Preterm Labor: One Syndrome, Many Causes

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Introduction

- Preterm birth is associated with 5-18% of pregnancies
- Is a leading cause of infant morbidity and mortality
- Spontaneous preterm labor, a syndrome caused by multiple pathologic processes

The prevention and treatment of preterm labor have been a long-standing challenge

Definition

All births before 37 weeks of gestation are defined as preterm and these are subdivided according to the gestation at delivery into:

- **Extreme (<28 weeks), which occurs in about 0.25% of pregnancies**
- **Early (28-30 weeks), which occurs in about 0.25% of pregnancies**
- **Moderate (31-33 weeks), which occurs in about 0.6% of pregnancies**
- **Mild or late (34-36 weeks), which occurs in about 3.0% of pregnancies**

The occurrence of regular uterine contraction associated with cervical changes before 37 completed weeks

Threatened PTL: regular uterine contractions without cervical changes

Preterm birth and neonatal complications

- The leading cause of neonatal death
- The second cause of childhood death below the age of 5 years
- Neonates born preterm are at an increased risk of short-term complications attributed to immaturity of multiple organ systems
- Neurodevelopmental disorders, such as cerebral palsy, intellectual disabilities, and vision/hearing impairments
- Preterm birth is a leading cause of disability-adjusted life years, the number of years lost due to ill health, disability or early death

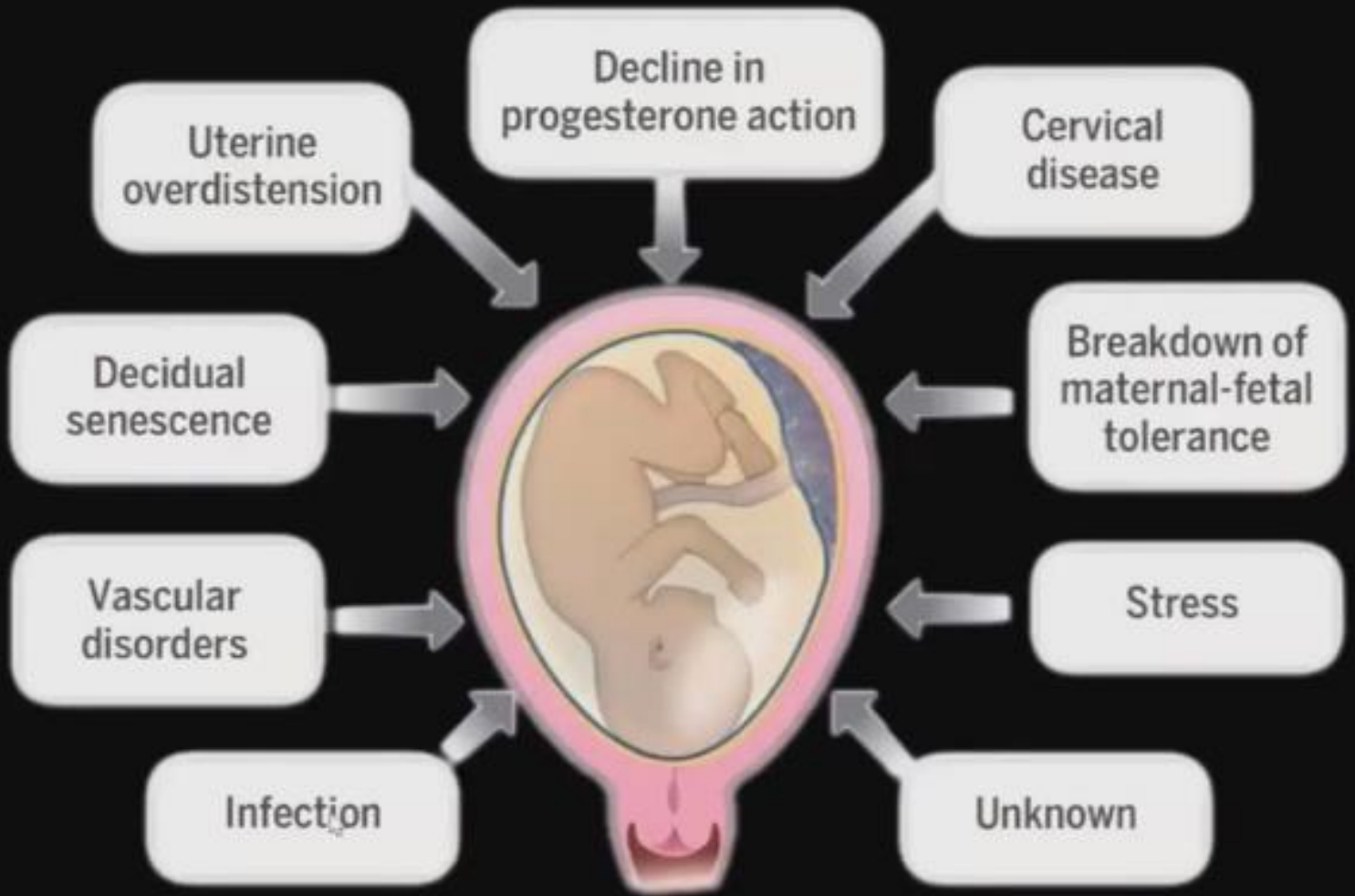
Preterm uterine contraction are not the case of preterm labor But the clinical manifestations of the pathological insult

Risk factors

- Strongest predictor and most significant risk factor is previous PTL

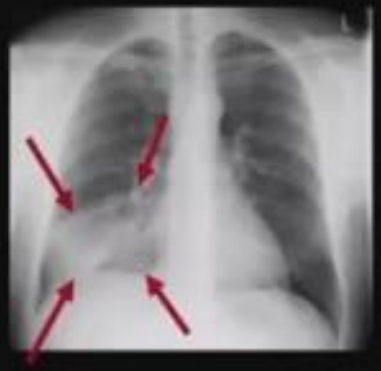
- Previous 1 PTL recurrence 15 %
- Previous 2 PTL 30 %
- Previous 3 PTL 45 %

Preterm Labor: Not Just Labor Before Term



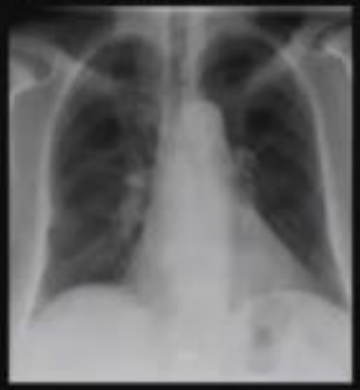
Cough

Pneumonia



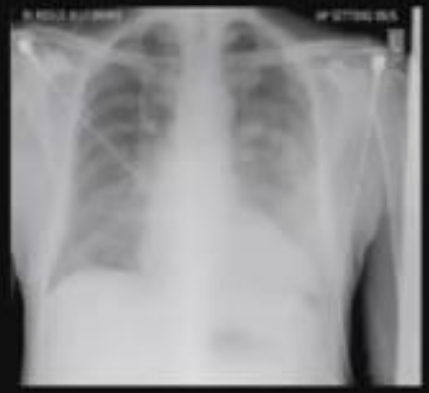
Antibiotics

Pulmonary embolism



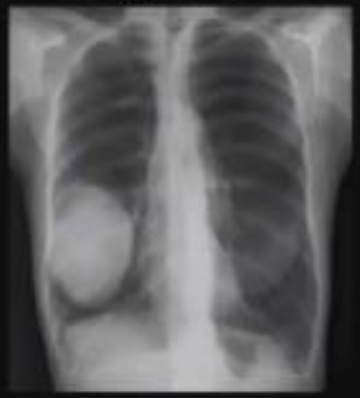
Thrombolysis

Pulmonary edema



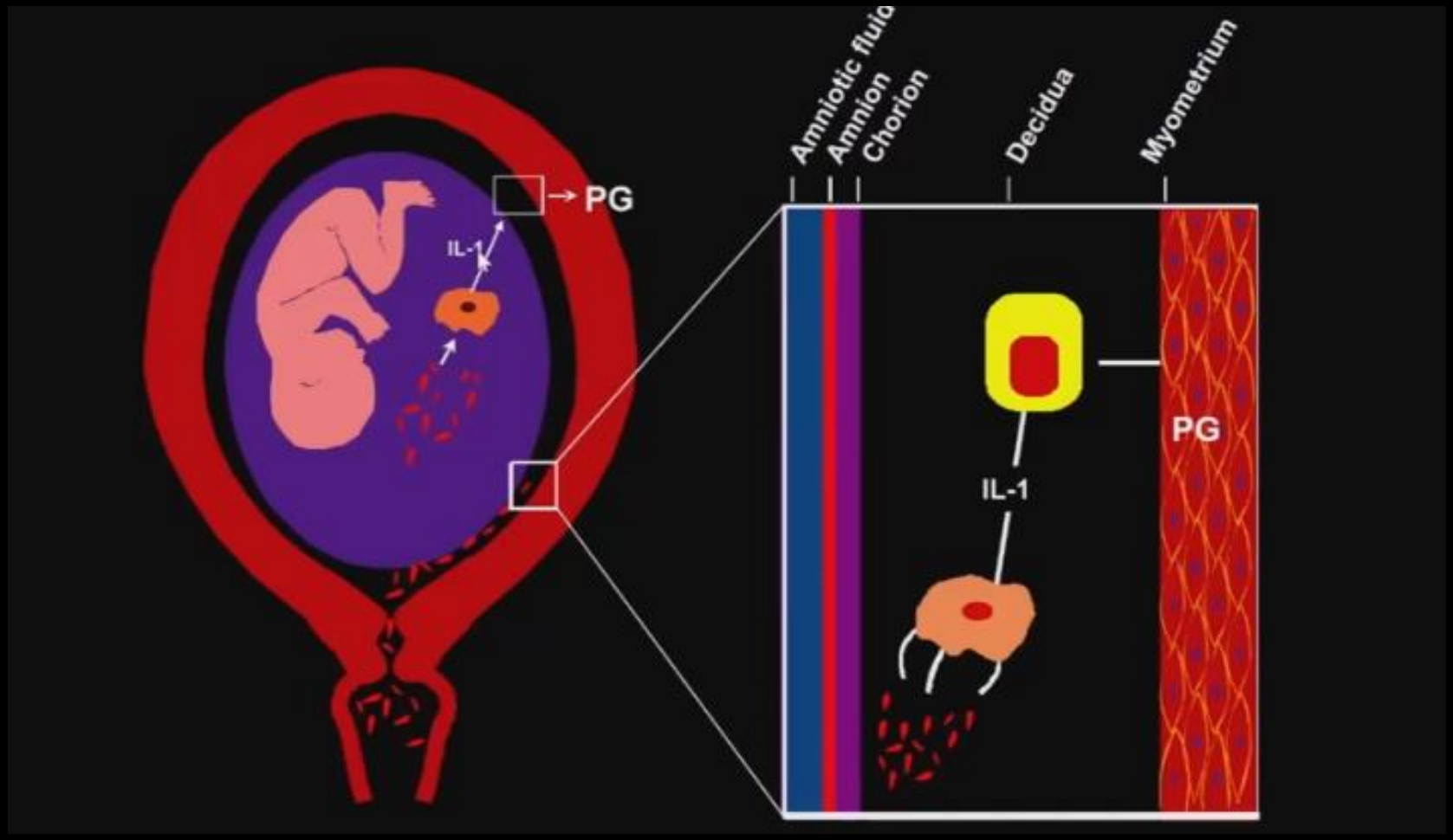
Diuretics

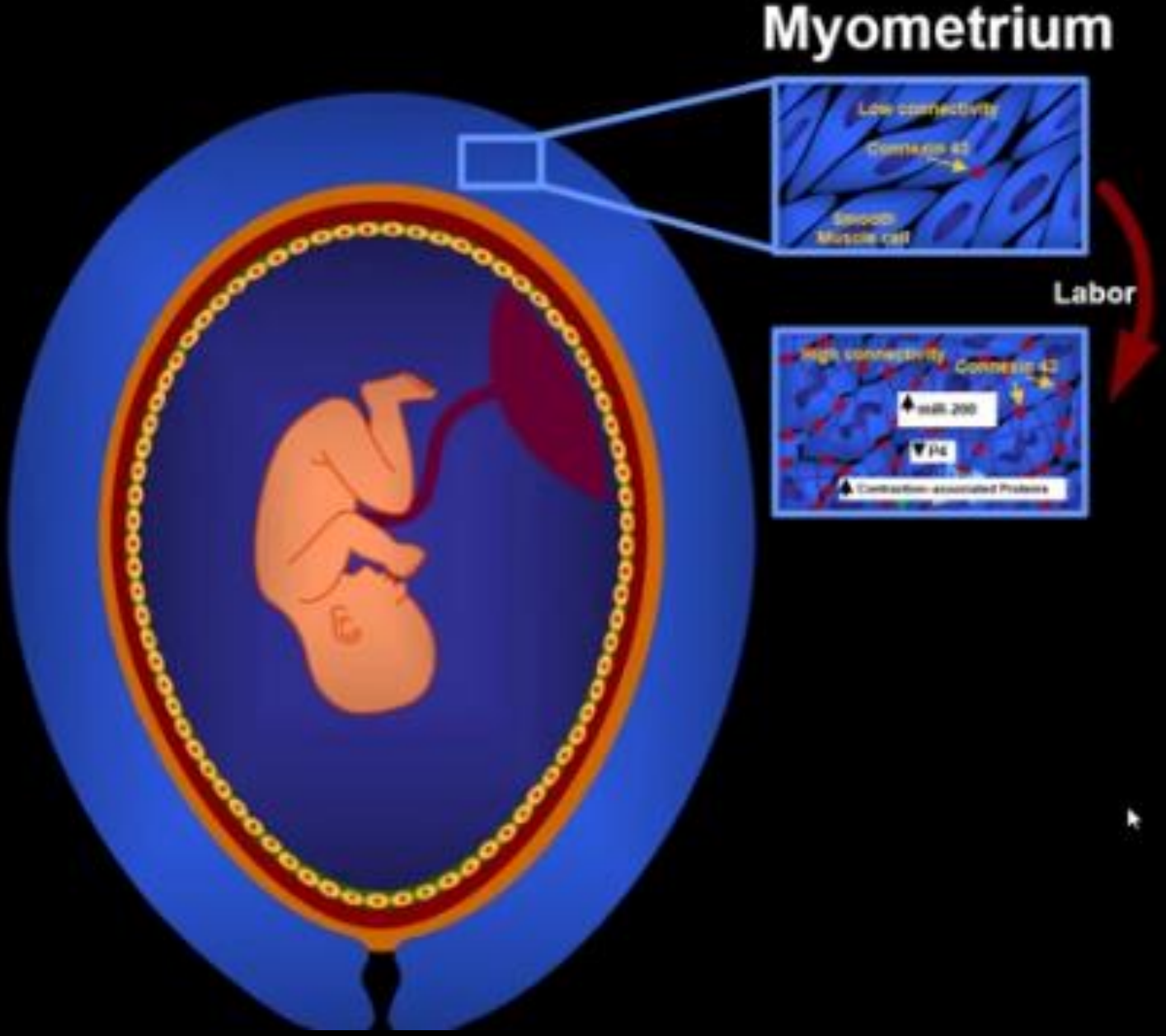
Lung cancer



Chemotherapy

Infection as a pathophysiology




Myometrium
Low connectivity
Connexin 43
Smooth Muscle cell
Labor
High connectivity
Connexin 43

Amniotic fluid tests

Intra-amniotic Infection

- Gram stain
- PCR
- Culture
  - Aerobic / anaerobic bacteria
  - Genital Mycoplasmas

Intra-amniotic Inflammation

- Amniotic Fluid WBC
- Glucose
- IL-6 ≥2.6 ng/mL
- MMP-8 >23 ng/mL

Highlighted points

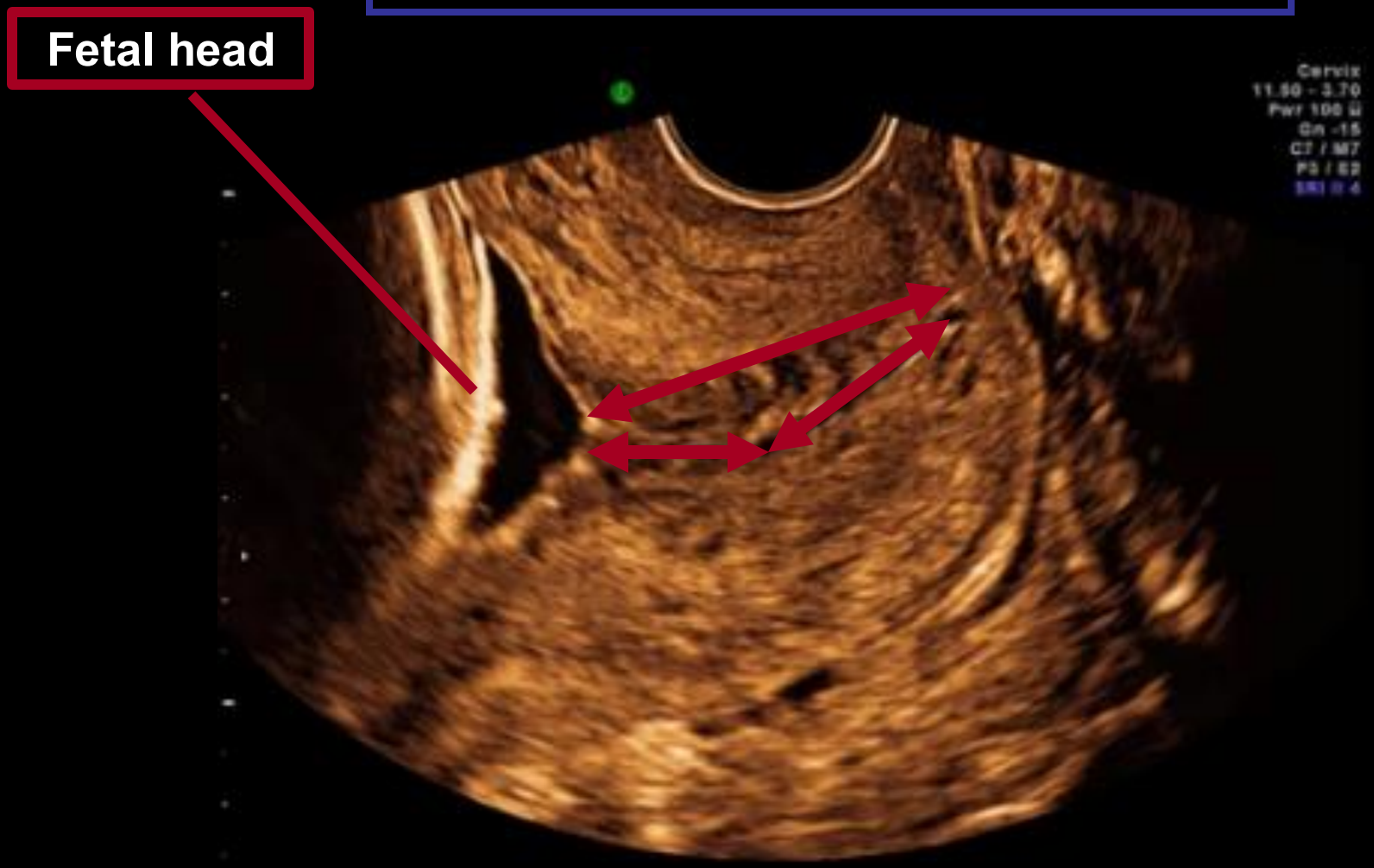
- History
- Sure date and confirmation by early first trimester records
- Vital signs(temperature>38 fever ,hypotension with abruption)
- Abdominal pain –tenderness—localized—PTL true—(Braxton hicks)
- Assessment of presentation
- Assessment of engagement
- Sterile speculum (swab vaginal, group B strep)
- Discharge offensive and possible pooling liquor
- CTG
- Ultrasound

Screening

The two most important predictors of spontaneous preterm birth are:

- **Sonographeic short cervix in the midtrimester**
- **Spontaneous preterm birth in a prior pregnancy**

Cervical length



Cervical length at 18-22 weeks in pregnancies that deliver at term is normally distributed with a mean of 34 mm

In pregnancies with sPTB at <34 weeks there is a bimodal distribution in cervical length. The cervical length is <15 mm in 1% of the population and this group contains 20% of cases of sPTB at <34 weeks. The cervical length is <25 mm in 10% of the population and this group contains 40% of cases of sPTB at <34 weeks

Screening

- **Cervico-vaginal fetal fibronectin**

- **Fetal fibronectin is an extracellular matrix glycoprotein produced by amniocytes and by cytotrophoblast**
- **It is localized between chorion and decidua and acts as a ’glue’ between the pregnancy and the uterus**

Cell-free Fetal DNA

- A role for cell-free fetal (cff) DNA as a signal for the onset of labor has recently been proposed
- In pregnant women, cff DNA is normally present in the plasma, and concentrations increase as a function of gestational age - peaking at the end of pregnancy just prior to the onset of labor
- cff DNA (in contrast with adult cell-free DNA) is hypomethylated and induce an inflammatory response

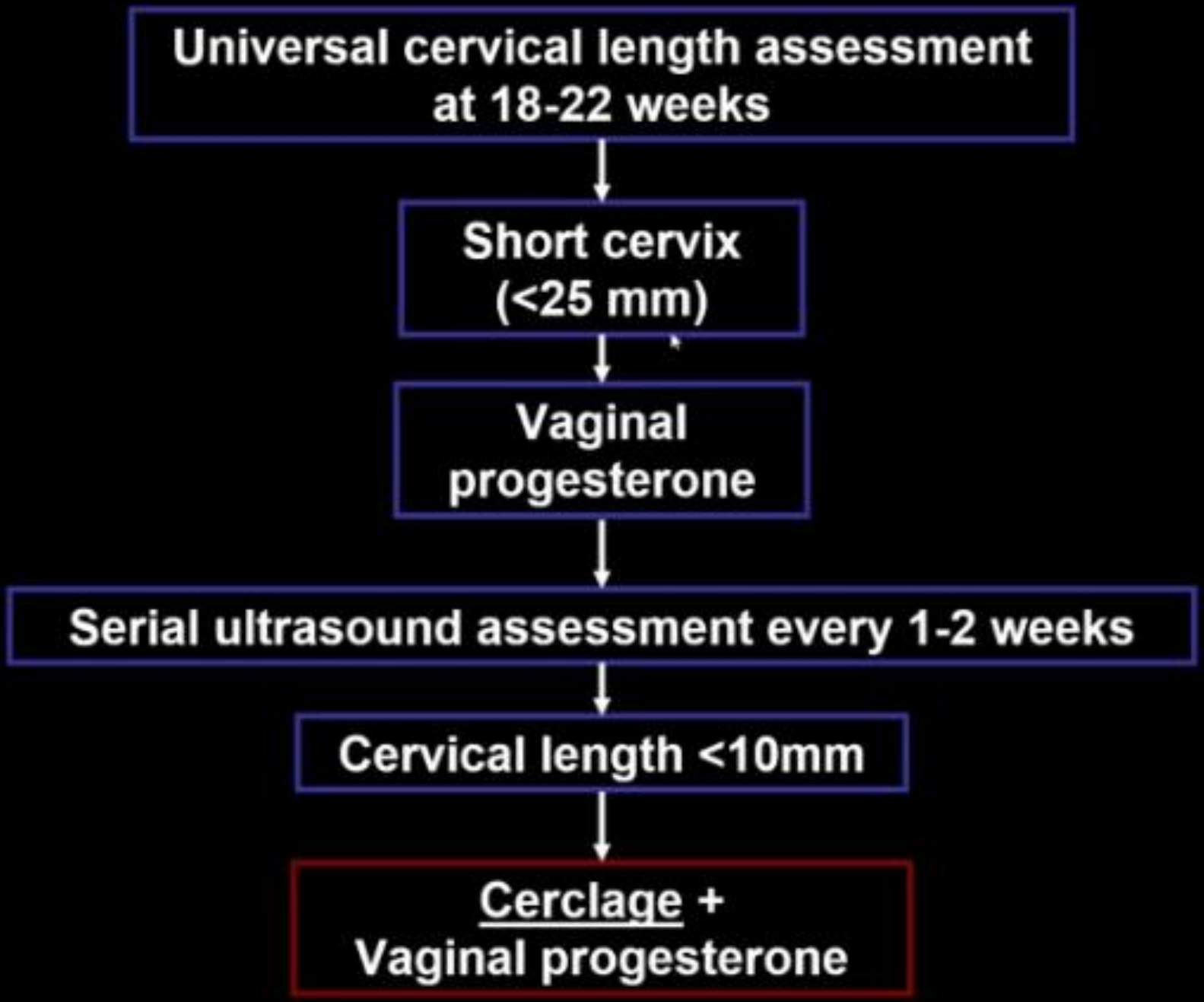
Cell-free Fetal DNA

- The downstream consequences could include activating the common pathway of labor
- Patients who have an ***elevation of cff DNA in the midtrimester*** are at increased risk for spontaneous preterm delivery later in gestation
- Patients with preterm labor and high plasma concentrations of cff DNA are also at increased risk for preterm delivery

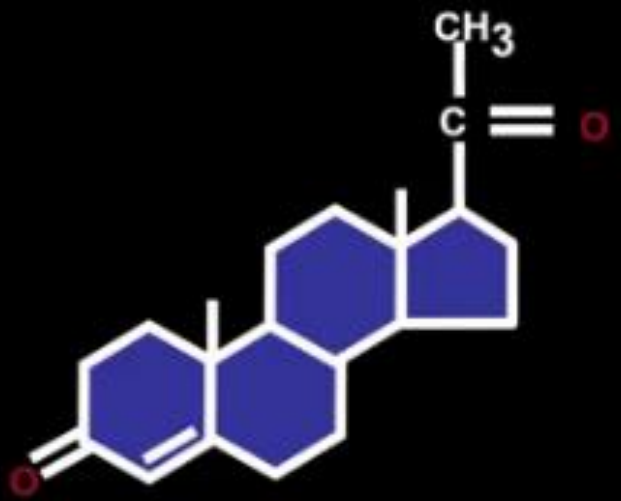
Management

Goals :

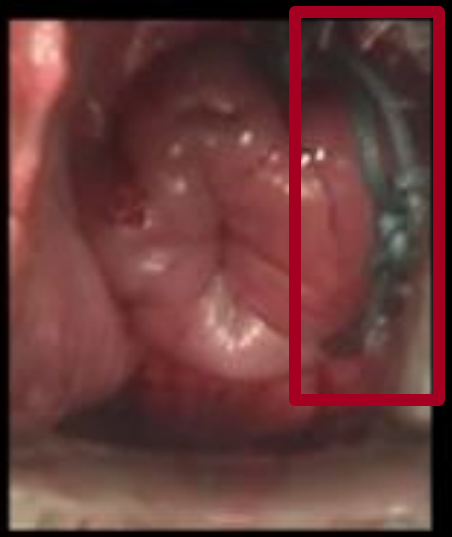
- Delay delivery
- Identification etiology
- Administration of steroids
- GBs prophylaxis


Universal cervical length assessment at 18-22 weeks
Short cervix (<25 mm)
Vaginal progesterone
Serial ultrasound assessment every 1-2 weeks
Cervical length <10mm
Cerclage + Vaginal progesterone

Prevention PTB in short cervix



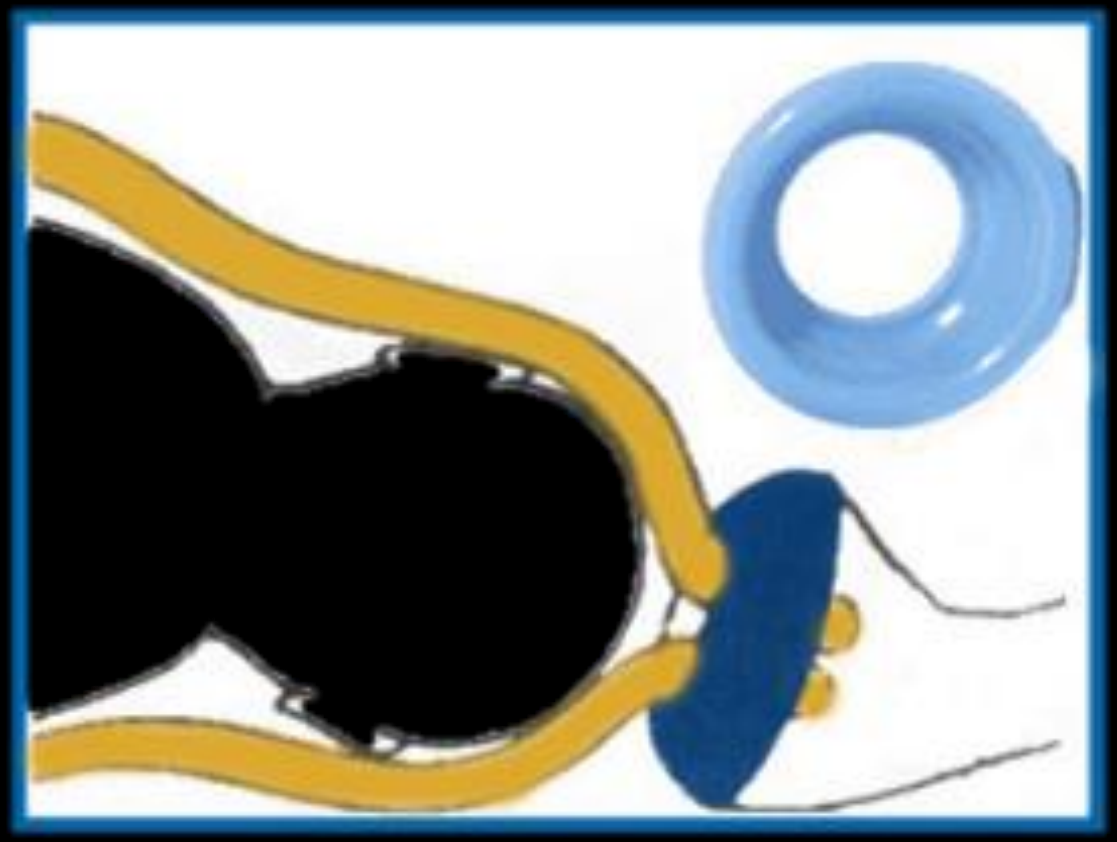
Progesterone



Cerclage

Pessary

Cervical pessary



Weak evidence

According to obstetric history Studies investigating the value of preventative measures have essentially focused in two groups of women:

Women with a previous preterm birth

Women with no previous preterm delivery but found through a screening test in pregnancy to be at increased risk of preterm birth

Preventions

Bed rest in hospital or at home is widely recommended for the prevention of preterm birth but there is *no scientific evidence* to support this practice
Bed rest may also have some adverse effects for women, including increased likelihood of venous thrombosis, muscle atrophy and stress

Betamimetics given prophylactically.

Life style interventions, such as decrease in manual labor, increase in visits to antenatal clinics, psychological support, or diet supplementation with iron, folate, calcium, zinc magnesium, vitamins, or fish oil.

women with previous preterm birth

- No benefit from bed rest, prophylactic tocolytics or lifestyle interventions
- Vaginal progesterone every night from 20 to 34 weeks reduces PTB by 25%
- Measurement of cervical length every 2 weeks between 14 and 24 weeks and cervical cerclage if the cervix becomes less than 25 mm reduces PTB by 25%

women with no previous preterm birth but positive screening test

- Short cervix at 20-24 weeks consider Cervical cerclage it may reduce PTB at <34 weeks by 15%
- Vaginal progesterone every night from 20 to 34 weeks reduces PTB at <34 weeks by 35-40%

- In women with asymptomatic bacteruria the risk of PTB and pyelonephritis is increased
- Antibiotic treatment reduces the risk of pyelonephritis but does not reduce the risk of PTB

Threatened preterm labor

Management Women presenting with threatened preterm labor are often with:

- **Hospitalization in a unit with facilities for neonatal intensive care**
- **Administration of tocolytics to prevent preterm birth**
- **Administration of steroids to improve fetal lung maturity**

Tests For Fetal Lung Maturity

Fetal Lung Maturity

- Respiratory distress syndrome of the newborn infant is caused by immaturity of the fetal lung
- Measurement of pulmonary surfactant production is the most effective way to evaluate pulmonary maturity

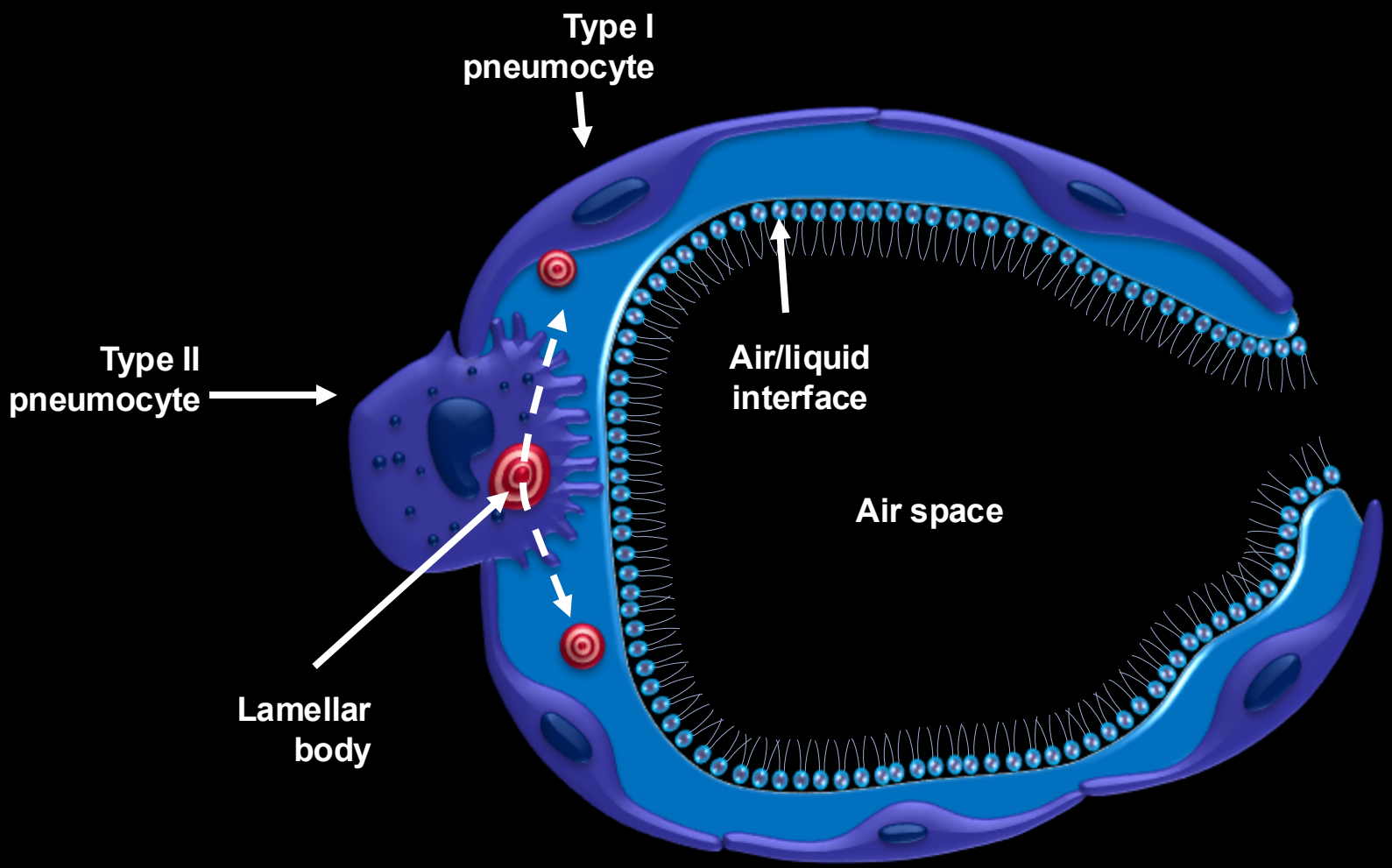
- As the lung develops, significant quantities of surfactant are washed out of the fetal lung and accumulate into the amniotic fluid
- The amount of surfactant in fetal lungs can be estimated by measuring the amount of surfactants and surface tension in amniotic fluid.

What are the benefit to perform a lung maturity test

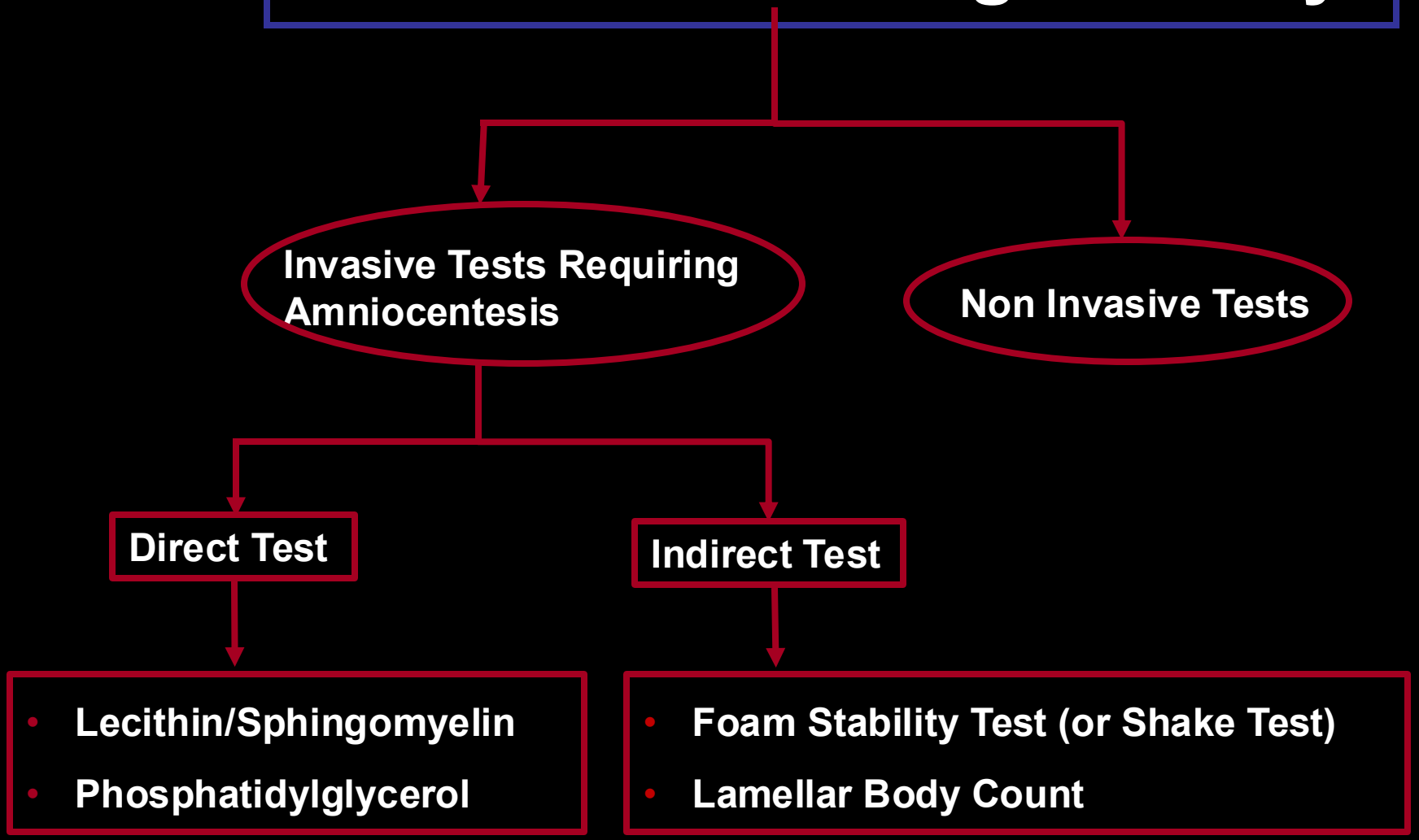
- Assessment of the risk/benefit ratio in case of elective delivery in late pregnancy complications (iatrogenic preterm delivery)

- Decision on the administration of corticosteroids

Surfactant


Type I
pneumocyte
Type II
pneumocyte
Air/liquid
interface
Air space
Lamellar
body

Tests for fetal lung maturity



Direct Tests

Lecithin/Sphingomyelin Ratio

The most popular test was reported in 1971 using by thin layer chromatography procedure

- 3-4 ml amniotic fluid centrifuged at low speed mixed with methanol
- Lipid extraction and then application to thin layer chromatography plate vs controls
- Visualization of phospholipid components
- L/S ratio of 2.0 or greater indicates maturity

Phosphatidylglycerol (PG)

- It can be detected by two-dimensional thin-layer chromatography or polyclonal antibodies
- The detection decreases the rate of false immature results
- The presence of PG in amniotic fluid specimens contaminated with blood or meconium remained a valid finding even when the results of the L/S ratio were called into question.

Phosphatidylglycerol

- Presence indicates a more advanced state of fetal pulmonary maturity
- But the disadvantage they are late appearance in pregnancy

Indirect tests

Foam Stability

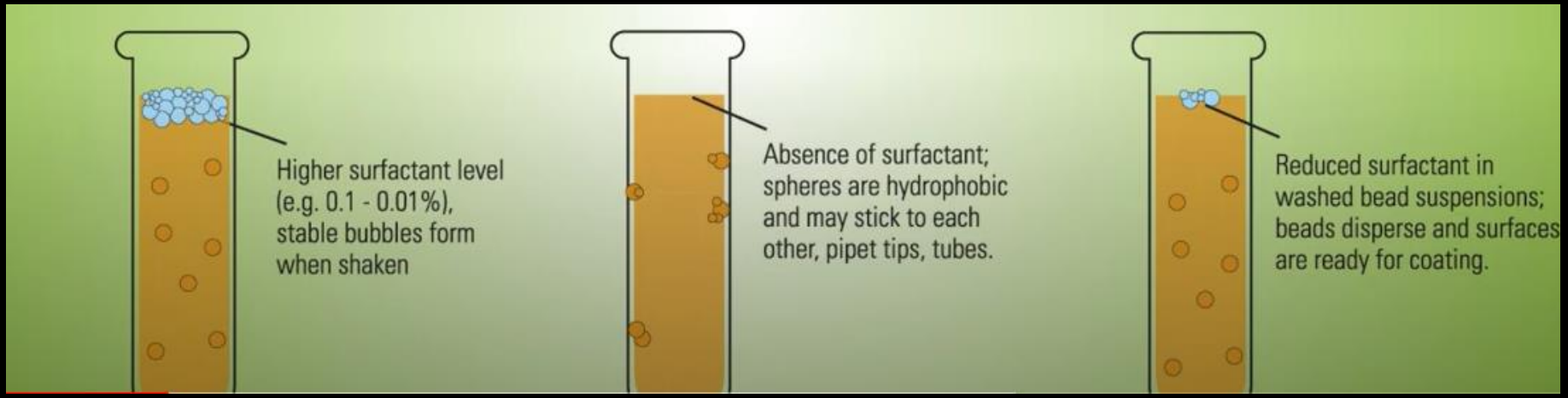
The principle:

Addition of amniotic fluid to different concentrations of 95% ethanol solution followed by shaking and observing the meniscus for the presence of a ring of bubbles

Shaking test

https://www.youtube.com/watch?v=t_HLIbPNCuM

Shaking test



https://www.youtube.com/watch?v=t_HLIbPNCuM

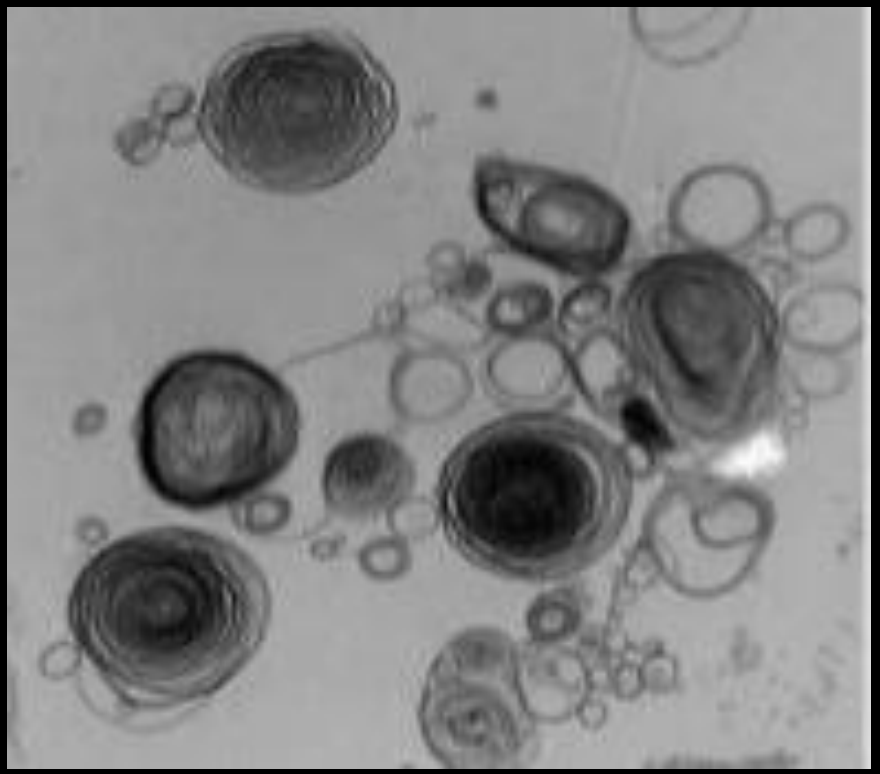
Lamellar Body Count

- Phospholipids are packaged into multi-layered lamellar bodies
- They are similar in size to platelets
- Therefore they can be counted with automated cell counter
- The lamellar body count method is a indirect reflection of surfactant concentration

Lamellar body count

If the count :

- <= 8.000 immature no further testing
- 9.000-32.000 transitional perform L/S and PG
- >32.000 mature no further testing

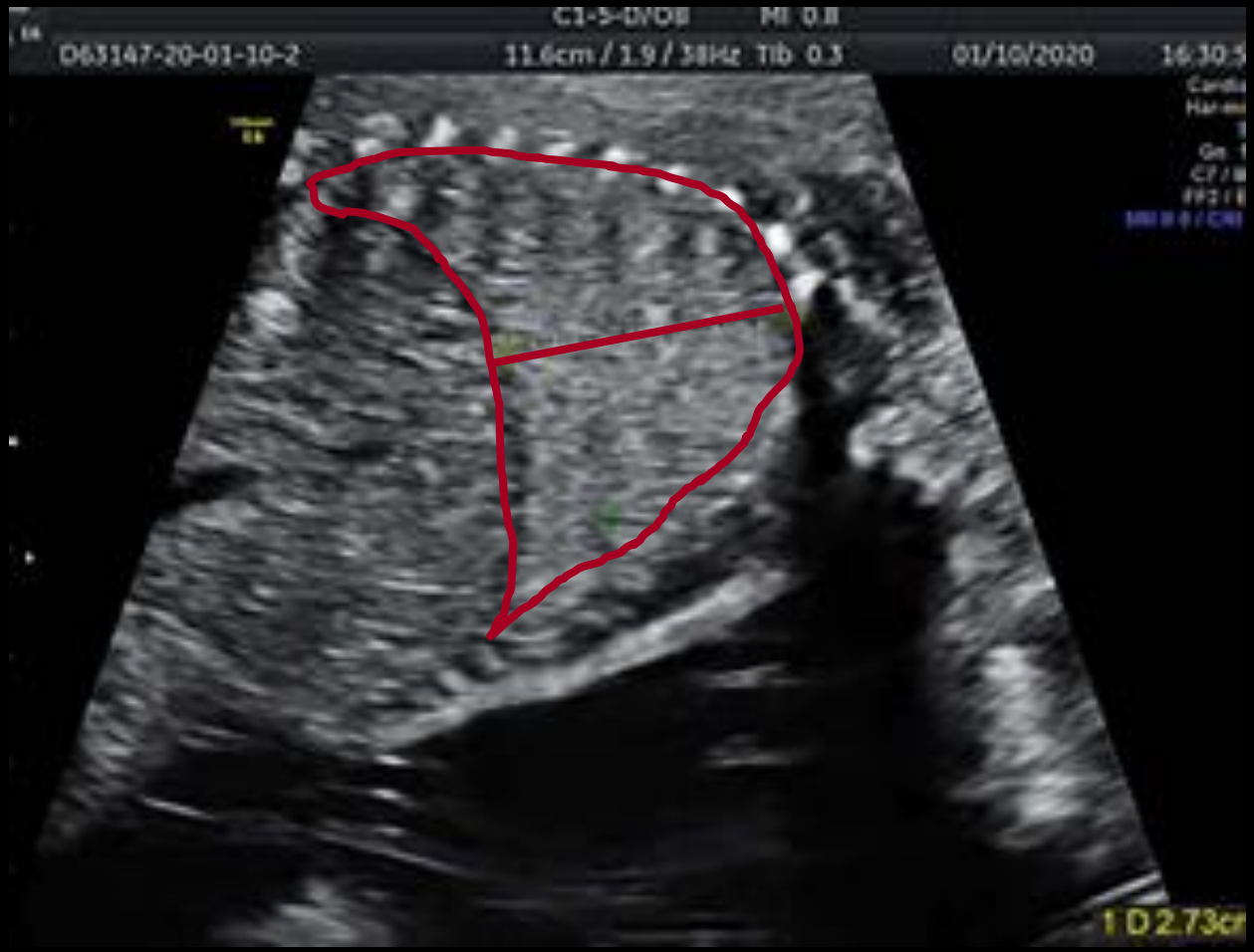


Non invasive tests

The Fetal Pulmonary Maturity: the Ultrasound Role

- Ultrasound can evaluate the development of fetal pulmonary parenchyma by measuring the diameter and area of fetal lungs
- Color Doppler can show the distribution of fetal pulmonary vessels, helping to understand the development of fetal pulmonary circulation, as well as the fetal pulmonary maturity

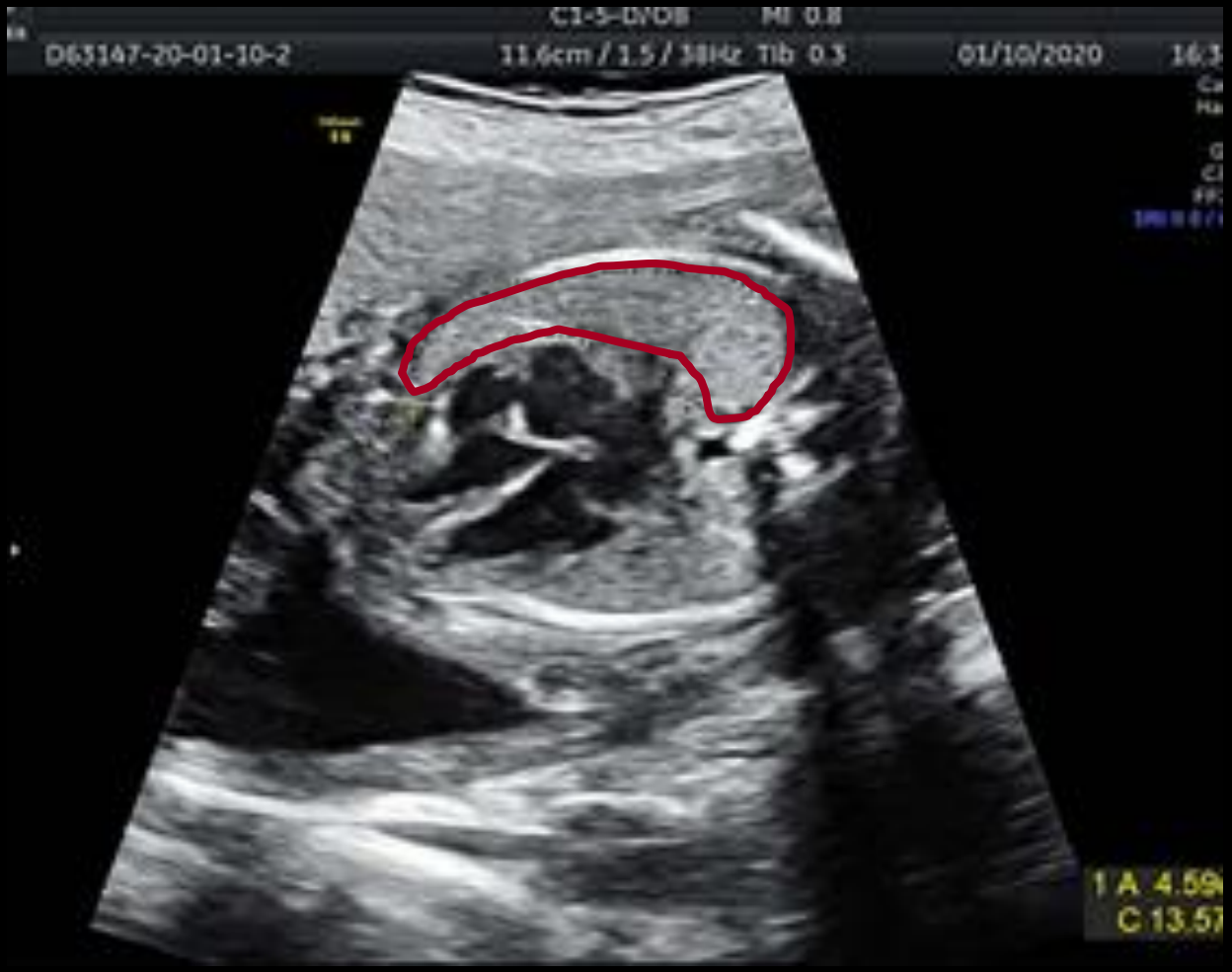
Measurement Methods Of Fetal Lung



Ultrasound features for fetal lung maturity detection

- Gray-Scale Measurements
- Lung Tissue Motion
- Relationship Between Image Features of Fetal Lung vs Placental or Liver Tissue
- Doppler ultrasound

Ultrasound Test For Lung Maturity



Neonates delivered at 36-38 weeks after confirmed fetal lung maturity are at higher risk of adverse outcomes than those delivered at 39- 40 weeks

Treatment

Patients with following complications are not candidate for tocolysis:

1. **APH**
2. **Infections**
3. **advanced labour active phase**
4. **PROM**

B -mimetics

- Ritodrine and salbutamol
- Stimulate B2 receptors and relax smooth muscle (uterus)
- Highly side effects : tremor ,nausea, hyperglycemia, pulmonary edema

Calcium channel blockers

- Nifedipne ---inhibit myometrial contractions
- Effective –reduce PTD within 7 days and decreased RDS
- Fewer side effects comparing B-agonist
- Inexpensive and easy to use
- Side effects : hypotension ,flushing. diarrhea, constipation ,headaches.

NSAIDs

- Indomethacin :Prostaglandin inhibitor (PGf2a)—50-100 mg orally
- Side effects ---oligohydramnios , constriction of the ducts arteriosus, renal effect

Magnesium sulfate use in pregnancy

- For managing preeclampsia – eclampsia
- As tocolytics agent
- As fetal-neonatal neuroprotective agent

RESEARCH ARTICLE

Assessing the neuroprotective benefits for babies of antenatal magnesium sulphate: An individual participant data meta-analysis

Caroline A. Crowther[1,2]*, Philippa F. Middleton[2,3], Merryn Voysey[4], Lisa Askie[5], Lelia Duley[6], Peter G. Pryde[7], Stéphane Marret[8,9], Lex W. Doyle[10,11,12], for the AMICABLE Group[¶]

Use 4 g, the smallest effective dose, with or without a 1 g/hour maintenance dose

Atosiban (tractocile)

- Oxytocin-vasopressin antagonist
- Fewer side effects
- The most common side effect with Tractocile is nausea
- Reported cases of fetal demise
- Expensive

Preterm prelabor rupture of membranes

PPROM

- Rupture of the membrane before the onset of labor <37 week
- PPROM complicates 2-4% of all birth and 30-40 of all preterm births
- Associated with inflammatory reaction +- infection

PPROM and complications

- Prolonged maternal hospitalization
- Early onset neonatal sepsis
- Fetal Pulmonary hypoplasia depending on gestational age
- Higher neonatal morbidity and mortality
- Inflammation related adverse neurodevelopmental outcomes

Complications of PPROM

- Infection includes chorioamnionitis
- Retained placenta
- Placental abruption

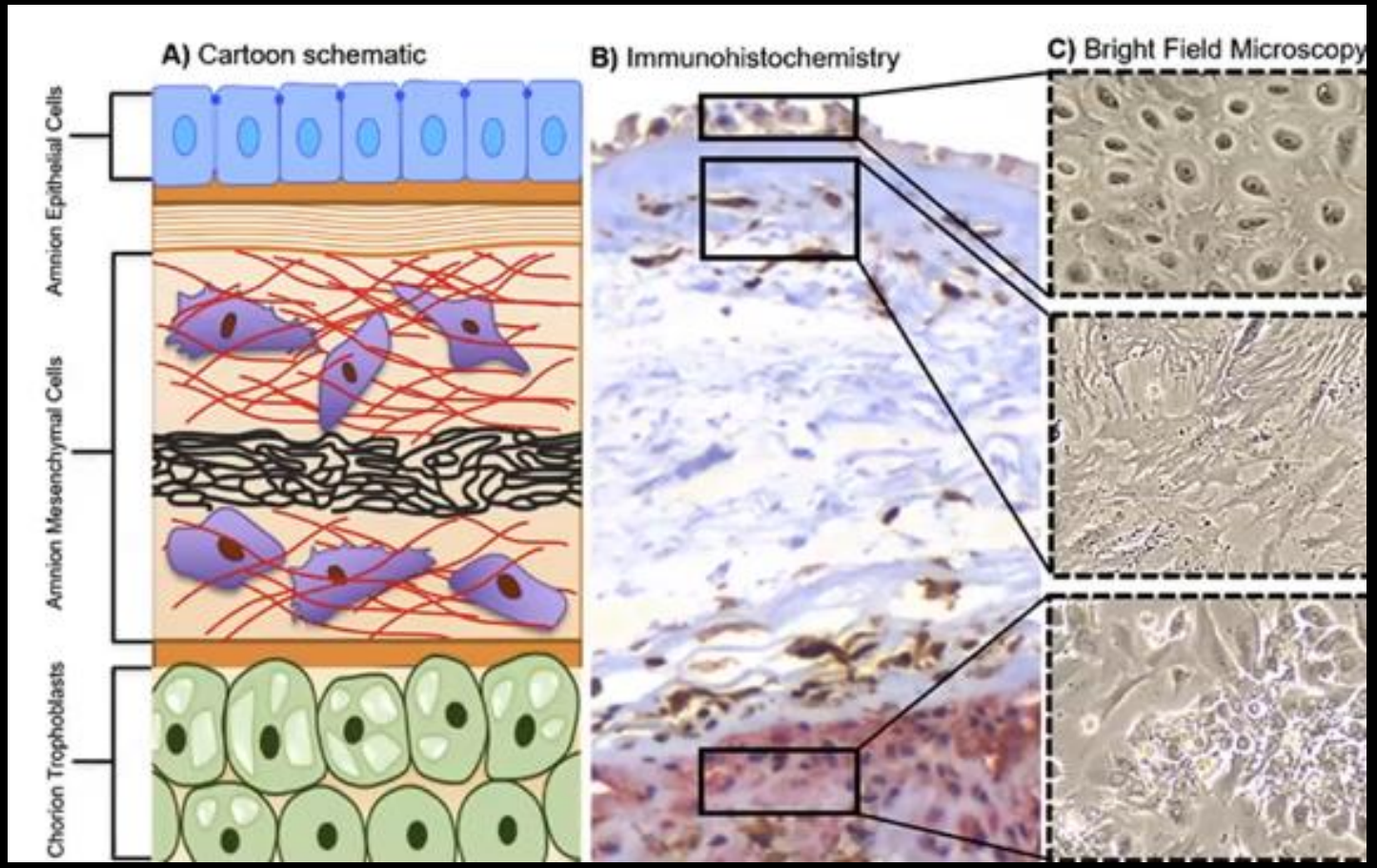
Risk factors

- Prior PPROM or PTL of any cause
- Bleeding in any trimester
- Genital tract infections
- Tobacco exposure
- Collagen disease
- Psychosocial stressors

Fetal membranes

- Surface area of 1500 cm2
- 200-300 um thick at term
- Resistant and elastic mechanical barrier
- Rich source of functionally relevant biochemicals
- Fetal membrane matrix is maintained by progesterone
- Provide mechanical ,structural ,immune ,antimicrobial and endocrine functions

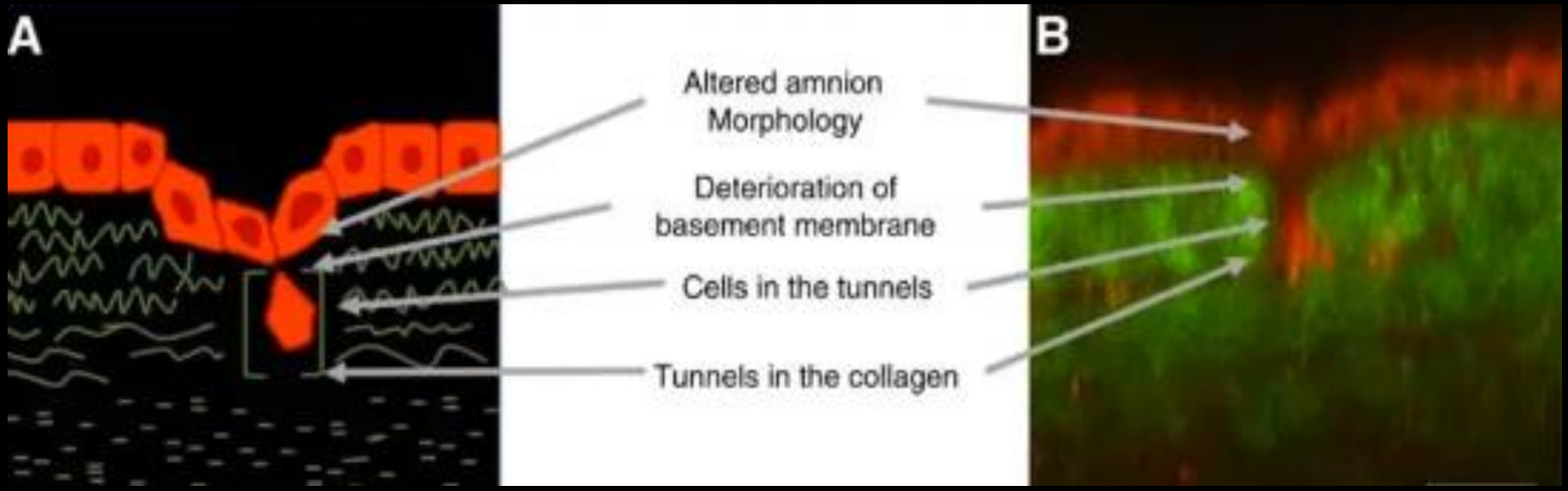
Fetal membranes



Protection mechanism reduced in inflammation

Etiology

- Inflammation
- Microfractures
- Fetal membrane aging

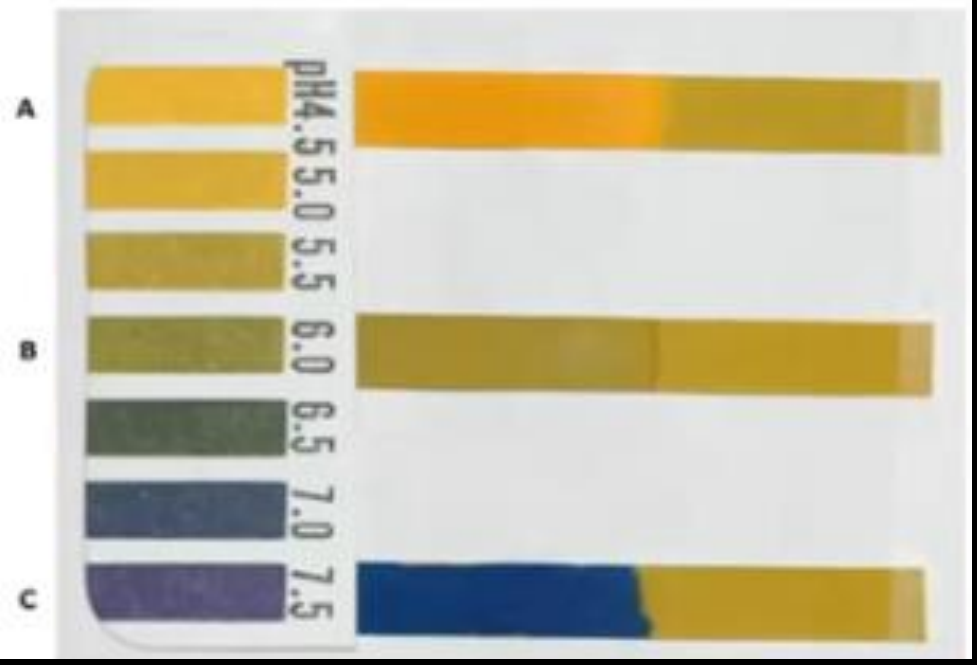

A
Altered amnion
Morphology
Deterioration of
basement membrane
Cells in the tunnels
Tunnels in the collagen
B

Clinical evaluation

- History
- (sudden gush of fluid , soaking clothes, dampness of underwear mistaken urinary incontinence)
- Odder and color
- Abdominal pain , contractions
- Mild pyrexia , feeling unwell ,abnormal vaginal discharge
- Vaginal bleeding
- Dysuria
- Cord prolapse

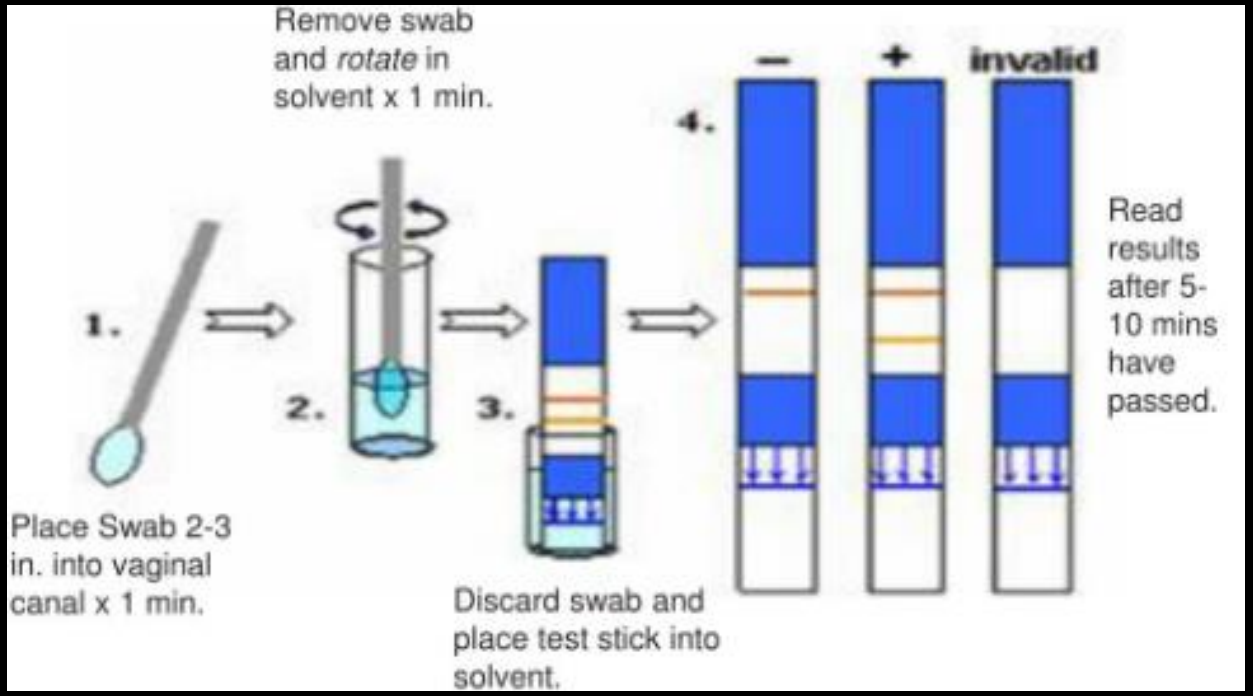
Diagnosis

Nitrazine



Ferning

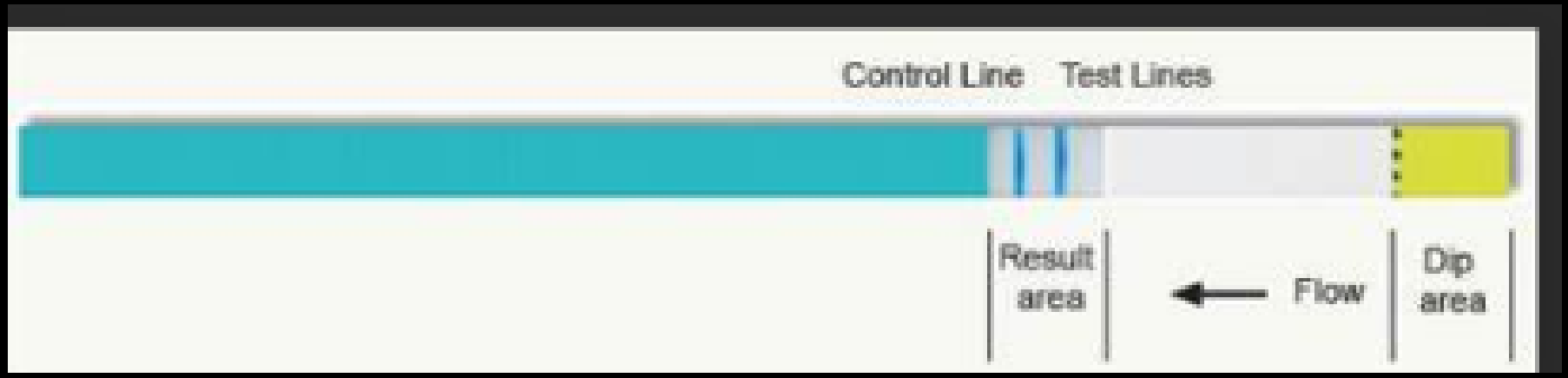
PPROM Diagnosis



Amnisure –sensitivity 94-99% specificity 87-100%

non-invasive strip test for the detection of the placental alphamicroglobulin-1 protein

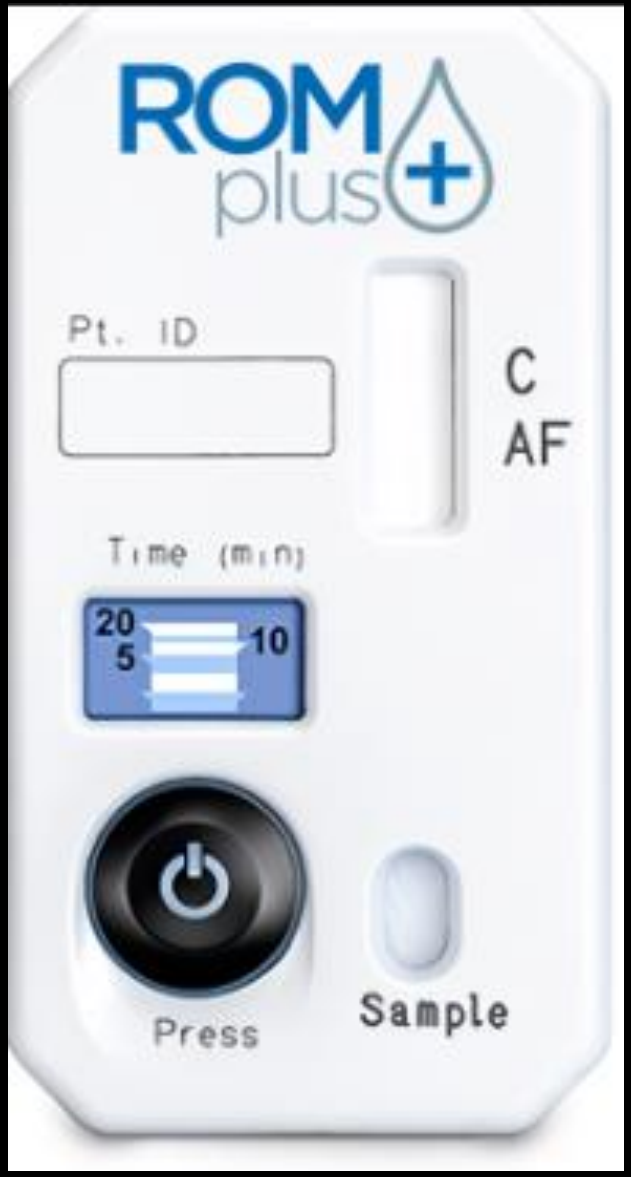
Actim PPROM



Actim-PPROM sensitivity 95-100%
Specificity 93-98%

rapid test that reliably detects PROM, even before any visible signs can be detected

ROM Plus



- Sensitivity 99% specificity

  91%

- Detect IGFBP-1 and AFP

Differential diagnosis

- Urinary incontinence: leakage of small amounts of urine is common in the last part of pregnancy
- Normal vaginal secretions of pregnancy
- Increased sweat or moisture around the perineum
- Increased cervical discharge
- Semen
- Douching

Investigation

- CBC
- Urinalysis
- High vaginal swab
- CRP
- US

Management

- Screening for infection including GBS
- Antenatal corticosteroids
- Tocolysis only to achieve benefit of corticosteroids
- Antibiotics prolong latency based on numerous trial

(penicillin plus macrolide)

- Fetal monitoring NST,AFV and fetal growth
- Maternal monitoring for infection or labor
- Timing of delivery –dependent on NICU capability

Majority of pregnancies with PPROM deliver within one week of rupture

Managements

- Malpresentation may require cesarean delivery
- Risk of cord prolapse should be evaluated
- Delivery at 34 weeks or sooner if indicated

Chorioamnionitis

Acute chorioamnionitis is the most frequent diagnosis in placental pathology reports, and is generally considered to represent the presence of intra-amniotic infection or "amniotic fluid infection syndrome"

Clinical chorioamnionitis

- Diagnosed by the presence of maternal fever (temperature ≥37.8°C)

plus two or more of the five following clinical signs:

- Maternal tachycardia (heart rate >100 beats/min)
- Fetal tachycardia (heart rate >160 beats/min)
- Uterine tenderness
- Purulent or foul-smelling amniotic fluid or vaginal discharge
- Maternal leukocytosis (white blood cell count >15,000/mm3)

The most frequent microorganisms identified in the amniotic fluid of women with clinical chorioamnionitis include *Ureaplasma* urealyticum, Gardnerella vaginalis, Mycoplasma hominis, Streptococcus agalactiae, Lactobacillus species, and Bacteroides species

The standard treatment for clinical chorioamnionitis has been administration of antibiotics and antipyretics and expedited delivery

PPROM

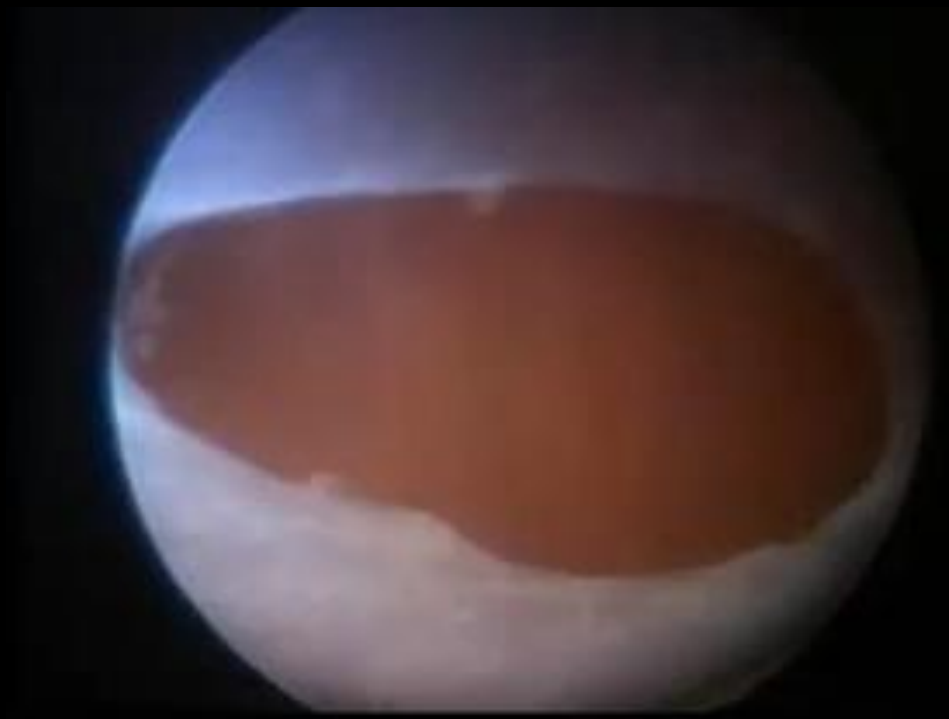
Spontaneous

- Infection or bleeding commonly implicated
- Site of rupture over the cervix
- Unlikely to seal spontaneously

Iatrogenic

- Infection not implicated
- Site of rupture at site of procedure
- May seal spontaneously

Surgical treatment of rupture of membrane



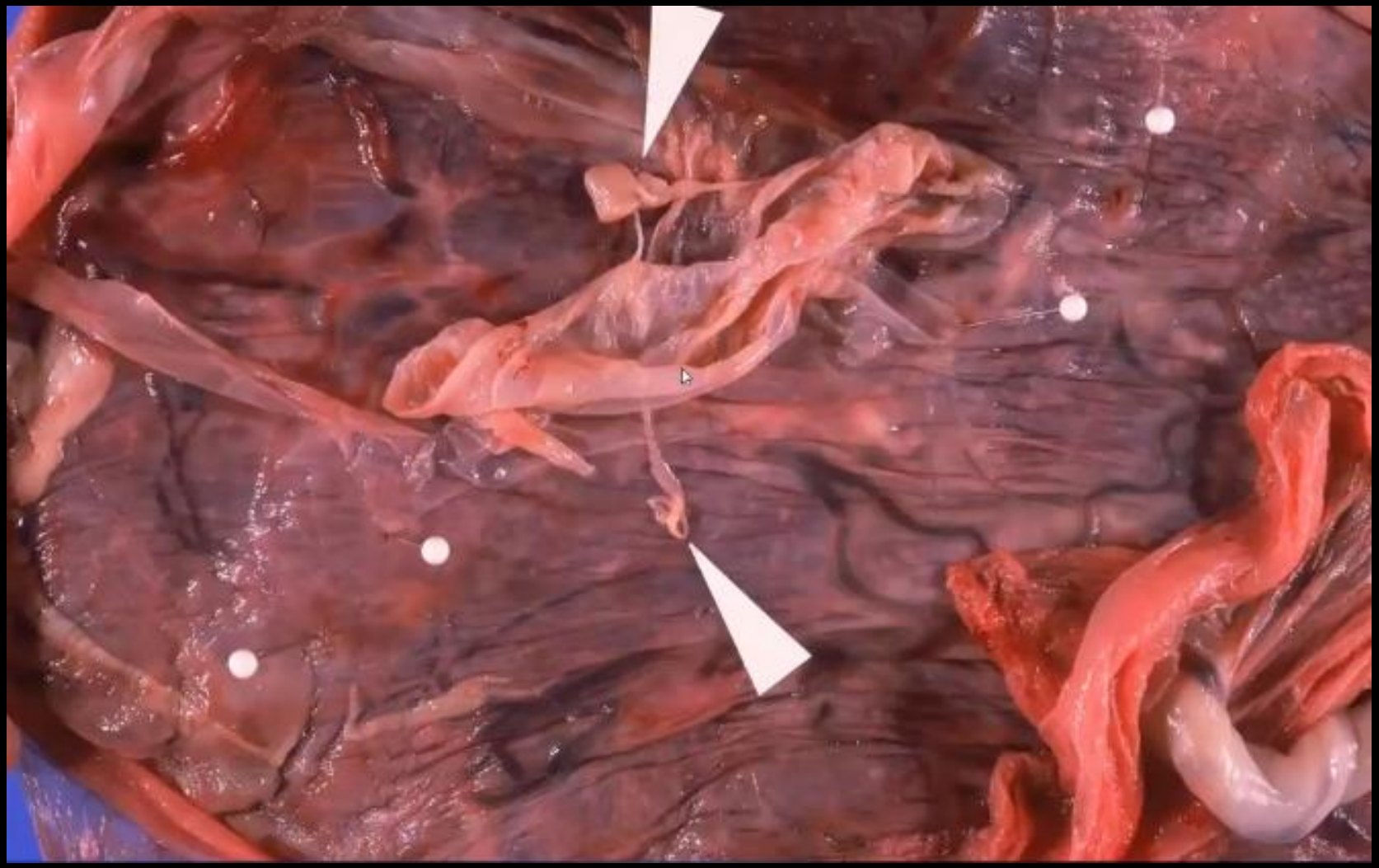
- Amniograft
- Amniotic patch

The procedure can seal membrane defects up to 4 mm in diameter

Amniopatch technique

- 22- gauge needle
- Injection into available pocket of fluid
- ½ unit of platelets
- 1 unit of cryoprecipitate

Amniopatch



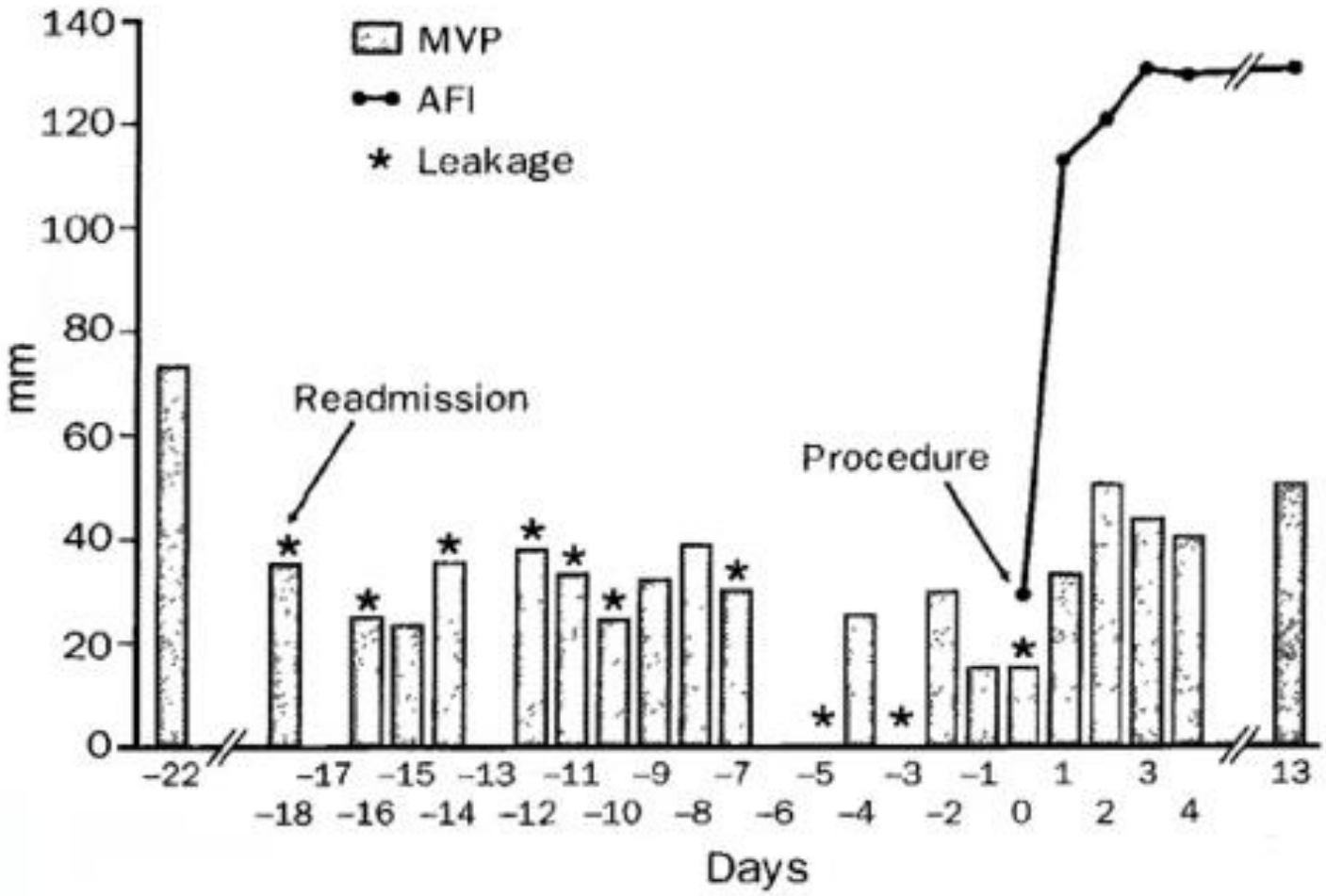


Figure: **Amniotic fluid leakage, maximal vertical pocket (MVP), and amniotic fluid index (AFI) after readmission**

Antenatal corticosteroids potent drugs with potent side effects

- Reduced placental weight
- Reduced fetal weight and height
- Reduced head circumference

Mgso4 is an important drug in early PPROM

Thank you