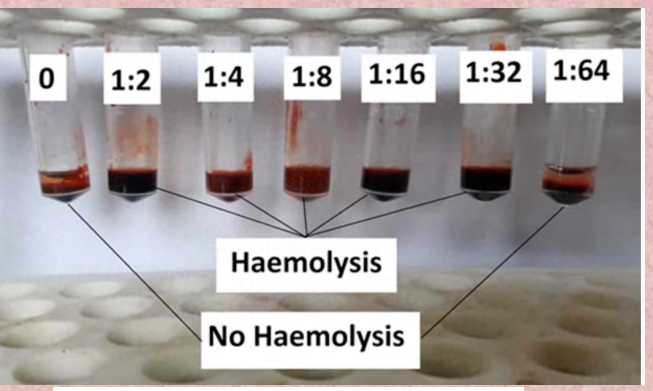


Middle Cerebral Artery – Peak Systolic Velocity



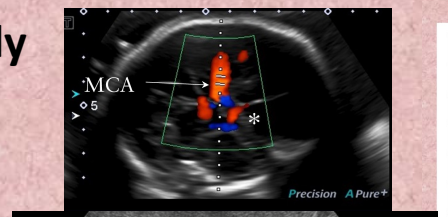
Gestation (wks)	Fetal Hb (g/dl) Mean	-6 SD's	MCA PSV (cm/s) Mean	1.5 SD's
18	11.0	5.3	23.1	30.8
20	11.3	5.6	25.6	34.2
22	11.6	5.9	28.4	37.9
24	11.9	6.3	31.5	41.9
26	12.2	6.6	34.9	46.5
28	12.5	6.9	38.6	51.5
30	12.8	7.2	42.8	57.1
32	13.1	7.5	47.4	63.3
34	13.5	7.8	52.6	70.1
36	13.8	8.1	58.3	77.7
38	14.1	8.4	64.6	86.1
40	14.4	8.8	71.5	95.4

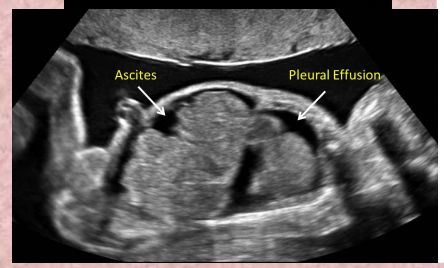




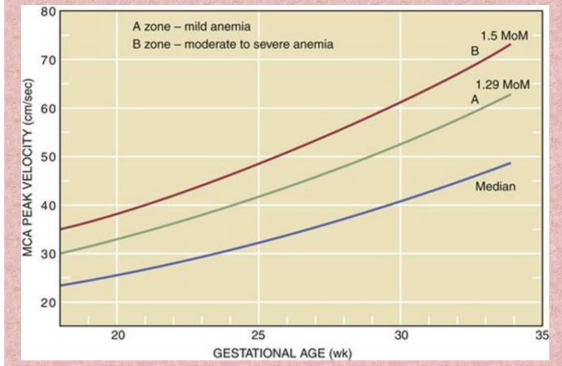
Rh Antibody < 15 IU → **Expectant Management**

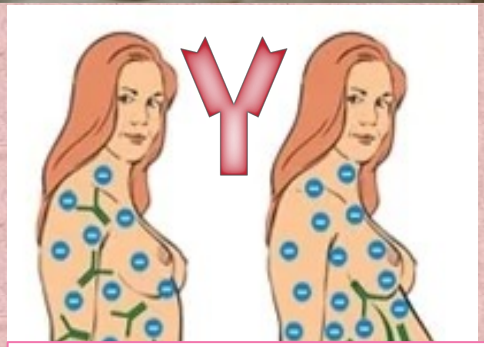
Rh Antibody ≥ 15 IU →





Gestation (wks)	Fetal Hb (g/dl)		MCA PSV (cm/s)	
	Mean	-6 SD's	Mean	1.5 SD's
18	11.0	5.3	23.1	30.8
20	11.3	5.6	25.6	34.2
22	11.6	5.9	28.4	37.9
24	11.9	6.3	31.5	41.9
26	12.2	6.6	34.9	46.5
28	12.5	6.9	38.6	51.5
30	12.8	7.2	42.8	57.1
32	13.1	7.5	47.4	63.3
34	13.5	7.8	52.6	70.1
36	13.8	8.1	58.3	77.7
38	14.1	8.4	64.6	86.1
40	14.4	8.8	71.5	95.4





History of previous affected pregnancies : fetal or neonatal death / fetal transfusion / birth of severely affected baby:

- First ultrasound and Doppler studies approximately 10 weeks before the time of (not before 17-18 weeks)
- Subsequent ultrasound and Doppler - Intervals of 1-2 weeks

Critical level of titres indicative of high risk of fetal anaemia (≥1:64 for anti-D and ≥ 1:8 of anti-Kell)

< 24 weeks
→ abnormal fetal heart rate
→ elective TOP

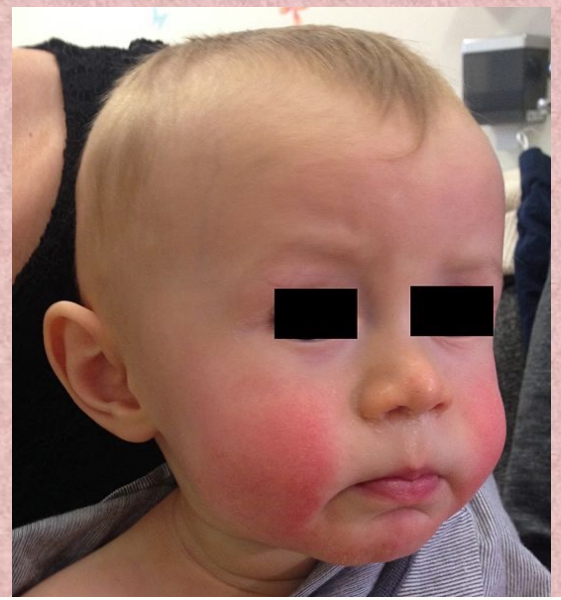
24 – 34 weeks
→ intrauterine transfusion
→ arrythmia digoxin/amiodarone
→ Fetal blood or albumin transfusion
→ Fluid drainage procedures

34 weeks
→ postnatal exchange transfusion

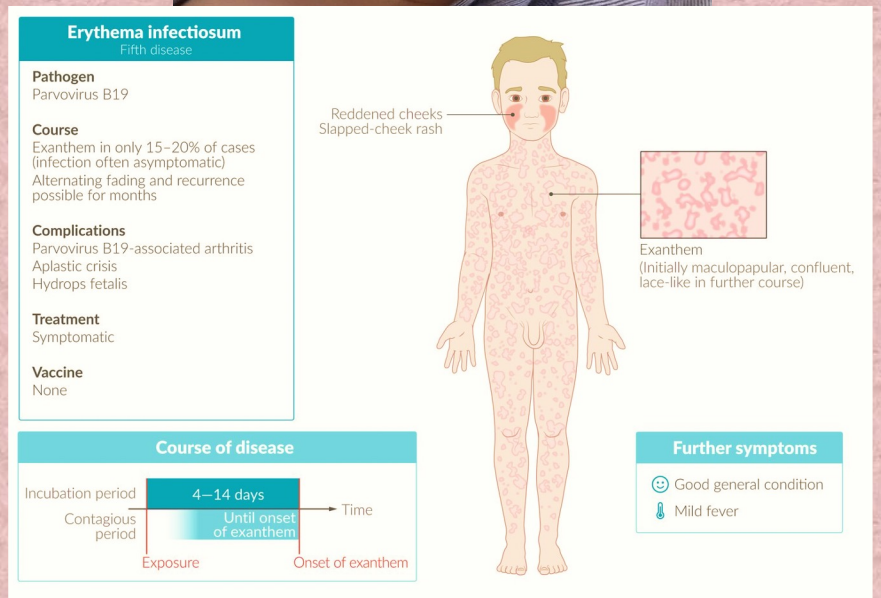
Maternal Red Blood Cell Alloimmunization

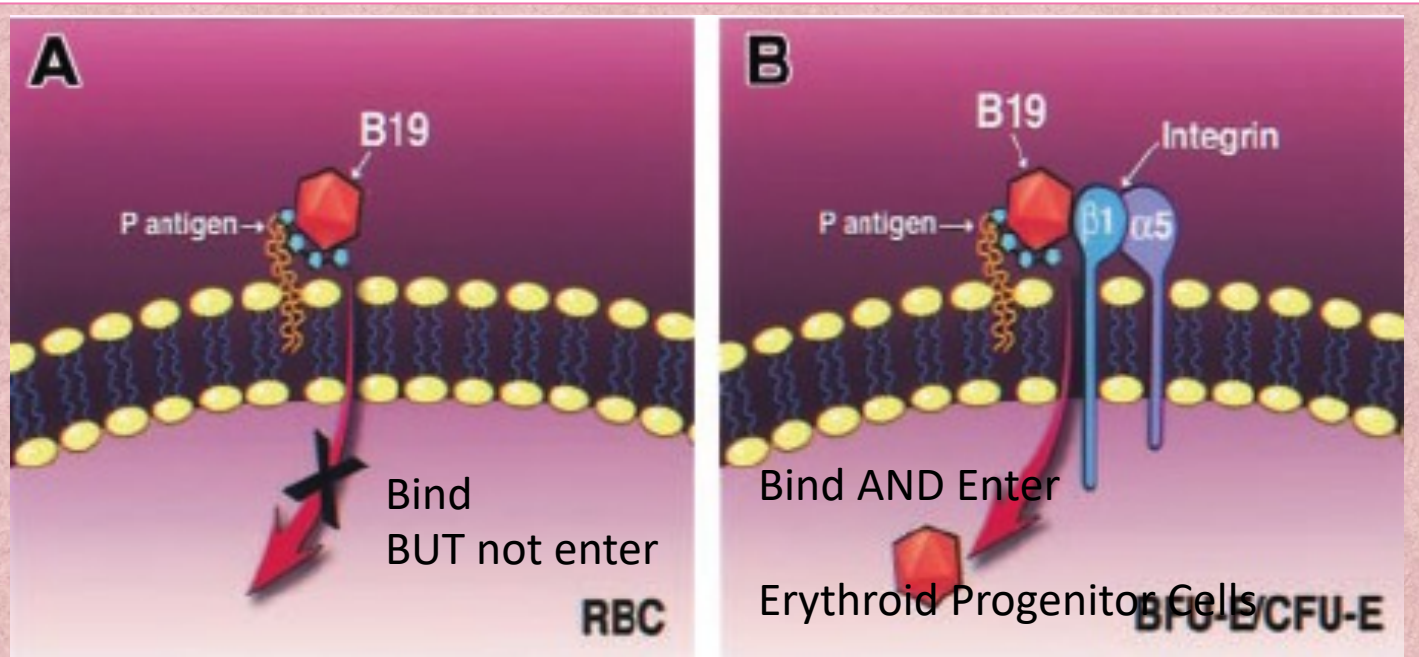
- Rhesus D
  - Standardized protocols for Rh D immune globulin prophylaxis
    - Unrecognized FMH events
    - Inadequate dosing
    - Missed prophylaxis for antenatal sensitizing events
    - Poor patient compliance
- Absence of prophylaxis for other RBC antigens
  - Other RH (c,C,e,E), anti-Kell (K,k), anti-Duffy (Fya) and anti-Kidd (Jka, Jkb)
- Omission of Kell typing of blood transfusion for women of child

Parvovirus B19

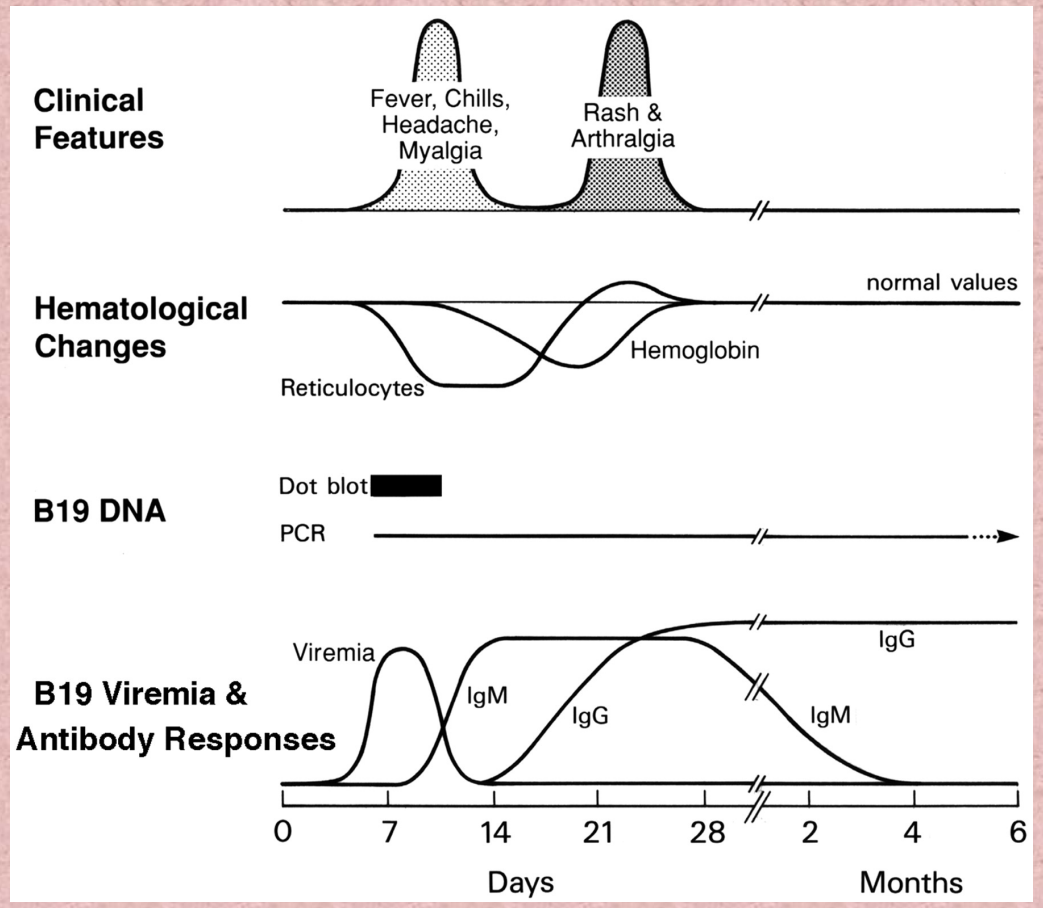


Most adults are asymptomatic or may experience polyarthralgia
65% of women of childbearing age are immune
1.5% of susceptible women will seroconvert during pregnancy
    17-33% vertical transmission with the highest risk occurring before the third trimester
Fetal infections are mostly asymptomatic without sequelae but may result in miscarriage, severe anemia with nonimmune hydrops, and stillbirth
The risk of fetal loss :
    13% when infection occurs <20 weeks
    0.5% when it occurs >20 weeks,
3% of affected fetuses develop hydrops(mother infected at 9-20 weeks)





PARVOVIRUS B19 MATERNAL INFECTION



IgM (Acute infection)

- Third day after rash
- Persist months after exposure
- Titre begin to decline by 30 to 60 days after infection

IgG

- Appear 7 days after infection remains IgG positive through life

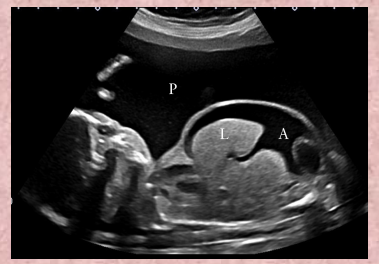
Polymerase Chain Reaction to detect Parvovirus B-19 DNA maternal serum generally unlikely to be positive after onset of rash (myalgias, fever and malaise coincide with peak viraemia)

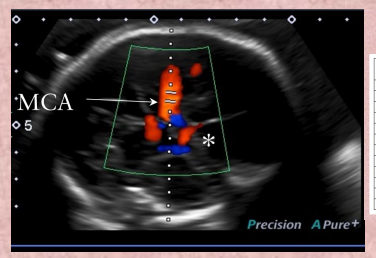
Clinically Suspicious
History of Infection

- ✓ First Trimester
  Thick nuchal translucency
  Congenital anomalies (ventriculomegaly, mild hydrocephaly, microcephaly)
- ✓ Second and Third trimester
  Ultrasound features of hydrops fetalis
  (Ascites, Pleural or pericardial effusion, skin thickening, cardiomegaly)

IgG tve IgM -ve	Mother is immune	Reassuarance of maternal immunity and low risk to fetus
IgG -ve IgM -ve	Mother is at risk for infection	Repeat IgM or IgG in 3 to 4 weeks for Seroconversion
IgG -ve IgM tve	Possible recent infection	
IgG tve IgM tve	Consistent with Recent Infection	

No intervention is available to prevent fetal infection or damage
Monitor every 1-2 weeks for 12 weeks
As fetal hydrops starts average 5 weekd of maternal infection





Middle Cerebral Artery – Peak Systolic Velocity

Gestation (wks)	Fetal Hb (g/dl) Mean	-6 SD's	MCA PSV (cm/s) Mean	1.5 SD's
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20	11.3	5.6	25.6	34.2
22	11.6	5.9	28.4	37.9
24	11.9	6.3	31.5	41.9
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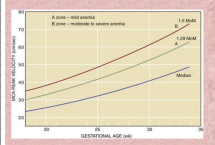

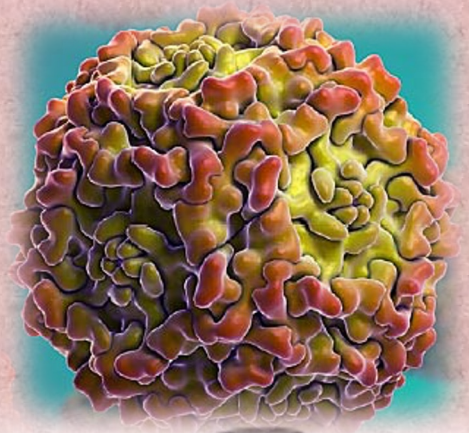

Non-immune hydrops secondary to Parvovirus B19

Spontaneously resolved -34 %

Fetal Demise 30 % in expectant management

Intrauterine Blood Transfusion

- 29 % resolved
- 6 % fetal demise 48 hours after procedure

Aggressive serial blood Transfusion

- Fetal survival 60-80% vs 15-30% without serial blood transfusion

Overall perinatal survival 50 – 98 %

Conclusion / Take Home Message

- Anti-D prophylaxis
  - Reduce incidence of alloimunisation and immune hydrops
- Non-invasive cffDNA
  - Reduce unnecessary anti-D prophylaxis
  - Reduce burden of fetal surveillance
- Non-invasive monitoring for severity of anaemia via Doppler ultrasound of fetal MCA-PSV
  - Improve the fetal loss rate results from serial amniocentesis
  - Timely judgment on further management either to terminate / deliver or continue pregnancy
- Refinement of intrauterine blood transfusion technique
  - Improve the survival rate for severe fetal anaemia and hydrops fetalis
- For Rhesus negative mother
  - The MCA-PSV should replace serial antibody titre
- For Parvovirus B19
  - Importance to understand the seroconversion during pregnancy to arrange for surveillance
- Appropriate preconception counseling and prenatal management of Fetal Anaemia are to be made available


THANK YOU