Preterm Labor and Preterm Prelabor Rupture of Membranes

SARAH WAGNER, MD, FACOG

Objectives

- Identify the risk factors and causes for PTL and PPROM
- Describe signs and symptoms of PTL and PPROM
- Describe initial management of PTL and PPROM
- List indications & contraindications of medications used in PTL
- Identify adverse outcomes associated with Preterm Delivery
- Counsel patient regarding risk reduction for PTB

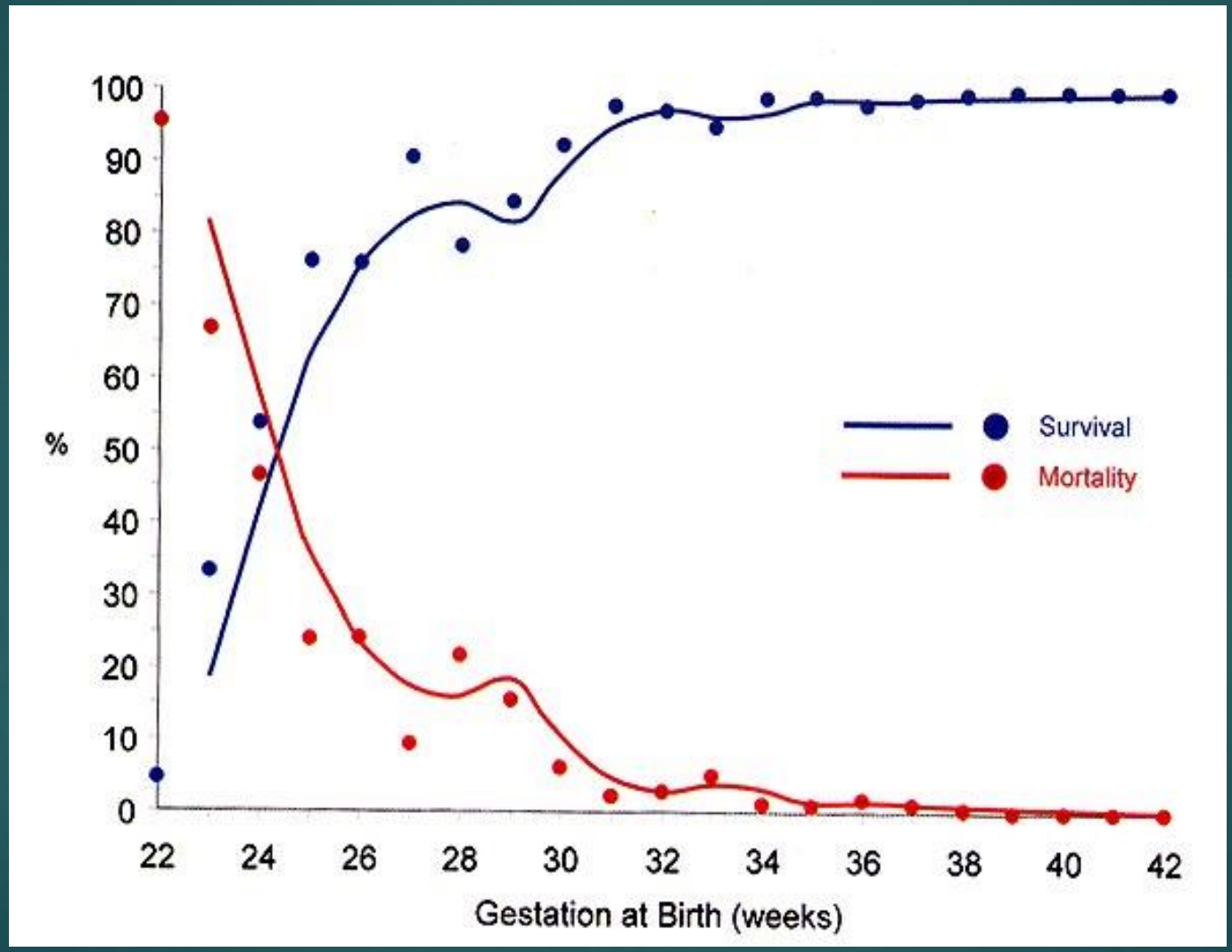
Preterm Labor: Definition

- Uterine contractions WITH any of the following:
  - Cervical “change”
  - > or equal to 2cm dilation
  - > or equal to 80% effacement
- Preterm delivery <37 weeks

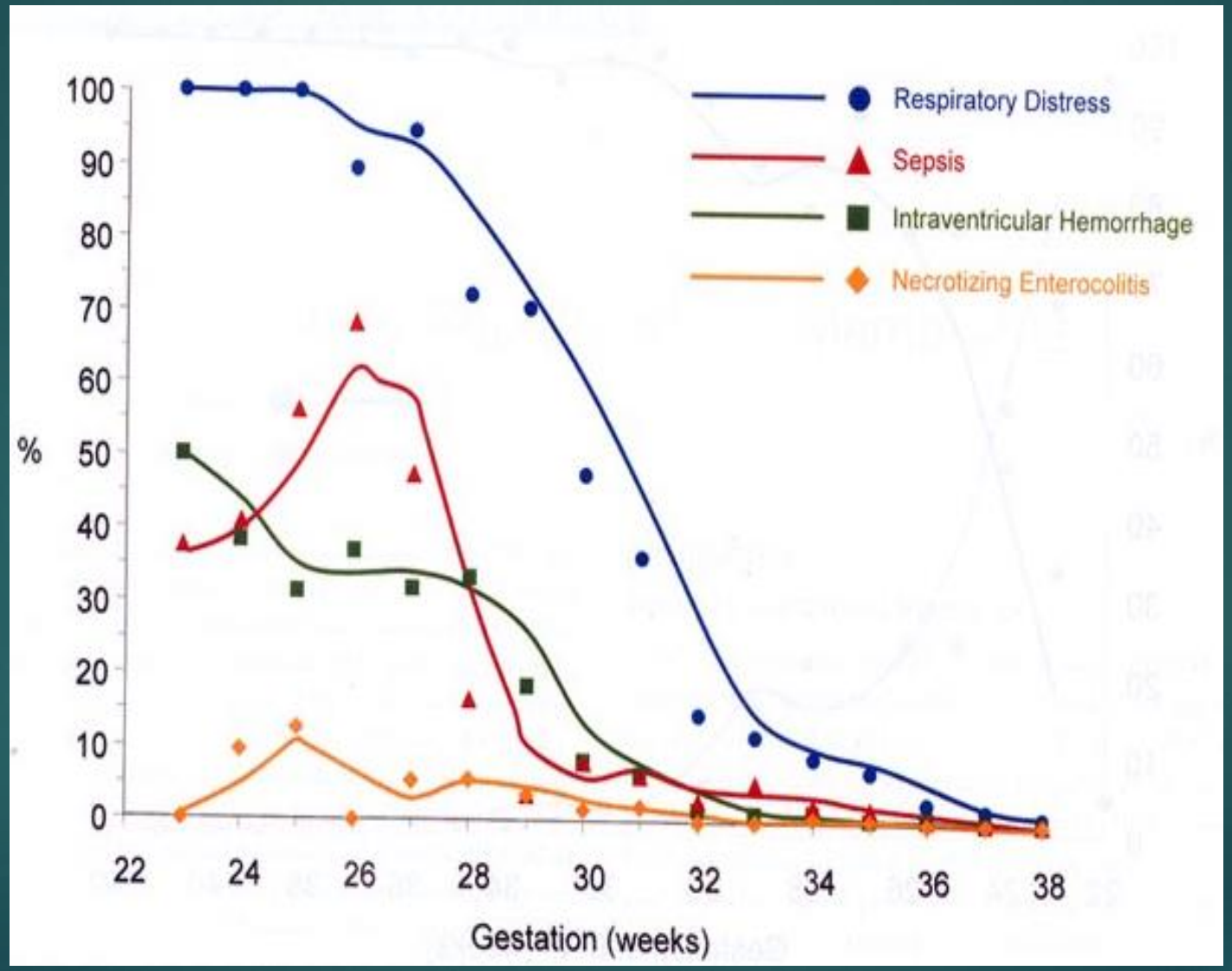
Epidemiology

- ~12% Incidence, 2% <32 weeks
- Preterm Birth accounts for:
  - 70% neonatal deaths
  - 36% infant deaths
  - 25-50% of long-term neurologic impairment
- Annual cost (2006) $26.2 billion = $51,000/infant
- No improvement with physician intervention ☹

Preterm Birth: Infant Mortality



Preterm Birth: Infant Morbidity



Risk Factors for Preterm Birth

- Non-modifiable
  - Prior PTB
  - Black
  - Age <18 or >40
  - Poor nutrition
  - Low SES
  - Uterine anomaly/fibroid
  - Cervical injury
  - Premature cervical dilation
  - Over-distended uterus
- Modifiable/Other
  - Cigarette smoking
  - Substance Abuse
  - Absent PNC
  - Short Pregnancy Interval
  - Anemia
  - Bacteriuria/UTI
  - Cervicitis
  - Periodontal disease
  - Depression and anxiety
  - Placental abruption
  - Vaginal bleeding

Preterm Birth: Recurrence

First Birth	Second Birth	Subsequent PTB Risk
Term		4.4%
Preterm		17.2%
Term	Term	2.6%
Preterm	Term	5.7%
Term	Preterm	11.1%
Preterm	Preterm	28.4%

- Prior PTB @ 23-27 weeks: 27%
- Prior PPROM: 13.5%

Pathogenesis

- 80% of preterm births are spontaneous
  - 50% Preterm Labor
  - 30% PPROM

- Pathogenic Process
  - Activation of the maternal or fetal hypothalamic pituitary axis
  - Infection
  - Decidual hemorrhage
  - Pathologic Uterine Distention

Pathogenesis: Inflammation

- Clinical/subclinical chorioamnionitis
  - Up to 50% of preterm birth < 30 wks GA
- Proinflammatory mediators
  - Maternal/fetal inflammatory response
  - Activated neutrophils/macrophages
  - TNF alpha, interleukins (6)
- Bacteria
  - Degradation of fetal membranes
  - Prostaglandin synthesis

Measures to Predict Preterm Birth

- History: Current and historical risk factors
- Mechanical: Uterine Contractions
- Biochemical: Fetal Fibronectin
- Ultrasound: Cervical Length

History of Preterm Birth <34 weeks

- May Consider Serial Transvaginal Cervical Length Screening, Q 2 weeks from 16-23 weeks.
  - If 25mm to 29mm increase to weekly screening
  - If <25mm→ cerclage

- If no history of PTB, and asymptomatic, but found to incidentally have a very short cervical length less than or equal to 20mm before 24 weeks→ Vaginal Progesterone

Mechanical: Preterm Contractions

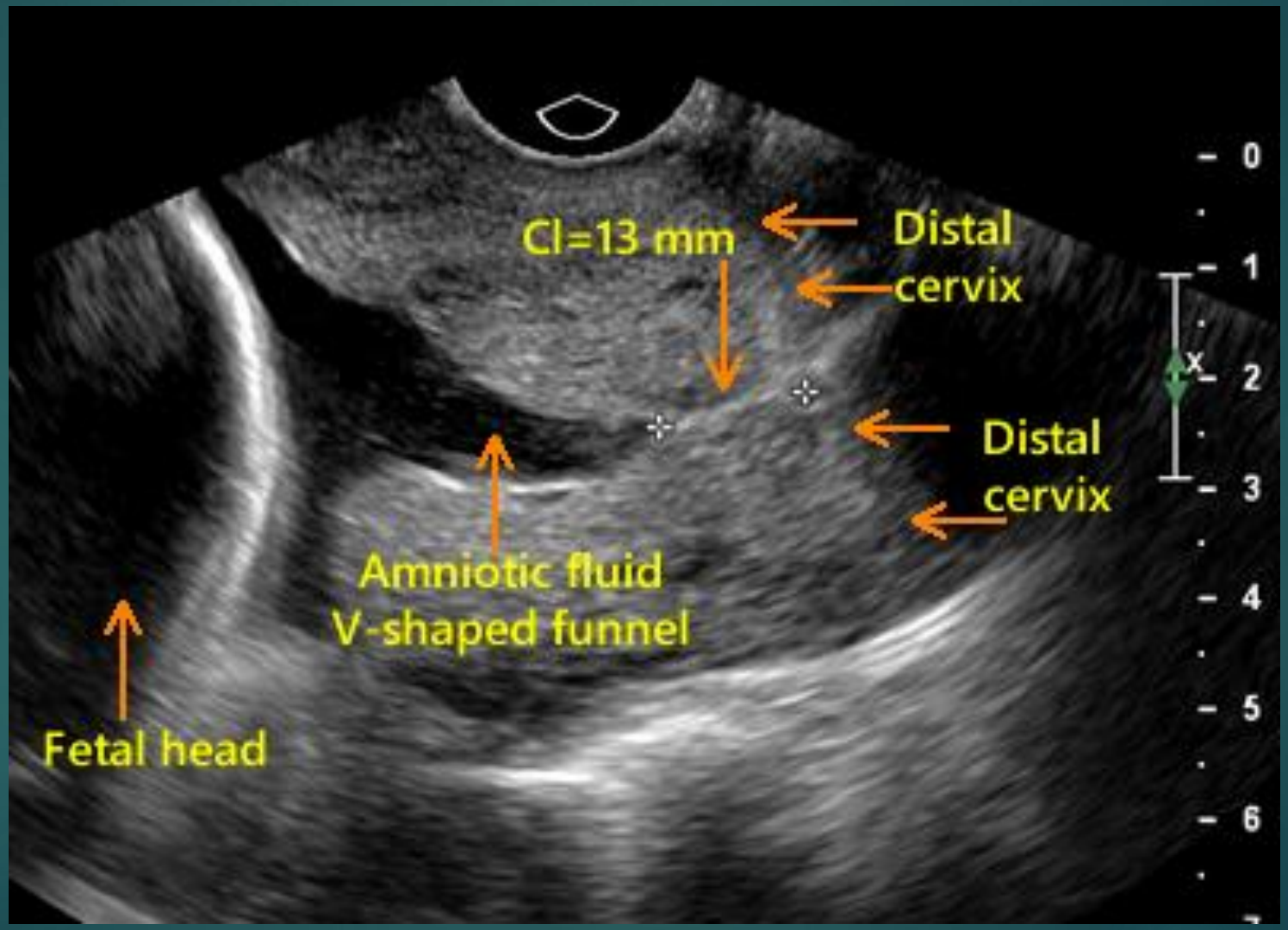
- 30% of preterm labor resolves spontaneously
- 50% of patients hospitalized for PTL give birth at term.
- <10% of patients with clinical dx of PTL give birth within 7 days.

- CONTRAINDICATIONS TO TOCOLYSIS
  - IUFD
  - Lethal fetal anomaly
  - NRFHTs
  - Severe preeclampsia or eclampsia
  - Maternal bleeding with hemodynamic instability
  - Chorioamnionitis
  - PPROM*
  - Maternal contraindications

Biochemical: Fetal Fibronectin

- Glycoprotein in amnion, decidua, cytotrophoblast
- Increased levels d/t breakdown of chorionic-decidual surface
- Inflammation, shear, movement
- Contraindications to collecting fFN:
  - <24 or >34 weeks
  - ROM
  - >/=3cm dilation
  - Active vaginal bleeding
  - Exam or sexual intercourse in last 24h
- Sensitivity (all): 93%, PPV 29%, NPV99%

Ultrasound: Cervical Length



Evaluating a ‘R/O PTL’

- PROMPT EVALUATION
- EFM/TOCO
- Where is the placenta? If you don’t know: abdominal u/s first
- UA and culture
- Speculum exam: determine status of cervix
  - Collect cultures: GC/CT, FFN
  - Rectovaginal Swab for GBS
  - Wet Prep/KOH, Ferning
- SVE
- US exam: Assess GA , CL, AFI, Presentation, Placentation

Management: Steroids

- Antenatal steroids are the most beneficial intervention of all to improve neonatal outcomes
  - 23-34 weeks if risk of delivery is <7d
  - Repeat course if prior course was >/= 7days before and still at risk for PTB <34 weeks

- Betamethasone: 12mg IM q24hr x2 doses
- Dexamethasone: 6mg IM q 12hr x4 doses

Management: Magnesium & Tocolysis

- Magnesium sulfate:
  - reduces the occurrence of cerebral palsy when given (RR, 0.71; 95% CI 0.55-0.91) prior to 32 weeks
- Tocolysis:
  - May be given to allow for the administration of steroids (48h)
  - Longer administration has no impact on neonatal outcomes

Drug	Mechanism	Efficacy	Side Effects	Contraindications
Beta adrenergic receptor agonist (Terbutaline*)	Interferes w/ myosin light chain kinase Inhibits actin myosin interaction	No change in perinatal outcome	Tachycardia, palpitations, hypotension, SOB, pulmonary edema, hyperglycemia, Fetal tachycardia	Maternal cardiac disease, uncontrolled diabetes
Magnesium Sulfate	Competes with Calcium at plasma membrane	Unproven	Diaphoresis, flushing, pulmonary edema	Myasthesthenia gravis, renal failure
Ca Channel Blocker (Nifedipine)	Directly block influx of Ca thru cell membrane	Unproven	Nausea, flushing, HA, palpitations	Caution: LV dysfunction, CHF
Cyclooxygenase Inhibitors/NSAIDS (Indomethacin)	Decrease prostaglandin production	Unproven	Nausea, GI reflux, spasm fetal DA, oligohydramnios, necrotizing enterocolitis in newborn	Platelet or hepatic dysfunction, GI ulcer Renal dysfunction, asthma

Management: Antibiotics

- Antibiotics should not be used to prolong gestation or improve neonatal outcomes in women with PTL and intact membranes

- GBS prophylaxis should be used for carriers or if patient is GBS unscreened and has risk factors.
  - Prior infant with invasive GBS disease or prior pregnancy with +GBS
  - GBS bacteriuria this pregnancy
  - **Delivery <37wks**
  - ROM greater or equal to 18hrs
  - Intrapartum temperature greater or equal to 100.4 F

Preventative Measures

- Progesterone Supplementation
  - Women with a prior singleton spontaneous PTB
  - Start at 16 weeks gestation
  - 17 alpha OH Progesterone (Makena): 250mg IM q week
  - Vaginal Progesterone 90-200mg daily

- 17-OH-P: Reduces Risk of Recurrent Preterm birth
  - <37 wks 36% vs 55%
  - <35 wks 21% vs 31%
  - <32 wks 11% vs 20%

Take Home Points: PTL

- Defined by "regular" uterine contractions, with cervical "change" or ≥ 2 cm dilation or ≥ 80% effacement, occurring before 37 weeks
- There are numerous risk factors – both modifiable and non-modifiable. Counsel patients regarding ways to reduce their modifiable risk factors
- Clinical assessment of risk includes consideration and evaluation of history, cervical length and fetal fibronectin
- There are a variety of tocolytic drugs available, though most have unproven efficacy
- Antenatal steroids are recommended for: Preterm labor 24 – 34 weeks

Preterm Prelabor Rupture of Membranes (PPROM)

- Prelabor rupture of membranes (PROM)
  - Rupture of the chorioamnionic membrane prior to the onset of labor at any stage of gestation
- Preterm prelabor rupture of membranes (PPROM)
  - PROM <37 wks

Incidence of PROM

- PROM – 12% of all pregnancies
- PROM – 8% term pregnancies
- PPROM – 30% of preterm deliveries

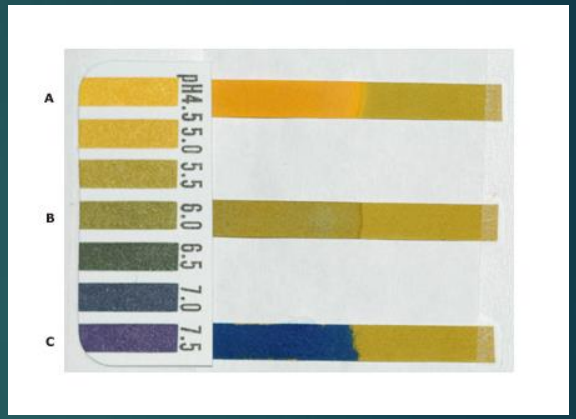
Evaluation: R/O PPROM

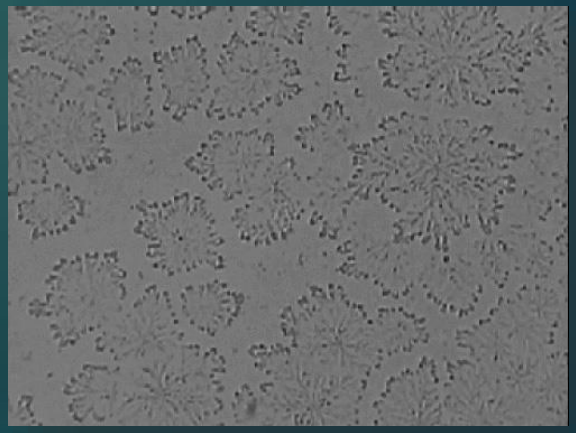
- History
  - "Gush" of fluid
  - Steady leakage of small amounts of fluid

- Physical
  - Sterile vaginal speculum exam
    - Minimize digital examination of cervix, regardless of gestational age, to avoid risk of ascending infection/amnionitis
    - Assess cervical dilation and length (visually if possible)
    - Obtain cervical cultures (Gonorrhea, Chlamydia)
    - Obtain amniotic fluid samples

Diagnosis

- Speculum Examination
  - Pooling of amniotic fluid in posterior vaginal fornix
  - Fluid per cervical os
- Nitrazine test
  - Fluid from vaginal exam placed on strip of nitrazine paper
  - Paper turns blue in presence of alkaline (pH > 7.1) amniotic fluid
- Fern test
  - Fluid from vaginal exam placed on slide and allowed to dry
  - Amniotic fluid narrow fern vs. cervical mucus broad fern





Testing pitfalls

- False positive Nitrazine test
  - Alkaline urine
  - Semen (recent coitus)
  - Cervical mucus
  - Blood contamination
  - Vaginitis (e.g. Trichomonas)
- False-Negative Nitrazine test
  - Remote PROM with no residual fluid
  - Minimal amniotic leakage

Diagnosis

- Ultrasound
  - Assess amniotic fluid level and compatibility with PROM
- Indigo-carmine Amnioinfusion
  - Ultrasound guided indigo carmine dye amnioinfusion (“Blue tap”)
  - Observe for passage of blue fluid from vagina

PPROM Risk Factors

- Risk Factors:
  - Prior PROM or PPROM
  - Prior preterm delivery
  - Multiple gestation
  - Polyhydramnios
  - Cervical Insufficiency
  - Vaginal/Cervical Infection
    - Gonorrhea, Chlamydia, GBS, S. Aureus
  - Antepartum bleeding (threatened abortion)
  - Smoking
  - Poor nutrition

Management of PPROM <23 weeks

- Patient counseling

Gestational Age (In Completed Weeks)	Death Before NICU Discharge	Outcomes at 18 to 22 Months Corrected Age*		
		Death	Death/ Profound Neurodevelopmental Impairment	Death/Moderate to Severe Neuro-developmental Impairment
22 Weeks	95%	95%	98%	99%
23 Weeks	74%	74%	84%	91%
24 Weeks	44%	44%	57%	72%
25 Weeks	24%	25%	38%	54%

- Expectant management vs. induction of labor
- GBS prophylaxis NOT recommended
- Antibiotics
  - Incomplete data
- Corticosteriods NOT recommended

Complications of Prolonged PPROM

- Fetal complications of prolonged PPROM
  - Pulmonary hypoplasia
  - Skeletal malformations
  - Fetal growth restriction
  - IUFD
- Maternal complications of prolonged PPROM
  - Chorioamnionitis

http://www.nichd.nih.gov/about/org/cdbpm/pp/prog_epbo/dataShow.cfm

Management of PPROM 23-33 weeks

- Expectant management
  - Deliver at 34 wks
  - Unless documented fetal lung maturity
- GBS prophylaxis
- Latency Antibiotics
- Corticosteroids
- Tocolytics
  - No consensus
- Magnesium Sulfate

Management of PPROM >/= 34 weeks

- Deliver: Induction of labor
- GBS prophylaxis

Rationale for Interventions

- Antibiotics
  - Prolong latency period
  - Prophylaxis of GBS in neonate
  - Prevention of maternal chorioamnionitis and neonatal sepsis
- Corticosteroids
  - Enhance fetal lung maturity
  - Decrease risk of RDS, IVH, and necrotizing enterocolitis
- Tocolytics
  - Delay delivery to allow administration of corticosteroids
  - Controversial, randomized trials have shown no pregnancy prolongation

Interventions

- Antibiotics
  - Ampicillin 2g q6h and Erythromycin 250mg q6h x48h
  - Amoxicillin 250mg q8h and erythromycin 333mg q8h x5d
- Corticosteroids
  - Betamethasone 12 mg IM q24 x 2
  - Dexamethasone 6 mg IM q12 x 4
  - *No consensus on whether to give 32-34 weeks
- Magnesium Sulfate
  - 4g bolus then 2g/h if <32 weeks
- Tocolytics
  - Indocin if <32 weeks 100mg PO x1, then 25mg PO q4h
  - Nifedipine 10 mg po q20min x 3, then q6 x 48 h, though

Surveillance

- Maternal: Monitor for signs of infection
  - Temperature
  - Maternal heart rate
  - Fetal heart rate
  - Uterine tenderness
  - Contractions
- Fetal: Monitor for fetal well-being
  - Kick counts
  - Nonstress tests (NSTs)
  - Biophysical profile (BPP)

Deliver if:

- Intrauterine infection
- Abruptio placenta
- Repetitive fetal heart rate decelerations
- Cord prolapse

Risks of Expectant Management

- Maternal
  - Increase in chorioamnionitis
  - Increase in Cesarean delivery
  - Spontaneous labor in ~ 90% within 48 hr ROM
  - Increased risk of placental abruption
- Fetal
  - Increase in RDS
  - Increase in intraventricular hemorrhage
  - Increase in neonatal sepsis and subsequent cerebral palsy
  - Increase in perinatal mortality
  - Increase in cord prolapse

Take Home Points: PPROM

- Preterm premature rupture of membranes refers to rupture of fetal membranes prior to labor in pregnancies < 37 weeks.
- A history of PPROM or PROM, genital tract infection, antepartum bleeding, and smoking are risk factors for PPROM and PROM.
- A clinical history suggestive of PPROM or PROM should be confirmed with visual inspection and laboratory tests including ferning and nitrazine paper.
- Management of PPROM at < 24 wks includes a discussion with the family reviewing the maternal risks against the fetal risks of significant morbidity and mortality during expectant management.
- For women with PPROM or PROM in whom intrauterine infection, abruptio placenta, repetitive fetal heart rate decelerations, or a high risk of cord prolapse is present, immediate delivery is recommended.
- Counseling after the delivery for the recurrence risk of PROM should occur, and modifiable risk factors addressed