Alloimmune disorders of pregnancy
&
Non-immune Hydrops fetalis

DR. MOATH SALEH BANI HANI

Alloimmune disorders of pregnancy

Alloimmune disorders of pregnancy

RANGE OF CONDITIONS SHARING SAME PATHOPHYSIOLOGY

- TRANSFER OF FETAL CELLS TO MATERNAL CIRCULATION
- STIMULATE PRODUCTION OF IG TO ANTIGENS ON FETAL CELLS/PLATELETS
- MATERNAL IG CAN CROSS THE PLACENTA
- DESTRUCTION OF FETAL CELLS

INCLUDE

- NEONATAL ALLOIMMUNE THROMBOCYTOPENIA
- NEONATAL ALLOIMMUNE NEUTROPENIA
- RH ALLOIMMUNISATION

Rh-alloimmunisation

Clinically relevant red cell antigens

- RH SYSTEM: D ALLOIMMINISATION
- KELL SYSTEM
- ABO SYSTEM

Rhesus system

- Contains 45 different antigens
- The most clinically relevant; D, c and E
- In practice; only anti-D + anti-c cause HDFN(hemolytic disease of fetus and newborn), others rarely give rise to problem

D alloimminisation

- RhD negative: a person who lacks D antigen on RBC
- RhD positive: has D antigen on RBCs

Frequency of RhD negative people

- 8% of African Americans
- 15% of white Americans

Kell system

- 26 antigens
- K1 or KEL1 most relevant
- Incidence of HDNB cause by D decreases due to anti-D Ig .Therefore, we became more aware of anti-K
- Most common immune RBC antibody outside the ABO & Rh system
- K antibodies are known to cause severe fetal anaemia
- Women with anti-K antibodies are difficult to manage, as the levels of antibody do not correlate as well with the severity of the disease as with anti-D

Rh alloimmunisation (D)

Pathophysiology

2 EXPOSURES TO RHD ANTIGEN ARE REQUIRED TO PRODUCE SENSITIZATION

- FIRST LEADS TO PRIMARY SENSITIZATION AND PRODUCES IGM
- SECOND CAUSES PRODUCTION OF IGG (CROSSES THE PLACENTA)

Effect on the fetus and neonate

- Placental transfer of Anti-D IgG is possible
- Transfer is slow initially, rising from 20 weeks until term
- At term, IgG levels in fetus can exceed levels in the mother
- IgG attaches to the D antigen on fetal RBCs
- Antibody-antigen complex formed then destroyed by the reticuloendothelial system
- Fetus is at risk of anaemia, may lead to hydrops and death

Pathophysiology

- **ANTI D ANTIBODIES REMAIN FOR LIFE**

IN SUBSEQUENT PREGNANCY

- **IF THE FETUS IS RH D POSITIVE**
  - A small FMH will elicit a big maternal immune response
  - Production of Anti-D IgG antibodies
  - Will cross the placenta to fetal circulation
  - Haemolyis of fetal Rh +ve RBCs in the spleen and liver

Pathophysiology

IN CASE OF PRIOR RH-D DISEASE, IT EITHER

- HAPPENED WITH THE SAME SEVERITY OR
- BECOMES PROGRESSIVELY MORE SEVERE

IF PREVIOUS FETAL HYDROPS

- RISK IN SUBSEQUENT PREGNANCIES: 90%
- DEVELOPS AT SAME GA OR EARLIER THAN IN PREVIOUS PREGNANCY

sensitizing events

DURING PREGNANCY AND DELIVERY

- MISCARRIAGE. ECTOPIC. SURGICAL MX OF MISCARRIAGE
- CHORIONIC VILLOUS SAMPLING
- AMNIOCENTESIS
- EXTERNAL CEPHALIC VERSION
- TRAUMA TO GRAVID UTERUS

OTHER SENSITISING EVENTS

- TRANSFUSION OF RHD +VE BLOOD: MISMATCHED BLOOD OR STEM CELLS
- NEEDLE INJECTION CONTAMINATED WITH RHD +VE RBC
- THE "GRANDMOTHER" THEORY (MATERNAL – FETAL HAEMORRHAGE)

How does the fetus respond?

IF HAEMOLYSIS IS MILD

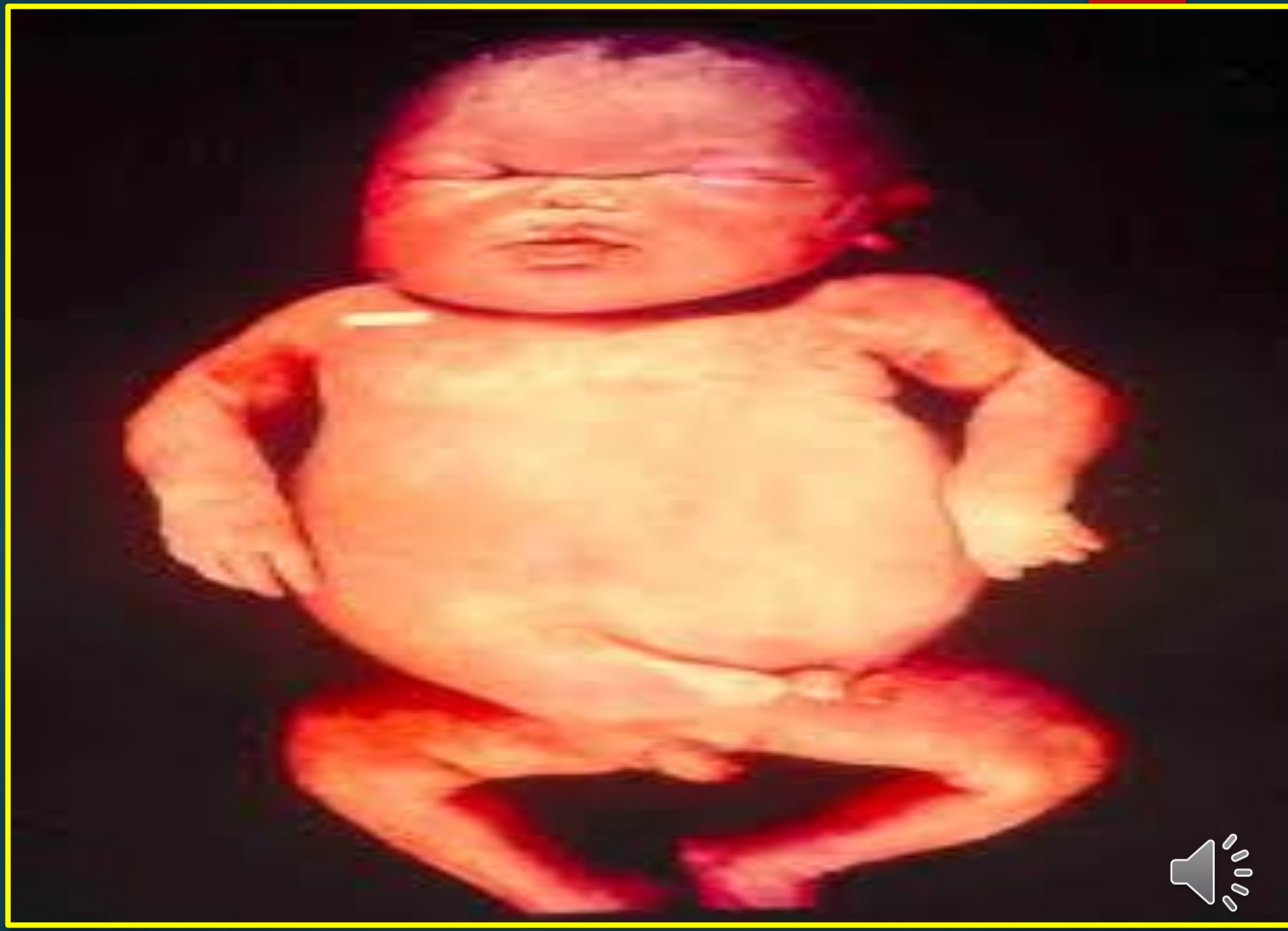
- COMPENSATES BY INCREASING ERYTHROPOIESIS

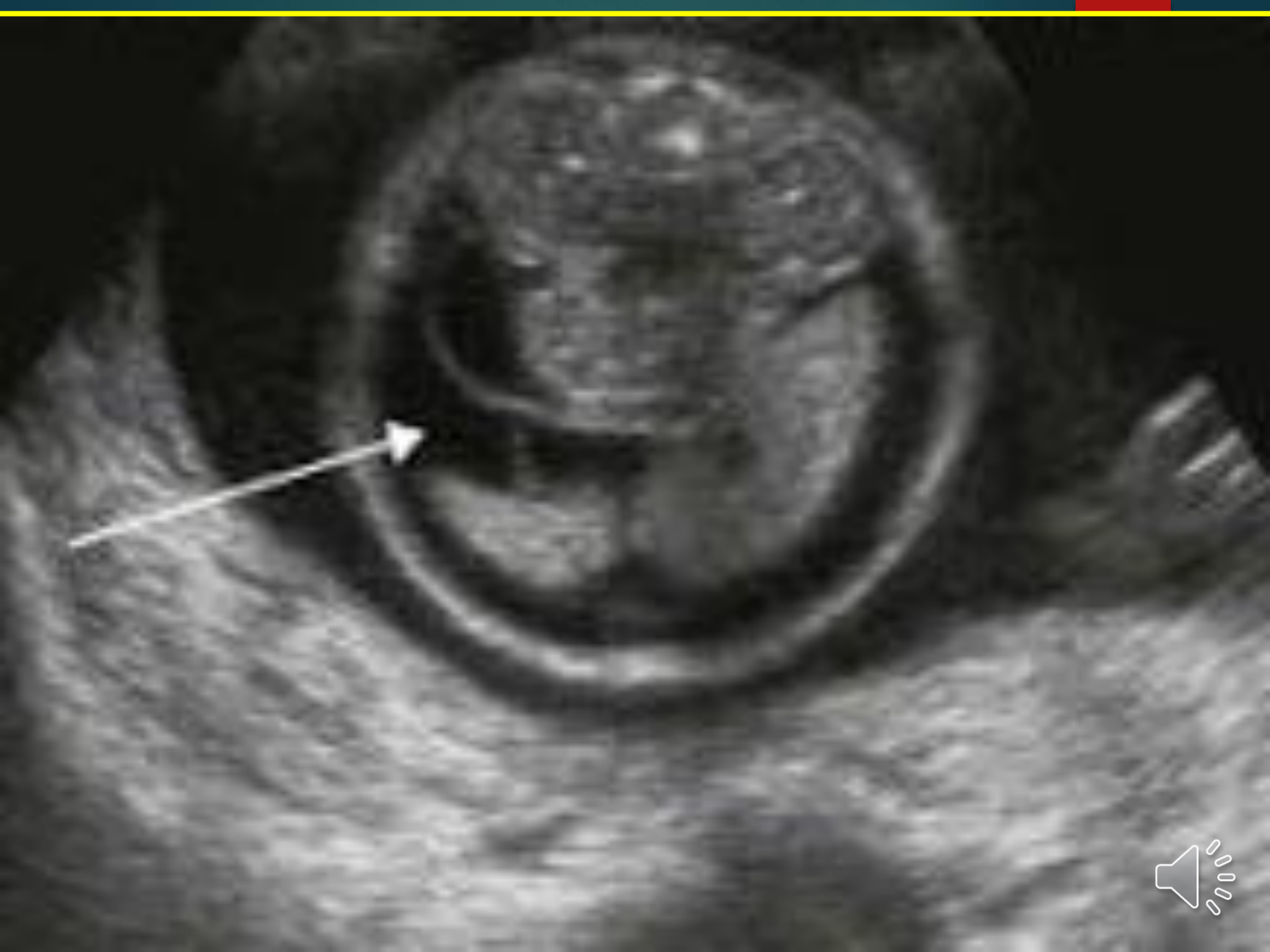
IF HEMOLYSIS IS SEVERE (SEVERE FETAL ANAEMIA)

- EXTRAMEDULLARY HAEMATOPOIESIS
- PORTAL HYPERTENSION
- HYPOALBUMINEMIA
- HYPERBILIRUBINEMIA
- HEART FAILURE (HYDROPS FETALIS)
- IUFD

HYPERBILIRUBINEMIA CAUSES CNS DAMAGE

- NEONATAL ENCEPHALOPATHY
- KERNICTERUS





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Screening

The aims of screening

- Identify women at risk to prevent immunisation
- Identify women already have D alloimmunity in order to identify at risk fetuses

Screening

- **Maternal booking visit blood tests should include blood group & Rh determination**

- **If Rh –ve: test for Anti-D antibodies**
  - If Anti D- Antibodies are negative:
    - Mother is **not sensitised**
    - A further check for antibodies at 28-30 weeks
    - Prevention is recommended (Anti-D Ig prophylaxis)
  - If Anti-D antibodies are positive:
    - Mother is sensitised either known or new
    - Managment of alloimmunisation started

Prevention of sensitisation

Principles of prevention

Avoid exposure

- Rh appropriate transfusion
- Avoid contaminated needles

Prevent sensitisation

- Anti-D immunoglobulins prophylaxis
- Given within 72 hours of sensitizing events

Limit sensitization if already exposed

- Anti-D after sensitising events (<72 hours)

Routine antenatal anti-D prophylaxis

Routine prophylaxis can be given as:

Antenatally

- 2 doses of anti-D at 28 weeks & at 34 weeks OR
- A single dose either at 28 weeks or 34 weeks

Give Anti-D

- After a potentially sensitising event
- May use Kleihauer test to calculate dose if indicated

Sensitising events …AGAIN !

DURING PREGNANCY AND DELIVERY

- MISCARRIAGE. ECTOPIC. SURGICAL MX OF MISCARRIAGE
- CHORIONIC VILLOUS SAMPLING, AMNIOCENTESIS, CORDOCENTESIS
- ANTEPARTUM HAEMORRHAGE
- EXTERNAL CEPHALIC VERSION
- TRAUMA TO THE GRAVID UTERUS
- DELIVERY: VAGINAL AND CS

OTHER SENSITISING EVENTS

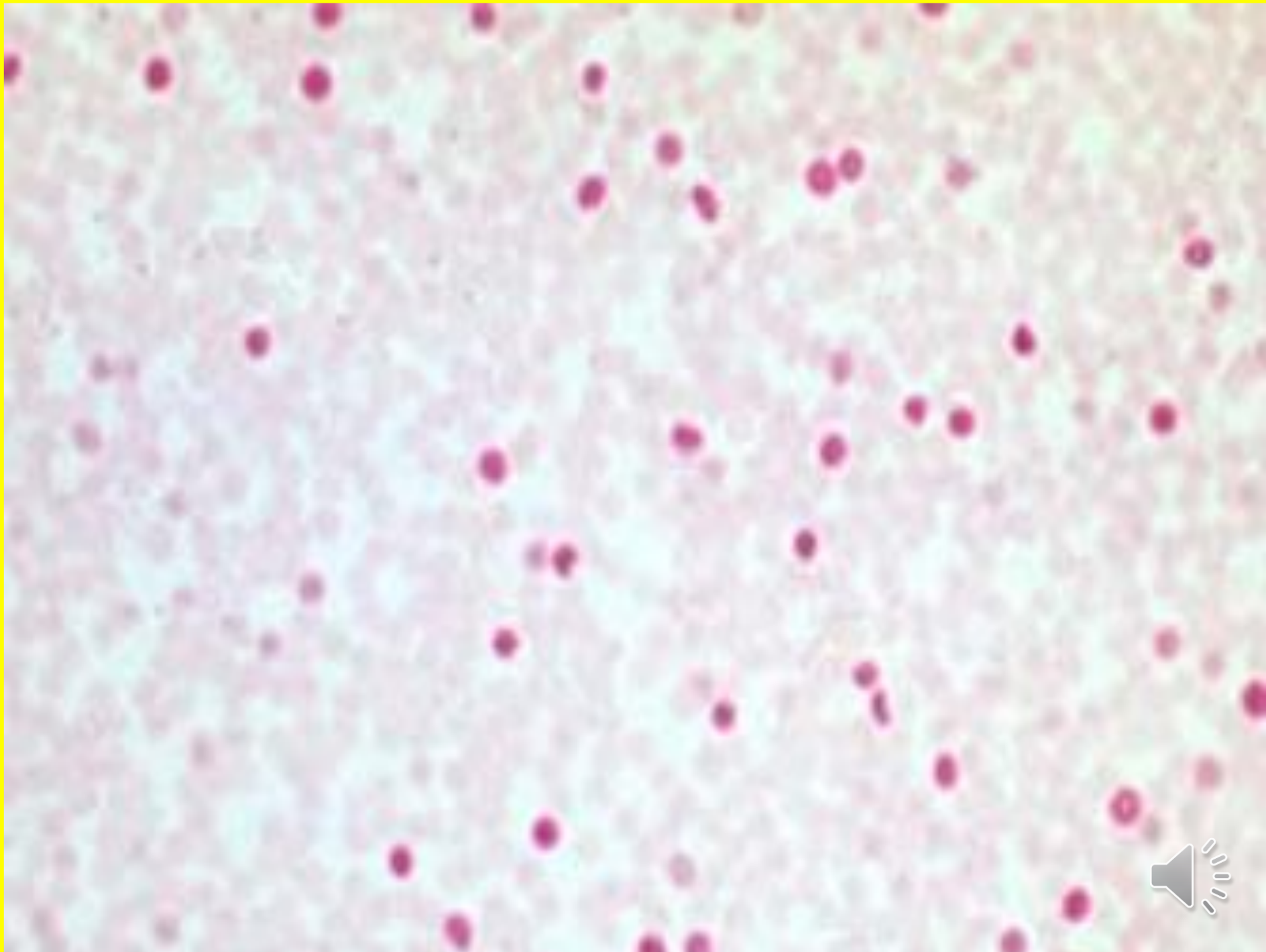
- EXPOSED TO RHD +VE BLOOD : MISMATCHED TRANSFUSION OR STEM CELL TRANSPLANTATION
- INJECTION WITH CONTAMINATED NEEDLES WITH RHD + RBC

Kleihauer - Betke test (Acid elusion test)

- **A METHOD OF QUANTIFYING FETO–MATERNAL HAEMORRHAGE (FMH)**
- **HAVE A THRESHOLD OF 5 ML OF FMH TO BE POSITIVE**
- **AMOUNT OF FMH TO CAUSE IMMUNIZATION: 0.01-0.03 ML …AGAIN !!**

THEREFORE

- estimate the amount of FMH
- This method detect the presence of fetal cells but NOT distinguish between Rh-D positive and negative cells .
  - If positive, it is used to determine additional(125 iu of anti d will neutralize 1 ml of FMH) Anti-D over the standard 150 to 300 mcg that should be administered
  - 300 mcg(microgram) Anti-D protects against 30 ml of fetal cells



FLOW CYTOMETRY

- This test is performed after kleihauer , to confirm the volume of FMH and determine whether the fetal cells are +ve or –ve .
- If negative test after +ve kleihauer test it suggest that the fetus is RH-D negative .
- Not available in all centres .

Guideline for anti-D

Routine Antenatal Anti-D Prophylaxis

- Administered regardless of and in addition to any anti-D that may have been given for a potentially sensitising event

Following birth

- Baby's ABO & Rh D status checked on cord blood
- If baby is D +ve, a previously non-sensitised mother, should be offered at least 500 IU of anti-D Ig within 72 h (AS SOON AS POSSIBLE)
- If indicated, maternal blood should be tested for the size of FMH to adjust extra dose(s) of Anti-D needed

For IUFD

- May not be able to obtain fetal blood sample
- Anti-D Ig should be administered to D -ve, previously non-sensitised mother within 72 h of the Dx of IUFD, irrespective of the time of subsequent delivery

Guideline for anti-D

THREATENED MISCARRIAGE BEFORE 12 WEEKS

- RH D ANTIGEN REPORTED ON FETAL RBC AS EARLY AS GA: 5-7 WK
- FMH HAPPENED IN 3–11% OF WOMEN WITH THREATENED MISCARRIAGE FROM GA OF 7 TO 13 WEEKS
- CONSIDER ANTI-D WHEN BLEEDING IS HEAVY, REPEATED, ASSOCIATED WITH ABDOMINAL PAIN AND CLOSE TO 12 WEEKS
- **DOSE: 250 IU**

GIVE ANTI-D

- AFTER MEDICAL OR SURGICAL MX OF ECTOPIC PREGNANCY
- AFTER SUCTION EVACUATION ? REGARDLESS OF GESTATIONAL AGE
- **DOSE: 250 IU**

A TEST FOR FMH IS NOT REQUIRED BEFORE 12 WEEK

Guideline for anti-D

- For sensitizing events between 12-20 week :

  -give anti-d 250 IU

  - **A TEST FOR FMH IS NOT REQUIRED**

- For sensitizing events after 20 weeks :

  - give anti-d **500 IU** (as soon as possible but within 72 H)

  -- A TEST FOR FMH IS REQUIRED

Management of Rh alloimmunisation

MOTHER SENSETISED

Management

History

- **Time of sensitisation / event (if possible)**
- **Same or new partner (check his Rh-D status)**
- **If new partner is:**
  - Rh-D negative: No further action
  - Rh-D positive : Mx

- **If known sensitised, ask about previous pregnancies outcome; GA at onset, development of hydrops (again !!)**
  - Tends to develop earlier and more severe
  - Risk of recurrence of hydrops > 90%

Mnagment

DETERMINE FETAL D ANTIGEN STATUS (IF POSSIBLE) BY

- **FREE FETAL DNA IN MATERNAL BLOOD FROM 8 WEEKS**
- **CVS OR AMNIOCENTESIS**
  - If free fetal DNA is not available

RESULTS AND ACTION

- **IF FETUS IS D –VE : NO FURTHER ACTION**
- **IF FETUS IS D +VE : NEEDS FOLLOW UP; MATERNAL ANTI-D ANTIBODY TITER**

Mx
Maternal Anti-D antibody titre

AN ANTI-D LEVEL > 4 IU/ML BUT < 15 IU/ML

- MODERATE RISK OF FETAL ANAEMIA

AN ANTI-D LEVEL OF > 15 IU/ML

- CAN CAUSE SEVERE FETAL ANAEMIA

ANTI-D LEVELS SHOULD BE MEASURED

- EVERY 4 WEEKS UP TO 28 WEEKS
- EVERY 2 WEEKS UNTIL DELIVERY

REFERRAL FOR FETAL MEDICINE ONCE ANTI-D LEVELS ARE > 4 IU/ML

Monitoring of pregnancies at risk of fetal anaemia

If anti-D antibody titre is rising > 4 iu/ml, perform;

- **Weekly Doppler study of the Middle cerebral artery (MCA) doppler to measure peak systolic velocity (MCA PSV)**
- **Ultrasound scan (USS).**

- **Early feature of fetal anaemia**
  - MCA PSV > 1.5 multiple of the median
  - USS evidence of anaemia (ascites is an early sign)

If anaemia develops, consider intrauterine transfusion

Monitoring of pregnancies at risk of fetal anaemia

FETAL HYDROPS

AN OVERT SIGN OF FETAL ANAEMIA

DEFINED AS AN ULTRASOUND FINDING OF FLUID IN TWO OR MORE COMPARTMENTS:

- Ascites
- Pleural effusion
- Pericardial effusion
- Scalp oedema
- Skin oedema

Intrauterine transfusion

- **Intra-vascular and Intra-peritonial**
- **May need to repeat several times**
- **Overall chance of survival of anaemic fetus is 85% to 90% if transfused**

Complication

- **Complication rate: 2% per IUT procedure**
- **Include**
  - PPROM , Preterm labour ,Infection .Fetal distress , IUFD
  - Advantages : improve survival rate , decrease neurological mobidity .

Delivery

TIMING OF DELIVERY DEPEND ON

- THE ANTIBODY LEVELS / TITRES RATE OF RISE
- IF ANY FETAL THERAPY HAS BEEN REQUIRED
- CONSIDER STEROIDS FOR LUNG MATURITY

- *EXAMPLE : IF IUT WAS NEEDED DELIVERY IS CONSIDERED BETWEEN 34-35 WEEK .

Mx of the neonate

- EARLY DISCHARGE IS NOT ADVISABLE
- REGULAR ASSESSMENT OF NEUROBEHAVIOURAL STATE
- OBSERVED FOR DEVELOPMENT OF JAUNDICE AND / OR ANAEMIA
- REGULAR ASSESSMENT OF BILIRUBIN AND HB LEVELS
- ENCOURAGE BREAST FEEDING
- PREGNANCIES WITH A MINIMAL OR NO RISK OF FETAL OR NEONATAL ANAEMIA REQUIRE NO SPECIFIC TREATMENT

Non-immune hydrops (NIHF)

NIHF

Definition

- **Hydrops not mediated by red cell antigens (rhd,kell)**
- **Accounts for 90% of fetal hydrops**

Incidence : 1/1500 to 1/3800 births

AGAIN !!!

Fetal hydrops is diagnosed by the presence of excess fluid in two or more fetal compartments including:

- Pleural cavity
- Pericardial cavity
- Abdominal cavity (ascites)
- Amniotic sac (polyhydramnios)
- skin edema

Causes

Genetic disorders (10%)

- Aneuploidy: monosomy X, trisomy 21, trisomy 18
- Metabolic diseases: Hurler syndrome, Gaucher disease

Cardiovascular (40%)

- Structural lesions: AVSD, hypoplastic left and right heart syndrome, cardiomyopathy
- Arrhythmias: tachy and bradyarrhythmia

Pulmonary (10%)

- Diaphragmatic hernia (causes Pulmonary HTN...)
- Pulmonary neoplasia and lymphangiectasia (Pleural effusion...)
- Bronchogenic cysts (compress thorasic vessels and lymphatic causing hydrops...)

Causes

Infectious diseases (8%)

- Parvovirus
- Cytomegalovirus
- Syphilis
- Coxsackie virus
- Toxoplasmosis
- Rubella virus

Gastrointestinal and renal

- Gut duplications and malrotation
- Hepatobiliary vascular malformation and tumours
- Congenital nephrosis
- Posterior urethral valves

Causes

Haematologic (10%-27%)

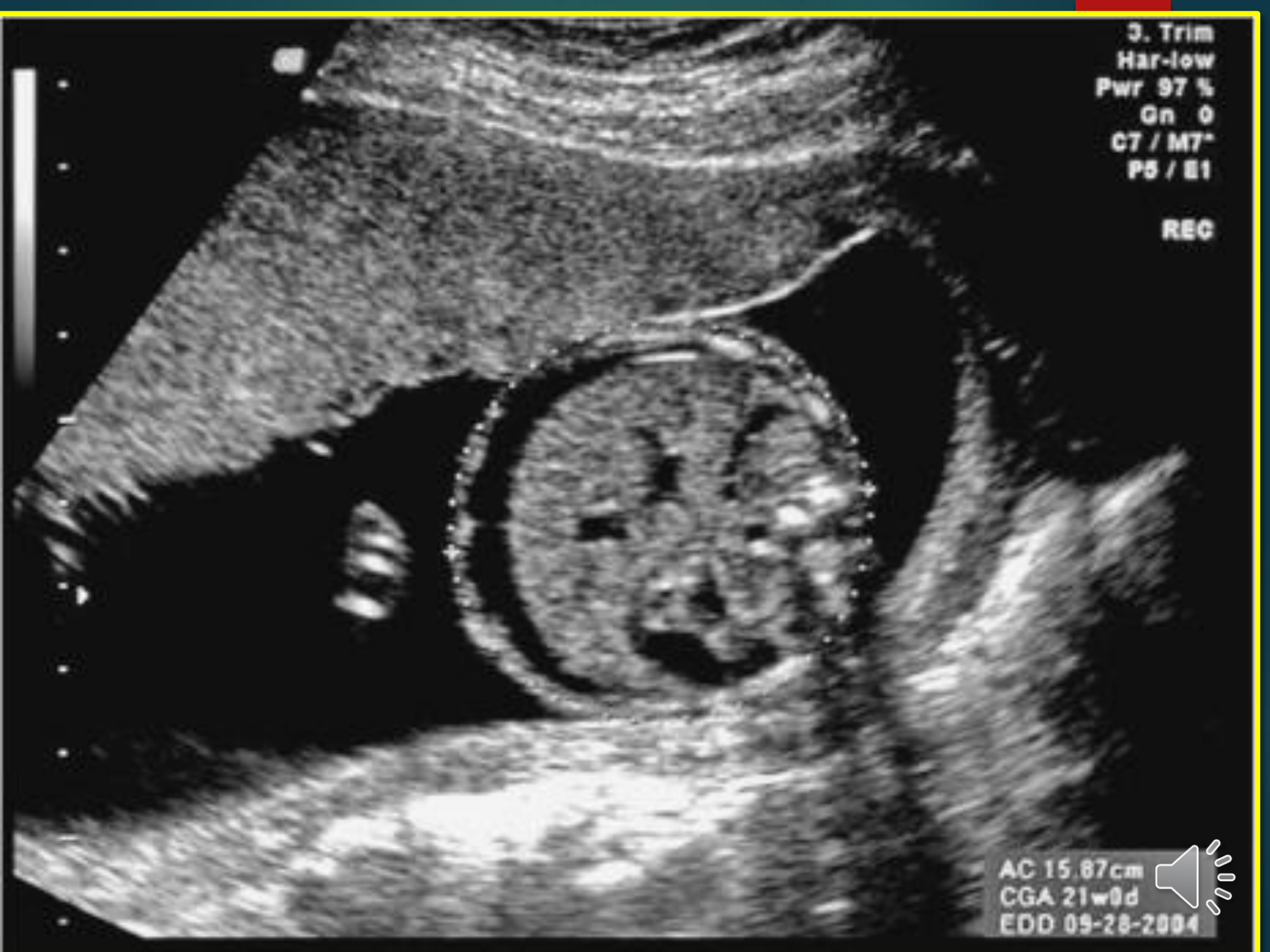
- a Thalassemia
- Aplastic anemia (Parvovirus infection……)
- Fetal hemorrhage

Placental abnormalities

- AV fistulae
- Chorioangiomas
- Umbilical cord thrombosis, and aneurysms

Other

- Twin to Twin Transfusion Syndrome


3. Trim
Har-low
Pwr 97 %
Gn 0
C7 / M7*
P5 / E1
REC
AC 15.87cm
CGA 21w0d
EDD 09-28-2004

Diagnosis ….AGAIN !!!

Ultrasound: abnormal fluid in 2 or more compartments

- **Pleural effusions: Uni or bilateral**
  - Lung hypoplasia:
    - Lung compression and restricted growth
    - More common when hydrops develops < 20 weeks
    - A common cause of neonatal mortality
- **Pericardial effusions**
- **Fetal ascites**
- **Polyhydramnios: AFI > 25 cm or SDP > 8 cm**
- **Skin edema: Late finding**
- **Placentomegaly: oedema of the intervillous spaces**

Approach

- **Maternal history**
  - Ethnicity, family hx of inherited disorders, travel history, infectious agent exposure
- **Fetal anatomical survey**
- **Maternal**
  - Blood type and antibody screen, CBC
- **Infectious studies**:
  - Toxo, Rubella, CMV, HSV, Coxsackie, adeno, parvo, syphilis
  - May be from maternal serology or amniotic fluid PCR studies
- **karyotype should be offered**
- **Fetal echocardiogram**
- **MCA doppler: Determine the presence of fetal anaemia**

Fetal risks

- Perinatal mortality rate > 50%
- Overall prognosis is related to etiology & GA at diagnosis
- Preterm labor and PROM due to uterine overdistention

Management

Rx specific to etiology

- e.g. In fetal anaemia due to parvovirus infection, red blood cell transfusion should be considered

Fetal wellbeing monitoring

- Serial fetal scans
- Twice weekly fetal surveillance

Delivery

- At a tertiary care center with NICU
- Neonatal consultations prior to delivery

THANK YOU ….

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