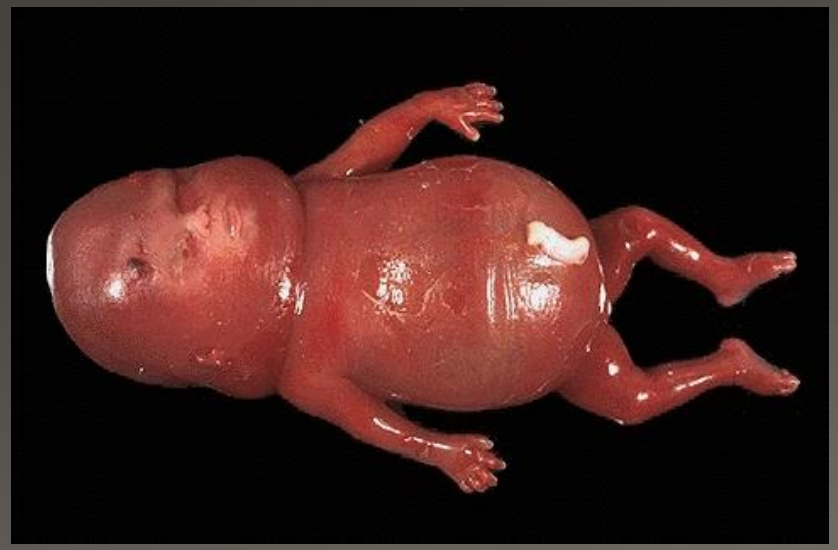
Rhesus Isoimmunization



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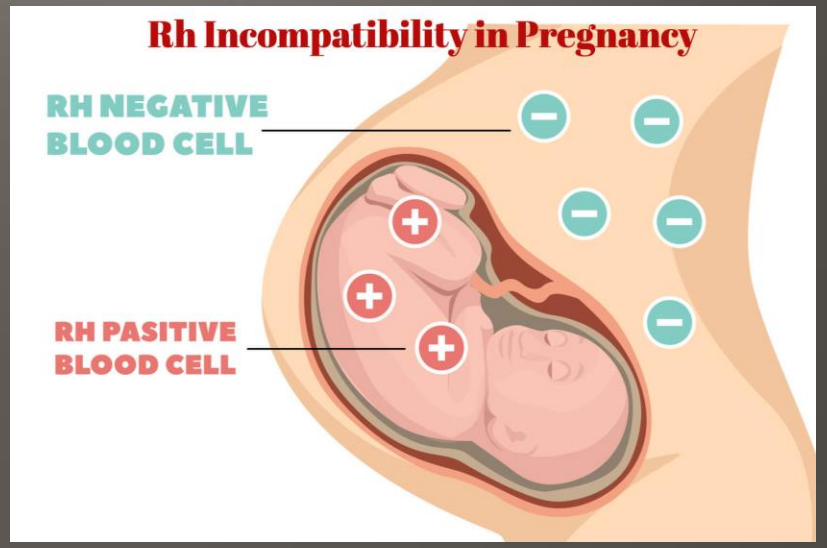
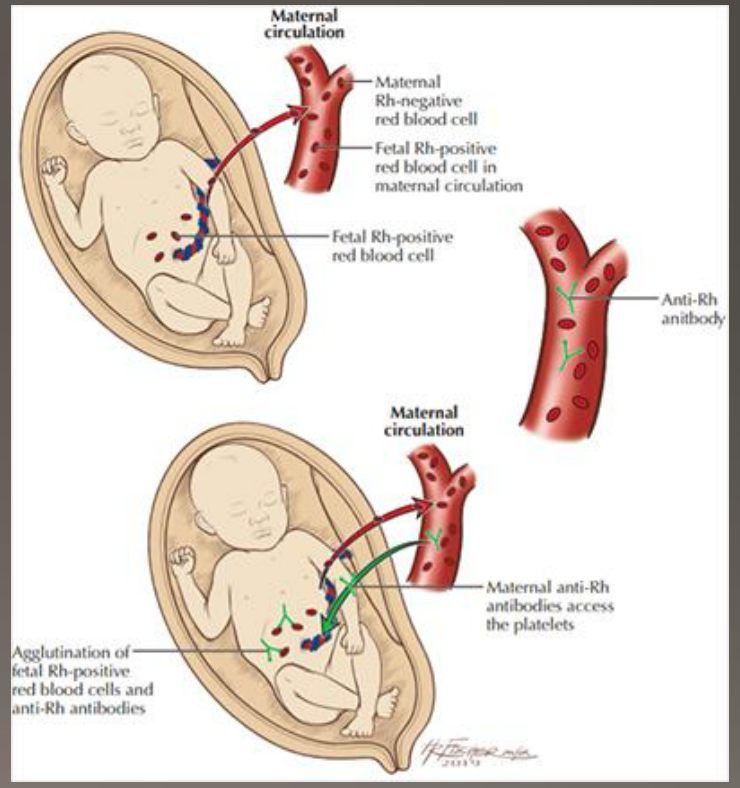
Introduction

- Rhesus (Rh) isoimmunization is an immunologic disorder that occurs in a pregnant, Rh-negative patient carrying an Rh-positive fetus.

- The immunologic system is stimulated to produce antibodies to the Rh antigen, which then cross the placenta and destroy fetal red blood cells.





Pathophysiology

- The Rh complex is made up of a number of antigens, including C, D, E, c, e, and other variants
- More than 90% of cases of Rh isoimmunization are due to antibodies to D antigens
- Rh negative :RBCs Lack D antigen on the surface an individual with
- Rh positive: RBCs surface has D antigen.
- When Rh-negative patients are exposed to the Rh antigen, they may become sensitized

Mechanism

- Two mechanisms theories are proposed for sensitization:
  1. Undetected placental leak of fetal red blood cells into the maternal circulation during pregnancy***. (most likely)***
  2. Rh-negative woman may have been sensitized from birth by receiving enough Rh-positive cells from her mother

Two exposures to the Rh antigen are required to produce any significant sensitization, unless the first exposure is massive.

1st exposure → primary sensitization

2nd Exposure → Anamnestic response leading to the rapid production of immunoglobulins.

Types of immunoglobulins

- The initial response to exposure to Rh antigen is the production of immunoglobulin M (IgM) antibodies for a short period of time

- Followed by the production of IgG antibodies that are capable of crossing the placenta and lasts for a life time.

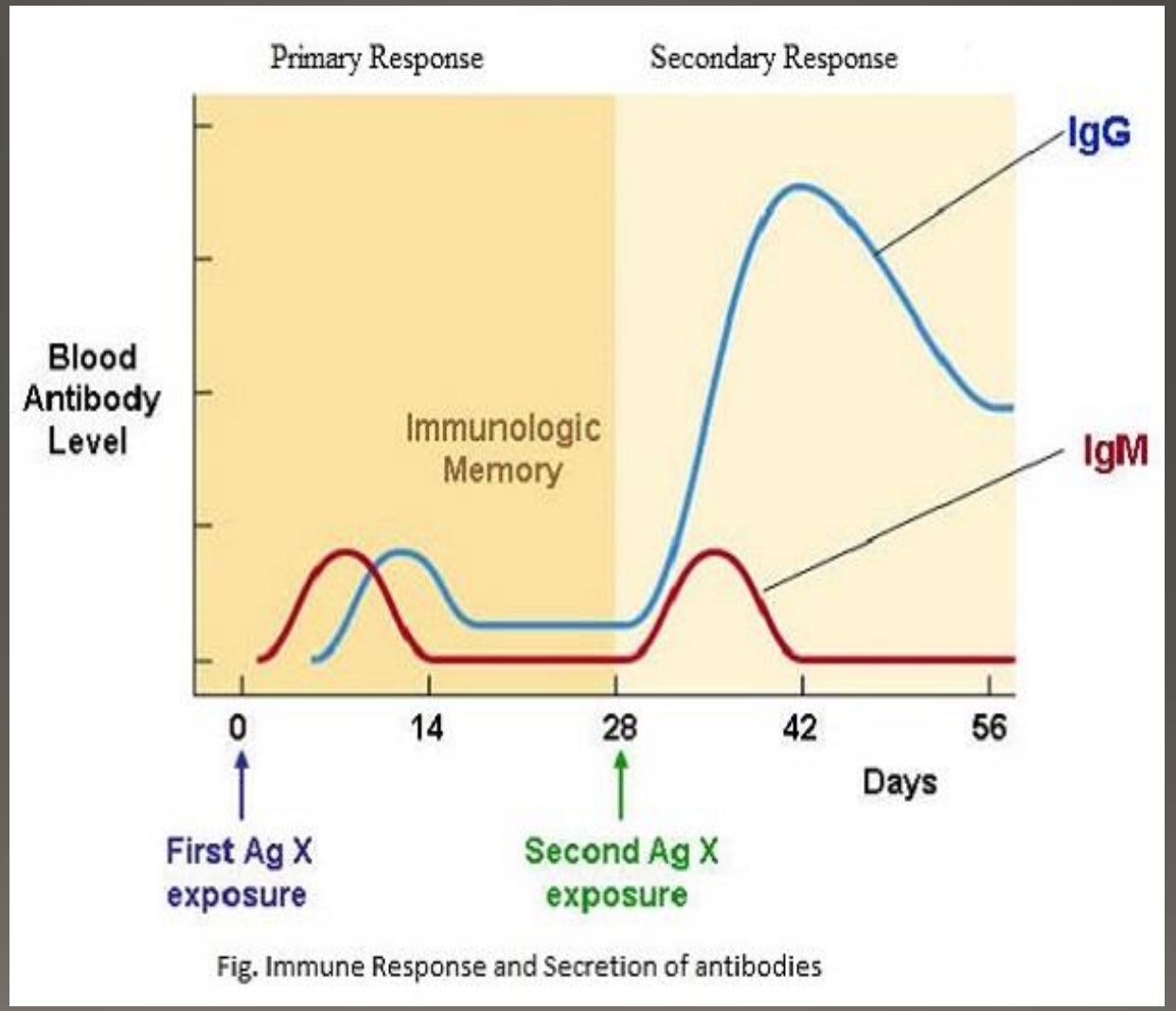


Fig. Immune Response and Secretion of antibodies

The effect on fetus

- antibodies will coat the fetal red blood cells and cause Hemolysis.

→Mild: fetus can compensate by increasing erythropoiesis.

→Severe: profound anemia, resulting in hydrops fetalis

What is the products results from hemolysis?

Note: High bilirubin levels can damage the central nervous system and lead to neonatal kernicterus.

When Rh systems develops in the fetus?

- Establishment of the fetal **circulation occurs at 4 weeks**
- the presence of the Rh D antigen has been demonstrated as early as **38 days after conception**.

- The risk is low in the first 8 wks, but it rises to significantly by 12 wks.

Cont.

- **Immunizations occur at the time of :**

A. 1st Trimester: Abortions, Ectopic (less likely at GA of 8 weeks)
B. 2nd half of pregnancy: transplacental hemorrhage (e.g second-third trimester vaginal bleeding, invasive procedures, abdominal trauma, or after external cephalic version)
C. Peripartum: Delivery , cesarean, manual removal of placenta .

Incidence of sensitization

- The overall risk of immunization for the second full-term Rh-positive fetus in:

1. ABO-compatible pregnancy →1 in 6 pregnancies. (16.5%)
2. ABO-incompatible*→ 2% **

Previous encounter	Risk incidence for immunization
Spont Abortion	3.5%
Induced abortion	5.5%
Ectopic	1%

***The protection is due to the destruction of the ABO-incompatible cells in the maternal circulation and the removal of the red blood cells by the liver.*

**A condition where the mother's blood type is O and the fetus has blood type A or B (inherited from the father). This can lead to hemolytic disease of the newborn (HDN), also known as ABO hemolytic disease.*

The natural history of RH isoimmunization and hemolytic disease

Without treatment:

- less than 20% of Rh D incompatible pregnancies actually lead to maternal isoimmunization
- 25-30% of the offspring will have some degree of hemolytic anemia and hyperbilirubinemia.
- 20-25% will be hydropic and die either in utero or in the neonatal period.
- Cases of hemolysis in the newborn that do not result in fetal hydrops still can lead to kernicterus.

Rhogam dosing (Anti-D)

- Estimation of maternal fetal blood can be done using the Kleihauer-Betke test.
- The standard dose of anti D is 0.3 mg will eradicate 15 ml of fetal red blood cells or **30 mls of fetal whole blood**
- Schedule for injection:

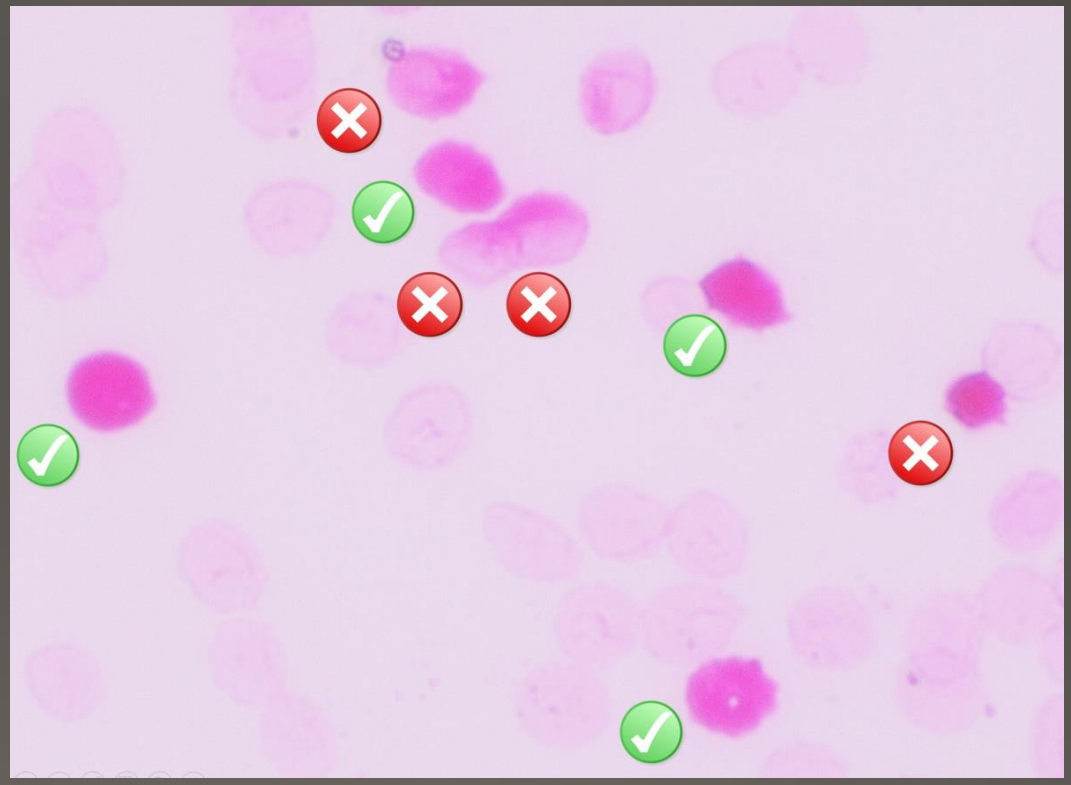
Trimester /procedure	dose
Antepartum bleeding 1st trimester	50 µg RhIgG
Antepartum bleeding 2nd &3rd	300 µg RhIgG
Prophylaxis GA 28 -32wks	300 µg RhIgG
delivery	<72 hr - 300 µg RhIgG

Kleihauer-betke test

- Used for detecting Fetomaternal or Transplacental Hemorrhage.
- The test is dependent on the fact that adult hemoglobin is more readily eluted through the cell membrane in the presence of acid than is fetal hemoglobin (HbF).

How is it done

- The maternal blood is fixed on a slide with ethanol (80%) and treated with a citrate phosphate buffer to remove the adult hemoglobin.
- After staining with hematoxylin and eosin, the fetal cells can readily be distinguished from the empty maternal cells.



The green marks is pointing to fetal HGB

Screening

- Identify mother blood group in first ANC visit
- If Rh-negative patients→ check father→ If Rh neg, the fetus will be Rh neg→ safe
- If the father is Rh positive, his Rh genotype and ABO status should be determined.
- If the father is:
  - Homozygous for the D antigen→ every fetus will be Rh positive
  - Heterozygous→ only half of his children will be positive.

Screening

- If it is not possible to test the antigen status and zygosity of the father, it must be assumed that he is antigen positive.
- MATERNAL Rh-ANTIBODY TITER Anti-D antibody titers
- Serial Ab titer gives +serial uss and past ob Hx → guides management

Follow up

- Cut off titer level below 1:16*
- If titer is < 1:16, repeat titers every 2 - 4 wks.
- If the titer rises to ≥1:16, a detailed assessment is indicated.

The timing and methods of invasive testing will depend on:

1. Current clinical status of the fetus
2. Gestational age
3. Patient's obstetric history**

* *Recommendations of ACOG , here the titer referes to how many times you can dilute the mother blood and still detect the Anti D Ab*

** Titers are not generally useful for following a patient with a Hx. of a prev. fetus with hemolytic disease

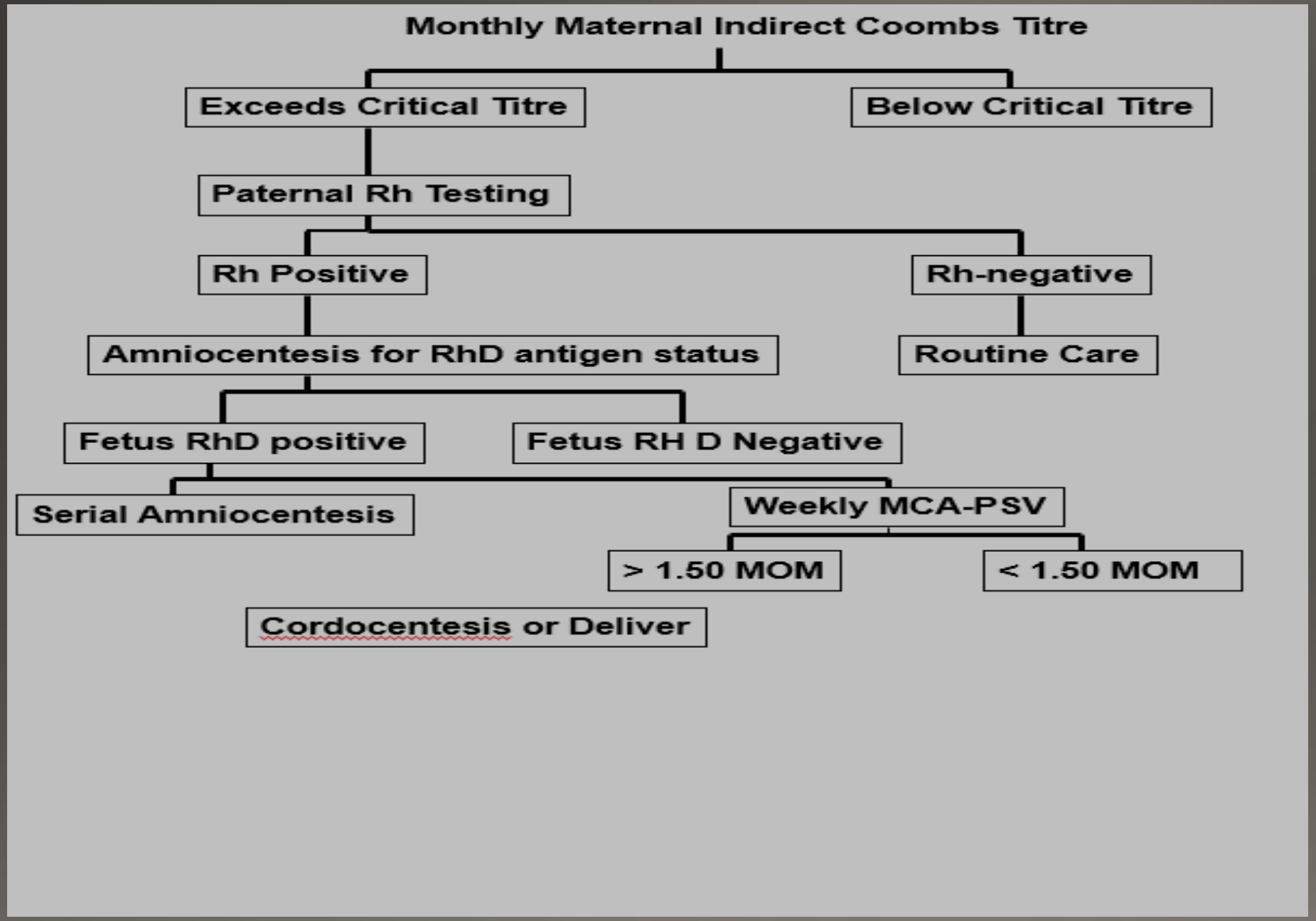
Follow up methods

Non-invasive

1. Ultrasonography
2. Doppler velocimetry of MCA

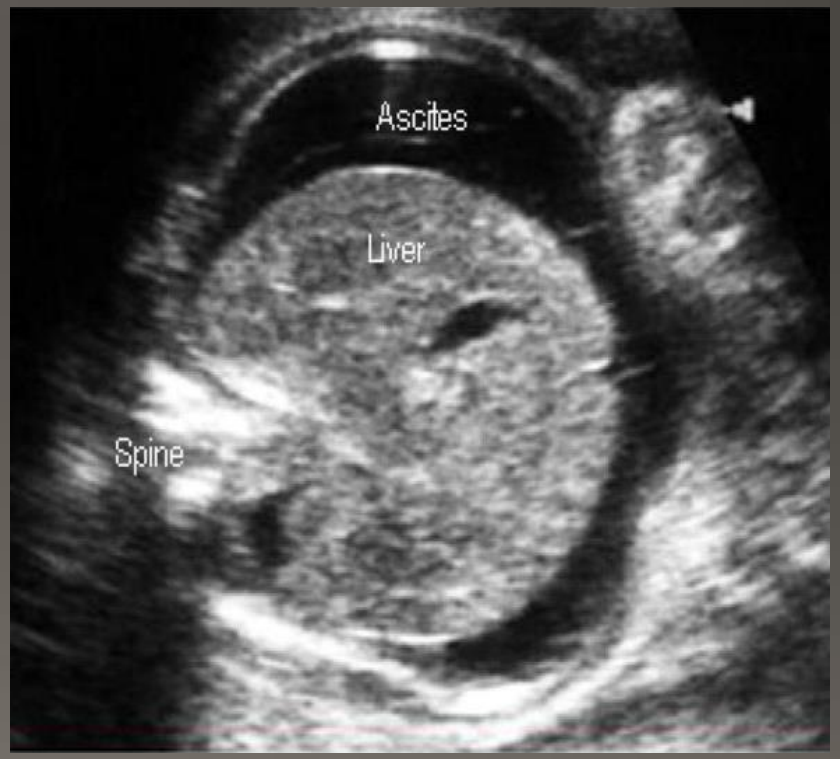
Invasive

1. Amniocentesis
2. Fetal blood sampling


Monthly Maternal Indirect Coombs Titre
Exceeds Critical Titre
Below Critical Titre
Paternal Rh Testing
Rh Positive
Rh-negative
Amniocentesis for RhD antigen status
Routine Care
Fetus RhD positive
Fetus RH D Negative
Serial Amniocentesis
Weekly MCA-PSV
> 1.50 MOM
< 1.50 MOM
Cordocentesis or Deliver

Ultrasonography

- To Establish The Correct Gestational Age.
- In Guiding Invasive Procedures And Monitoring Fetal Growth And Well-being.
- Ultrasonographic Parameters To determine Fetal Anemia:
  - Placental Thickness.
  - Umbilical Vein Diameter(increased)
  - Hepatic Size.
  - Splenic Size.
  - Polyhydramnios.
  - Fetal Hydrops (e.g. Ascites, Pleural Effusions, Skin Edema).
  - Blood velocity (increased)



Doppler velocimetry of Middle cerebral artey (MCA)

- Anemic fetus preserves oxygen delivery to the brain by increasing cerebral flow (sparing effect)
- For predicting fetal anemia
- Predict the timing of intrauterine fetal transfusion.

Why the invasive techniques?

- Critical anti-D titer:

A titer associated with a significant risk for fetal hydrops(Anti-d titer value between 8 and 32)

- Previous seriously affected fetus or infant

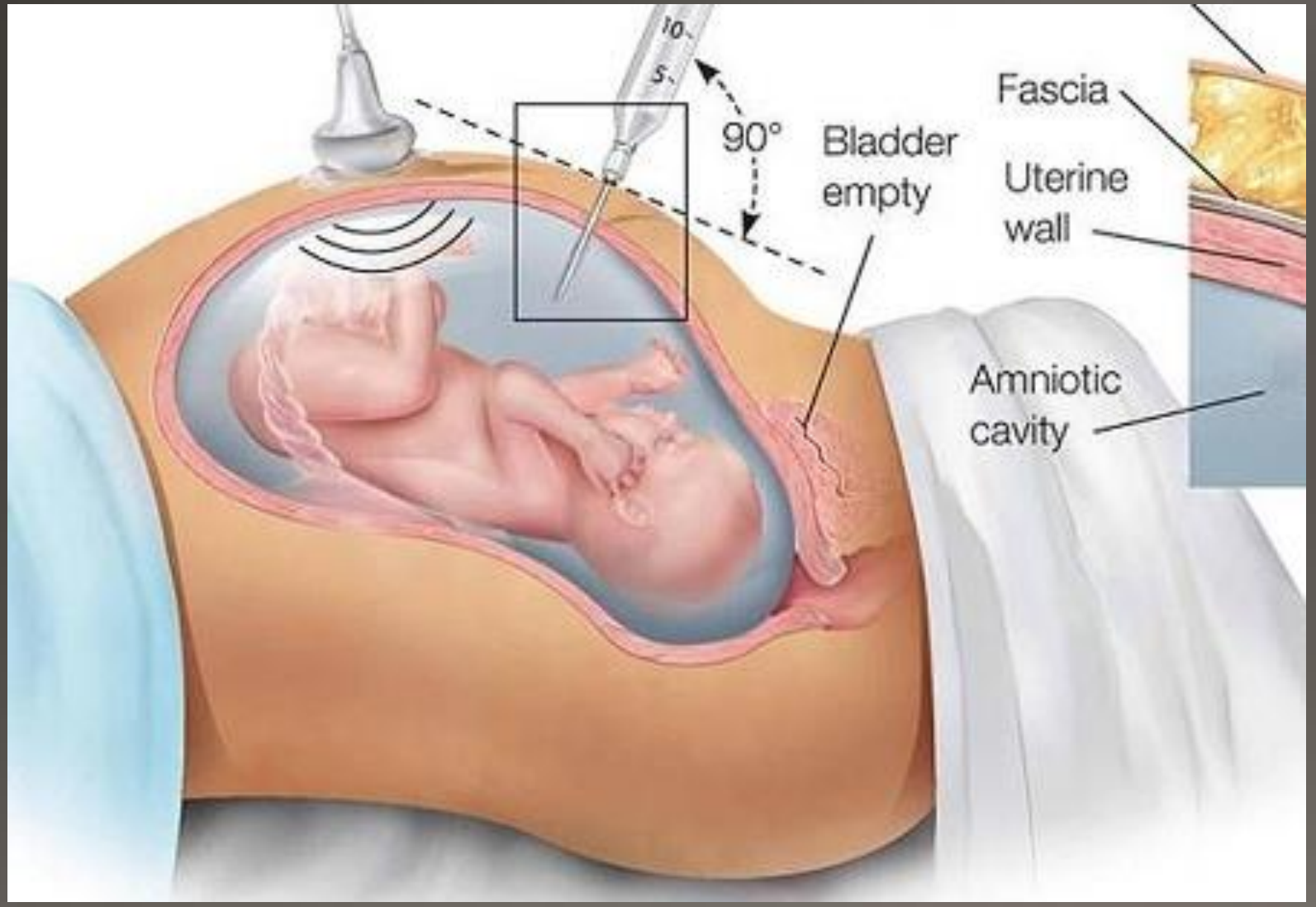
Amniocentesis

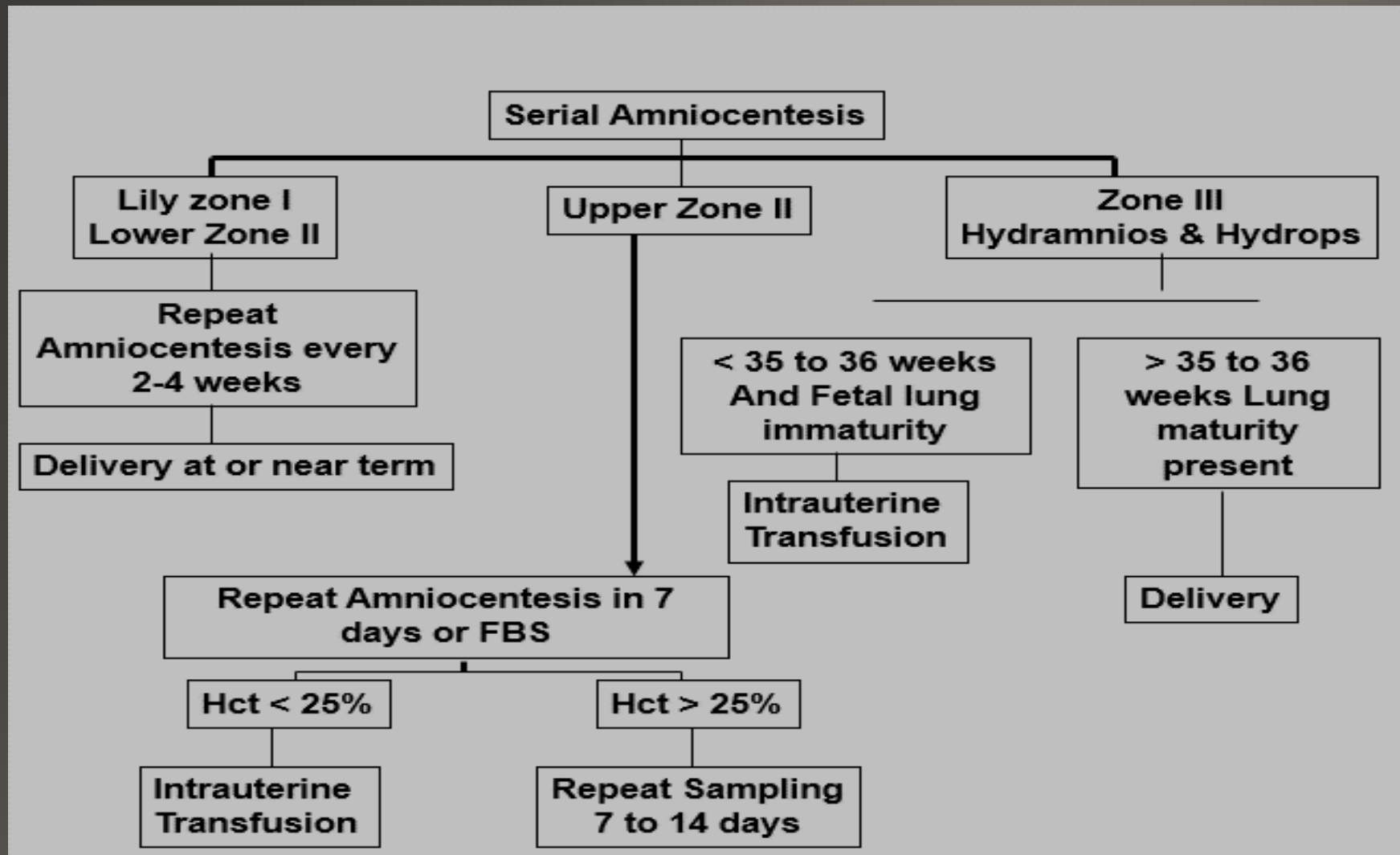
- Bilirubin in amniotic fluid decreases with advanced gestation.
- It derives from fetal pulmonary and tracheal effluents.
- Its level rises in correlation with fetal hemolysis

<u>Determination of amniotic fluid bilirubin:</u>

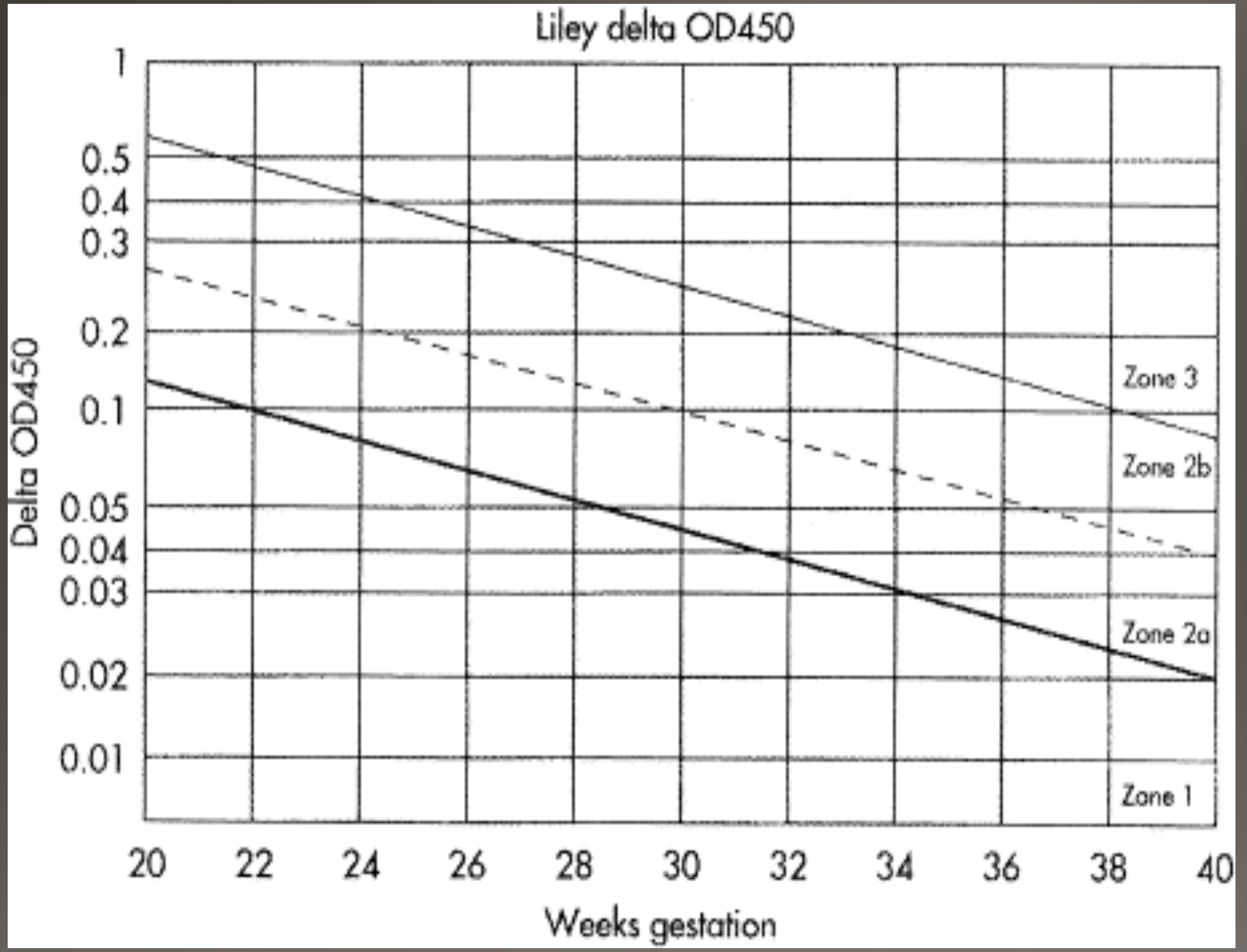
- By the analysis of the change in optical density of amniotic fluid at 450 nm on the spectral absorption curve (delta od450)

- Procedures are undertaken at 10-15 days intervals until delivery data are plotted on a normative curve based upon gestational age.

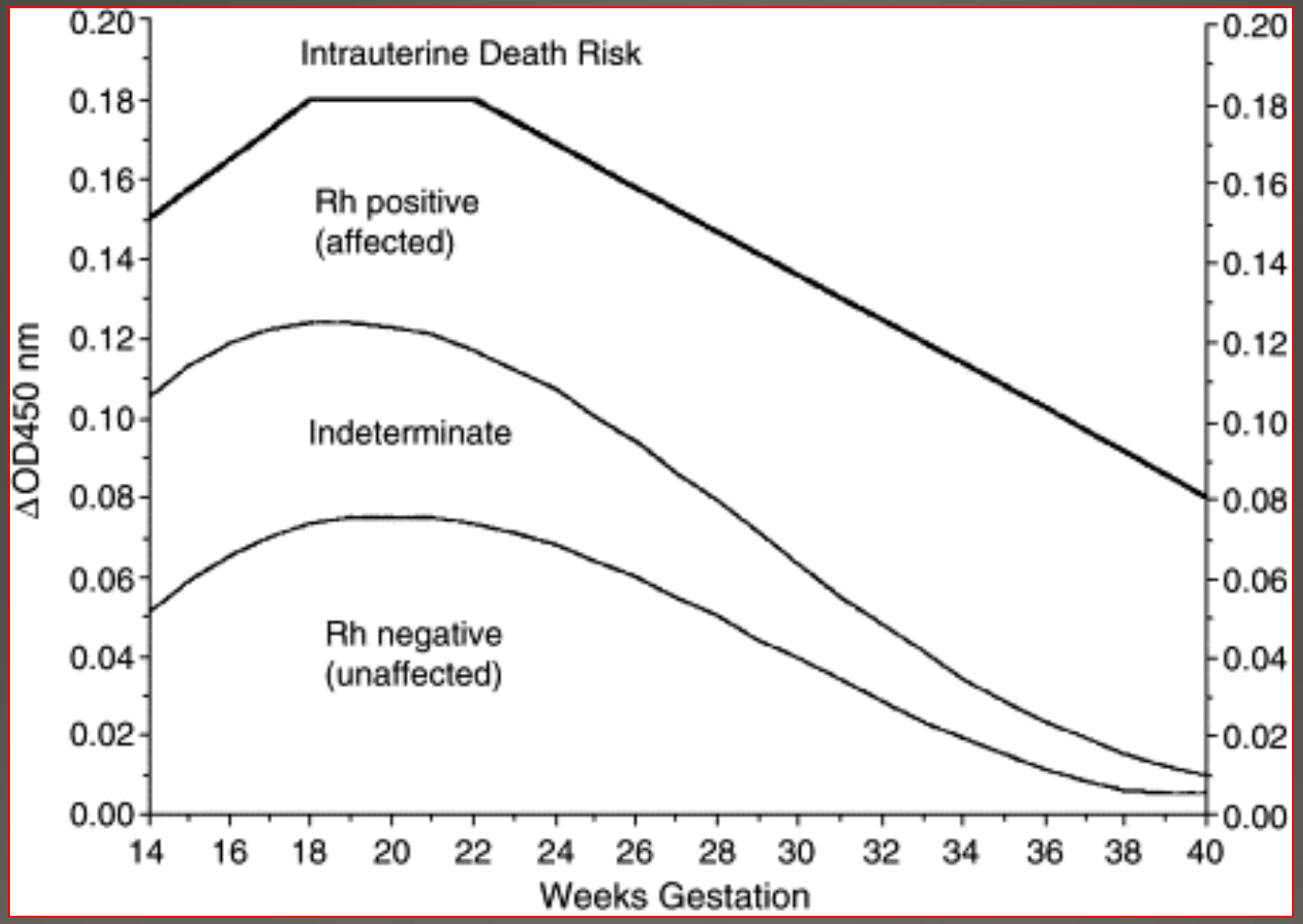

90°
Bladder empty
Fascia
Uterine wall
Amniotic cavity



Suggested management after amniocentesis for ΔOD 450


Liley delta OD450
Delta OD450
1
0.5
0.4
0.3
0.2
0.1
0.05
0.04
0.03
0.02
0.01
Zone 3
Zone 2b
Zone 2a
Zone 1
20
22
24
26
28
30
32
34
36
38
40
Weeks gestation

Queenan curve for delta-OD 450 values



Interpretation Of Amniotic Fluid Bilirubin:

- **A falling curve:** is reassuring (An unaffected or Rh D-negative fetus)

- **A plateauing or rising curve**: suggests active hemolysis

(require close monitoring & may require fetal blood sampling &/or early delivery).

- **A curve that reaches to or beyond the 80th percentile of zone II** on the Liley graph or enters the " intrauterine transfusion" zone of the Queenan curve necessitates investigation by fetal blood sampling

Fetal blood sampling

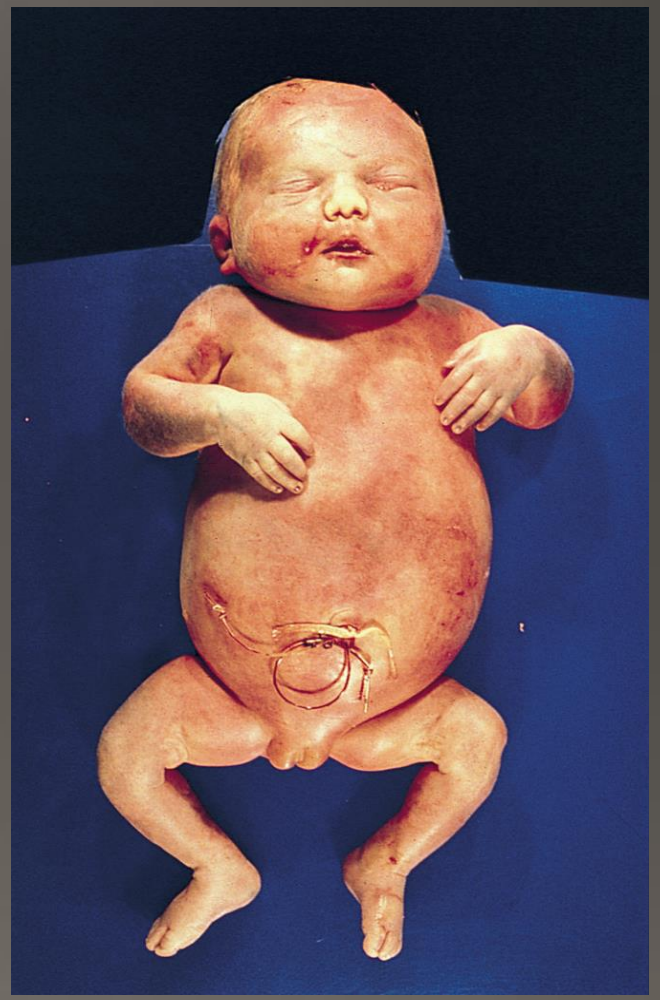
- Is the gold standard for detection of fetal anemia.
- Reserved for cases with: 1. With an increased MCA-PS
  2. Increased ΔOD 450
- **<u>Complications:</u>**
- Total Risk of Fetal Loss Rate 2.7%
- Bleeding from the puncture site in 23% to 53% of cases.
- Bradycardia in 3.1% to 12%.
- Fetal-maternal hemorrhage: occur in 65.5% if the placenta is anterior and 16.6% if the placenta is posterior.
- Infection and abruptio placenta (rare)

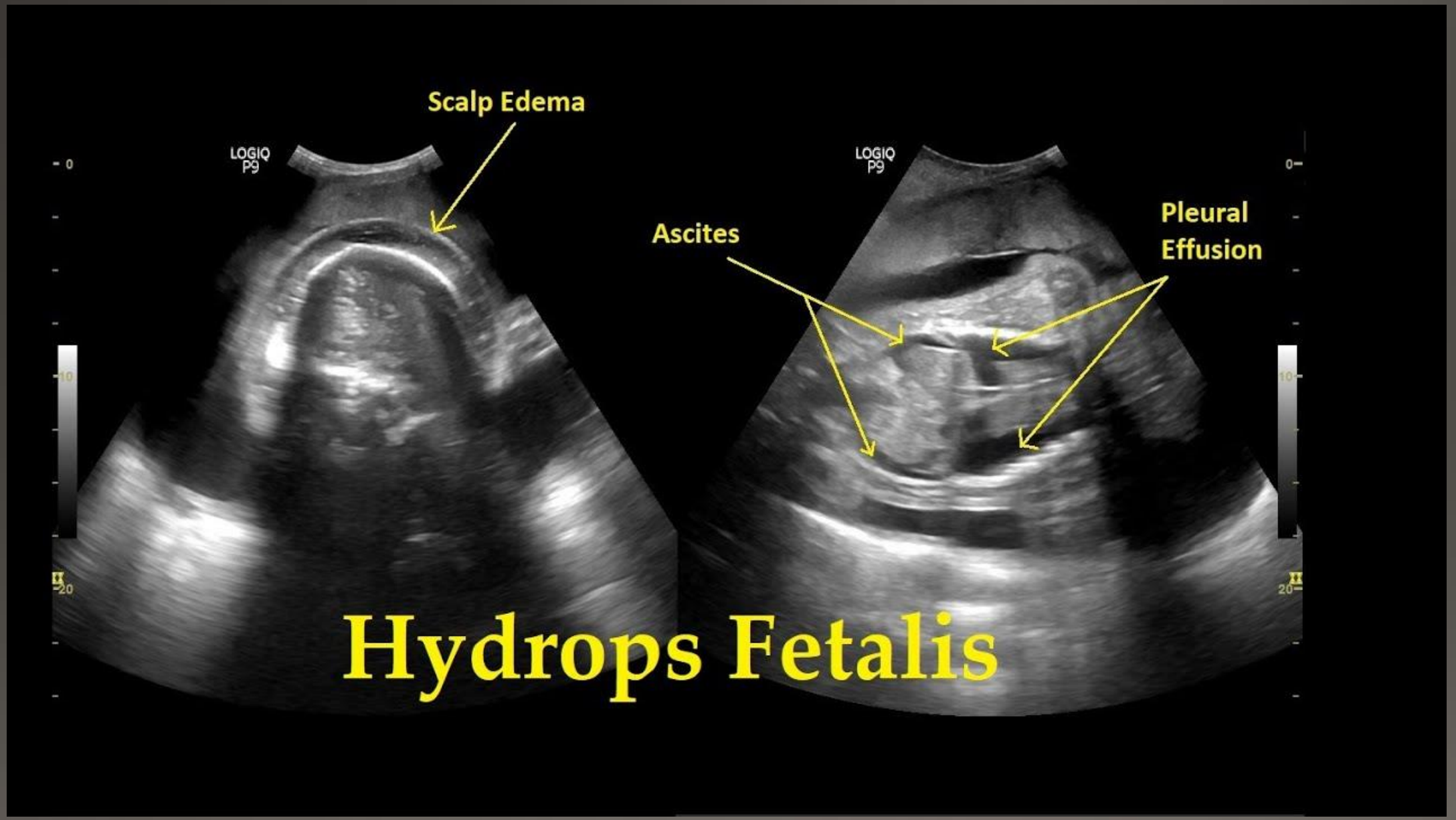
Complications of RH immunization

- **Fetal Hydrops And Stillbirth** (hgb less than 4 gm/dl
- **Hepatosplenomegaly**
- **Neonatal Jaundice (post delivery)**
- **Compilations Of Neonatal Kernicterus (Lethargy, Hypertonicity, Hearing Loss, Cerebral Palsy And Learning Disability)**
- **Neonatal Anemia** (Hgb < 11 gm/dl)

Hydrops fetalis

- is a form of in utero heart failure.
- In the setting of Rh alloimmunization, it is characterized by the presence of:
- fetal ascites
- pericardial effusion
- pleural effusion
- subcutaneous edema (best seen as scalp edema)
- polyhydramnios



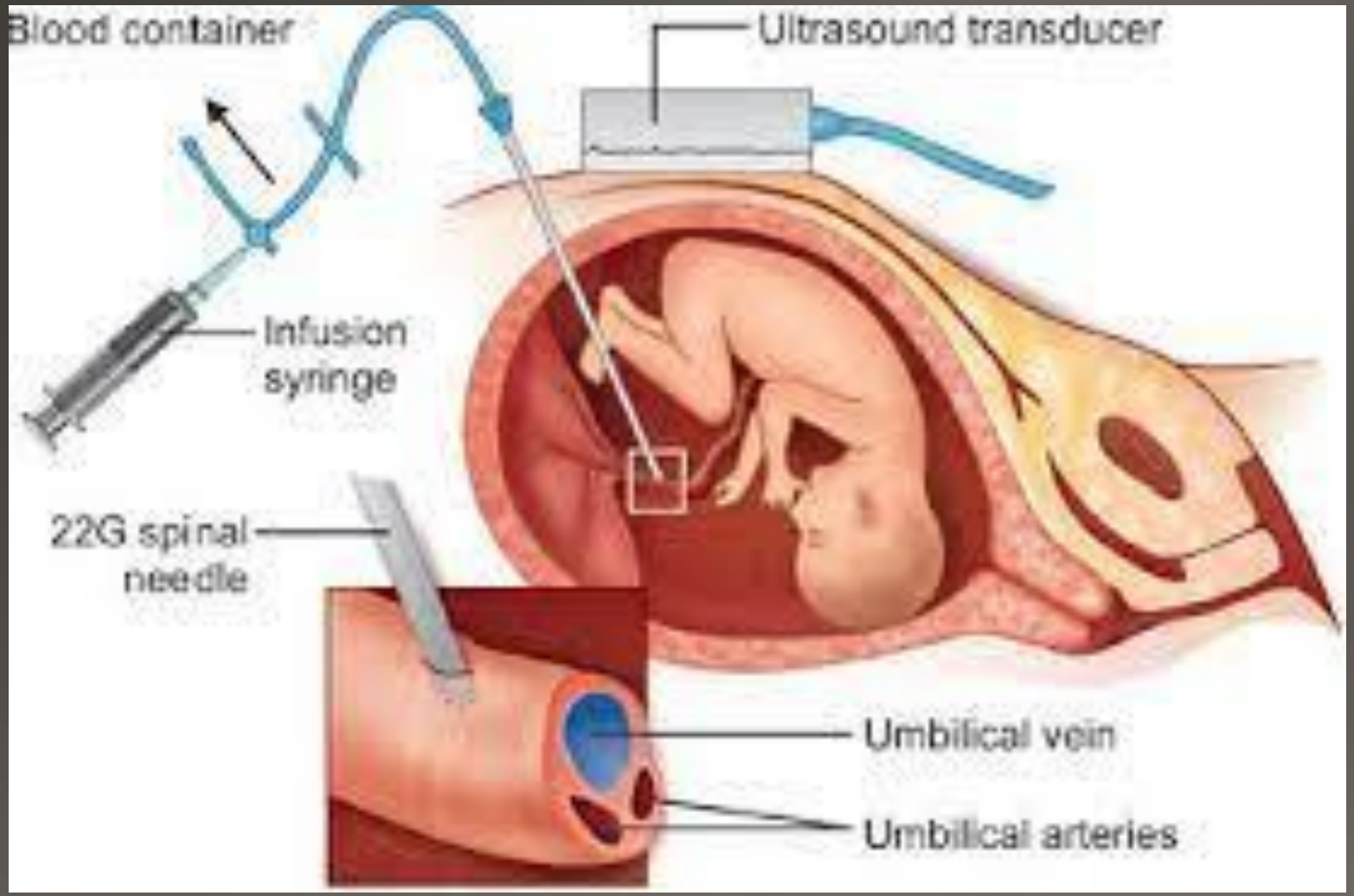

Scalp Edema
Ascites
Pleural Effusion
LOGIQ P9
LOGIQ P9
Hydrops Fetalis

INTRAUTERINE TRANSFUSION

- initially introduced in 1963
- Started as an intraperitoneal transfusion
- Currently is usually it is an intravascular transfusion
- The goal is to transfuse fresh group O, Rh negative PRBCs.
- blood is screened, irradiated, washed & processed through a leukocyte-poor filter.
- Curare is usually injected directly into the fetal thigh before transfusion,to immobilize the fetus during the procedure.
- Repeat transfusions are generally scheduled at 1- to 3-week intervals.
- The final transfusion is typically performed at 34 weeks' gestation.
- Delivery when the lungs are mature.

Intravascular Blood Tx

- Goal is to have post-transfusion Hct 40-45%
- Can infuse about 10 ml/min
- Estimate requirement based on EFW and pre-transfusion Hct
- Repeat in 1 wk., then about every 3 wk.
- Hct falls about 1%/day
- Goal: keep Hct > 25%
- Smaller volumes, therefore more procedures compared to IPT
- Fetal loss about 1.5% per procedure


Blood container
Ultrasound transducer
Infusion syringe
22G spinal needle
Umbilical vein
Umbilical arteries

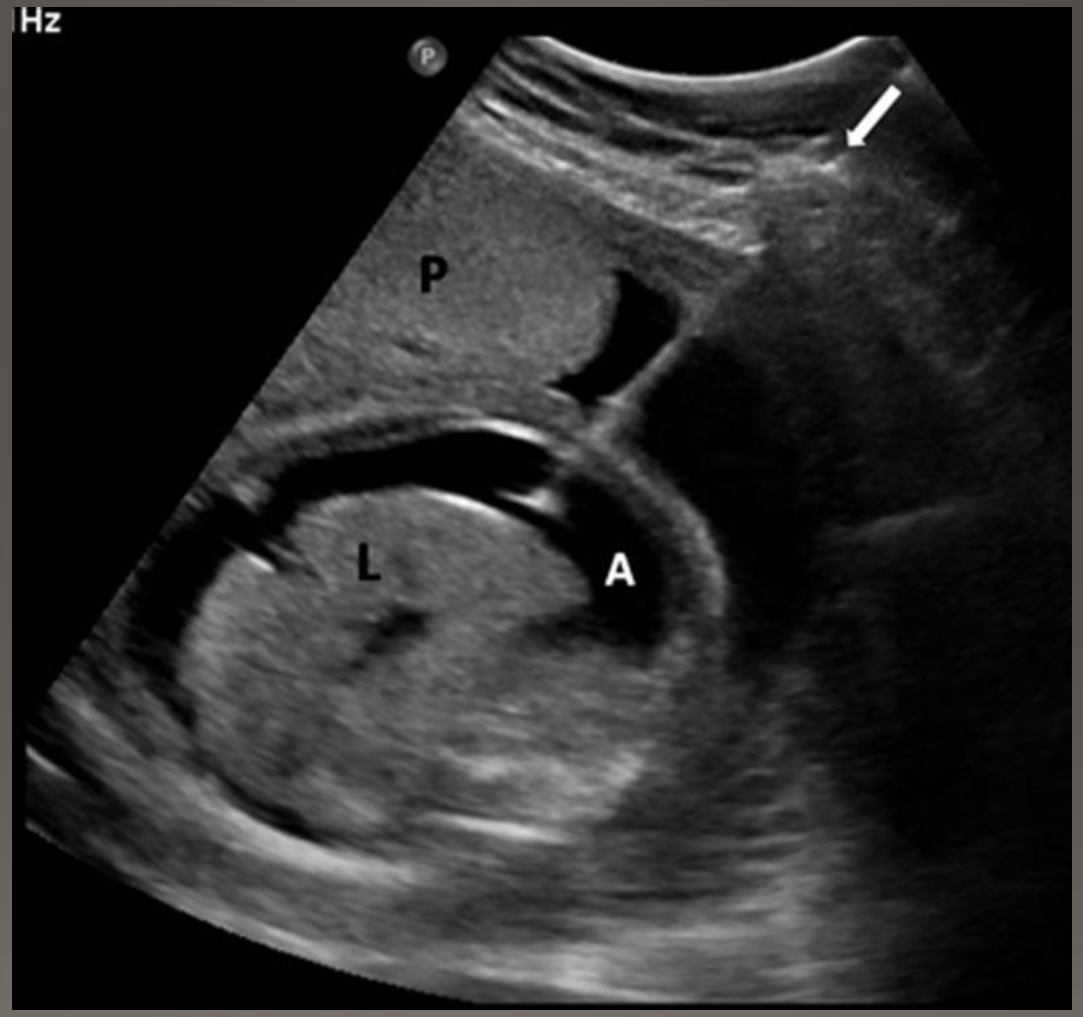
Fetal Intraperitoneal procedure

- Transfusion RBCS are absorbed through the subdiaphragmatic lymphatics proceed through the right lymphatic duct into the fetal intravascular compartment.
- Blood absorbed within 7 - 9 days.
- Removal of ascitic fluid at the time of transfusion.

Fetal Intraperitoneal Procedure

- A 20-gauge spinal needle is inserted into the peritoneal cavity.
- The RBCs are slowly injected manually in 10-mL aliquots
- If fetal bradycardia occurs during the procedure, the transfusion is terminated.
- For intraperitoneal transfusions, the volume to be infused is based on the following formula:

Volume = [gestational age (weeks) – 20]×10



Post Intrauterine transfusion prognosis

Infant status	Survival rate
Over all	85%
No hydrops	90%
With hydrops	75%

THANK YOU