Disclosures

• The speaker has nothing to disclose.
Objectives

• Explain the mechanism, dosing, adverse effects, and monitoring parameters of the tocolytic agents.

• Describe pharmacotherapy interventions performed in the preterm labor setting in order to have neonatal benefits.

• Identify appropriate antibiotic therapy for Group B Strep prophylaxis.

• Distinguish between the agents used for labor induction and identify dosing and adverse effects of these agents.
Overview

- Tocolytic Therapy
- Magnesium for Neuroprophylaxis
- Antenatal Steroids
- Progesterone
- Group B Strep Prophylaxis
- Preterm Premature Rupture of Membranes (PPROM)
- Induction of Labor
Statistics

- Preterm birth is the leading cause of neonatal mortality.
  - ~70% of neonatal deaths
  - ~36% of infant deaths
  - 25-50% of long-term neurologic impairment in children
  - 1 in 10 births in US was premature (2014).

Rates of Preterm Births

The 10 countries with the greatest number of preterm births –

India: 3 519 100
China: 1 172 300
Nigeria: 773 600
Pakistan: 748 100
Indonesia: 675 700
The United States of America: 517 400 (#6)
Bangladesh: 424 100
The Philippines: 348 900
The Democratic Republic of the Congo: 341 400
Brazil: 279 300

Preterm Birth

• Birth between 20 0/7 and 36 6/7

• Preterm Labor (traditional criteria) –
  • Regular uterine contractions
    PLUS
    • Change in cervical dilation
    AND/OR
    • Effacement
  • Regular uterine contractions and cervical dilation of at least 2 cm

Risk Factors

- **Maternal** Characteristics -
  - Familial risk
  - Low socioeconomic and educational status
  - Low or high maternal age
  - Single marital status
  - Race/Ethnicity
  - Smoking/Substance abuse/alcohol use
  - Depression
  - Stress
  - Long working hours with standing
  - BMI <20
  - Infection/Genital tract infection
  - Periodontal disease
  - Uterine anomalies
  - Cervical surgery

Risk Factors

• **Reproductive History** -
  - Prior spontaneous preterm birth
  - Short interpregnancy interval
  - Prior twin preterm birth
  - Prior indicated preterm birth
  - Prior stillbirth
  - Pregnancy termination

Risk Factors

- **Current** Pregnancy Characteristics -
  - Bleeding
    - Placental abruption
    - Placenta previa
  - Assisted Reproductive Technology/IVF
  - Multiple gestation
  - Uterine factors
    - Increased uterine volume
    - Cervical length – 25mm at 22-24 weeks
Figure 1. Pathways of preterm delivery resulting from preterm premature rupture of the membranes and/or preterm labour.

Preterm Birth

- Spontaneous
  - Preterm labor
  - PPROM
- Indicated
  - 25% of US preterm births
- Conditions that could create risk for mother, fetus, or both
  - Preeclampsia (40%), non-reassuring fetal status (25%), fetal growth restriction (10%), placental abruption (7%), fetal demise (7%)

Periviable Birth

• October 2015 - Consensus document released with suggestions for management of deliveries in the periviable period

• Defined as birth at 20 0/7 and 25 6/7 weeks

## Periviable Birth

<table>
<thead>
<tr>
<th></th>
<th>20 0/7 weeks to 21 6/7 weeks</th>
<th>22 0/7 weeks to 22 6/7 weeks</th>
<th>23 0/7 weeks to 23 6/7 weeks</th>
<th>24 0/7 weeks to 24 6/7 weeks</th>
<th>25 0/7 weeks to 25 6/7 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal Assessment for Resuscitation</td>
<td>Not recommended</td>
<td>Consider</td>
<td>Consider</td>
<td>Recommended</td>
<td>Recommended</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Consider</td>
<td>Recommended</td>
<td>Recommended</td>
</tr>
<tr>
<td>Tocolysis for steroid administration</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Consider</td>
<td>Recommended</td>
<td>Recommended</td>
</tr>
<tr>
<td>Magnesium for Neuroprotection</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Consider</td>
<td>Recommended</td>
<td>Recommended</td>
</tr>
<tr>
<td>Latency antibiotics for PPROM</td>
<td>Consider</td>
<td>Consider</td>
<td>Consider</td>
<td>Recommended</td>
<td>Recommended</td>
</tr>
<tr>
<td>GBS Prophylaxis</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Consider</td>
<td>Recommended</td>
<td>Recommended</td>
</tr>
</tbody>
</table>

Tocolytic Therapy

- Not indicated for use before neonatal viability
  - Exception - event known to cause preterm labor
  - May be considered at 23 weeks based on individual circumstances
- Generally not utilized after 34 weeks
  - Effective for ~ 48 hours
  - Steroid administration
  - Neuroprophylaxis
- Maintenance therapy is not recommended
  - Ineffective for preventing preterm birth
  - Does not improve neonatal outcomes

Tocolytic Therapy

- Contraindications
  - Intrauterine fetal demise
  - Lethal fetal anomaly
  - Non-reassuring fetal status
  - Severe preeclampsia or eclampsia
  - Maternal bleeding with hemodynamic instability
  - Chorioamnionitis
  - PPROM
  - Maternal contraindications to tocolysis

Patient Case

- PT is a 34 y.o. female, G2P1, at 25 weeks gestation who presents with contractions. She is found to be 3 cm dilated and has 100% cervical effacement. Her pregnancy is complicated by gestational diabetes mellitus requiring insulin. She has a history of PTL with her last pregnancy and delivered at 32 weeks. She is currently on 17-hydroxyprogesterone.

- What pharmacologic therapy should PT receive?
Tocolytic Agents

- NSAIDs
  - Indomethacin
- Calcium Channel Blockers
  - Nifedipine
- Beta-Adrenergic Receptor Agonists
  - Terbutaline
- Magnesium
Tocolytic Agents

Magnesium sulfate

Ca++

Nifedipine

Ca++

Oxytocin PGF₂

cAMP

Progesterone

Calmodulin + Ca++

β-adrenergic receptor

Terbutaline

Adenylate Cyclase

Progesterone (17OHP-C)

Reproduced from PM Witcher, with permission
Tocolytic Agents

NSAIDs

Phospholipids → Arachidonic Acid

Prostaglandin Synthesis Inhibitors → Cyclooxygenase

Cyclooxygenase → Prostaglandins

Prostaglandins → Gap Junction Formation

MLCK activation → ICF Calcium

ICF Calcium → MLCK activation

Gap Junction Formation → Synchronized uterine contractions

Reproduced from PM Witcher, with permission
# Tocolytic Agents

## Indomethacin

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Block the conversion of arachidonic acid to prostaglandins, which are necessary for parturition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy Category</td>
<td>C (1st trimester), C (2nd trimester), D (3rd trimester) Placental Passage</td>
</tr>
<tr>
<td>Dosing</td>
<td>50-100mg PO (PR) x 1; then 25-50mg PO Q 6 hours x 48-72 hours</td>
</tr>
<tr>
<td>Metabolism/Elimination</td>
<td>Liver; half life 4-5 hours</td>
</tr>
</tbody>
</table>

# Tocolytic Agents

## Indomethacin

| Maternal Side Effects | • Nausea, esophageal reflux, gastritis, emesis  
<table>
<thead>
<tr>
<th></th>
<th>• Platelet dysfunction</th>
</tr>
</thead>
</table>

| Fetal Side Effects    | • Constriction of ductus arteriosus (use >48 hours)  
|                       | • Oligohydramnios (use > 48 hours)  
|                       | • Necrotizing enterocolitis  
|                       | • Intraventricular hemorrhage |

| Contraindications     | • GA ≥ 32 weeks  
|                       | • Platelet dysfunction or bleeding disorder  
|                       | • Hepatic dysfunction  
|                       | • Gastrointestinal ulcerative disease  
|                       | • Renal dysfunction  
|                       | • Asthma (aspirin hypersensitivity) |

## Tocolytic Agents

### Nifedipine

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Block transmembrane flow of calcium through slowly inactivating voltage-gated L-type channels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy Category</td>
<td>C Placental Passage</td>
</tr>
<tr>
<td>Dosing</td>
<td>30mg loading dose; 10-20mg PO Q 4-6 hours</td>
</tr>
<tr>
<td>Metabolism/Elimination</td>
<td>Liver/Renal; half life 1-2 hours</td>
</tr>
</tbody>
</table>

# Tocolytic Agents

## Nifedipine

| Maternal Side Effects | • Dizziness, flushing, hypotension, palpitations, headache  
| | • Suppression of heart rate, contractility, and left ventricular systolic pressure when used with magnesium sulfate  
| Fetal Side Effects | • None known  
| Contraindications | • Hypotension  
| | • Preload dependent cardiac lesions, such as aortic insufficiency  
| | • Caution with left ventricular dysfunction or congestive heart failure  

# Tocolytic Agents

## Terbutaline

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Binds to β2-adrenergic receptors to increase intracellular cAMP. Leads to activation of protein kinase to inactivate myosin light chain kinases that lead to diminished myometrial contractility.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy Category</td>
<td>B Placental Passage</td>
</tr>
<tr>
<td>Dosing</td>
<td>0.25 mg SQ Q 20 mins for up to 3 doses; limited to 72 hours</td>
</tr>
<tr>
<td>Metabolism/Elimination</td>
<td>Liver/Kidney; half life 2.9-14 hours</td>
</tr>
</tbody>
</table>

# Tocolytic Agents

## Terbutaline

| Maternal Side Effects | • Tachycardia, hypotension, tremor, palpitations, shortness of breath, chest discomfort, pulmonary edema, hypokalemia, hyperglycemia, lipolysis, tachyphylaxis  
<table>
<thead>
<tr>
<th></th>
<th>• Hold if HR &gt;120 beats/min</th>
</tr>
</thead>
</table>
| Fetal Side Effects | • Fetal tachycardia  
| | • Hypoglycemia  
| | • Intraventricular hemorrhage ??? |
| Contraindications | • Tachycardia-sensitive maternal cardiac disease  
| | • Poorly controlled diabetes mellitus and hyperthyroidism  
| | • Caution with massive hemorrhage risk |

Terbutaline

FDA Warning

- Feb 2011
- Black Box Warning
- Injectable terbutaline should not be used for prolonged treatment (>48-72 hours) of preterm labor due to serious maternal heart problems and death
- Oral terbutaline should not be used

### Tocolytic Agents

**Magnesium**

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Exact is unknown; decreases levels of intracellular calcium, preventing activation of actin and myosin complexes to reduce myometrial contractility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy Category</td>
<td>D* Placental Passage</td>
</tr>
<tr>
<td>Dosing</td>
<td>4-6 gram bolus; 1-4 grams/hour infusion (generally infuse 2 grams/10 mins for loading dose)</td>
</tr>
</tbody>
</table>
| Metabolism/Elimination | Renally cleared  
**Use with caution in renal failure**  
Half life ~ 5 hours  |

Tocolytic Agents
Magnesium

- Level Monitoring –
  - 5-8 mg/dL – Therapeutic
  - 9-12 mg/dL – Loss of deep tendon reflexes
  - 12-15 mg/dL – Respiratory Depression
  - ≥ 15 mg/dL – Cardiac Arrest

- Serum Mg level if –
  - Altered consciousness, absence of DTRs, decreased respiration, muscle weakness, or MD order
  - Calcium gluconate 1g IV push over 5 to 10 mins for life-threatening magnesium toxicity
# Tocolytic Agents

## Magnesium

| Maternal Side Effects | • Flushing, diaphoresis, nausea, loss of deep tendon reflexes, respiratory depression, cardiac arrest, pulmonary edema  
|                       | • Suppresses heart rate, contractility and left ventricular systolic pressure as well as produces neuromuscular blockade when used with nifedipine |

| Fetal Side Effects    | • Neonatal depression  
|                       | • Bone demineralization  
|                       | • Hypotonia |

| Contraindications     | • Myasthenia gravis  
|                       | • Avoid in known myocardial compromise or cardiac conduction defects |

---

Magnesium
FDA Warning*

• May 2013

• Fetal and neonatal bone demineralization and fractures associated with long-term in utero exposure

• Changed from Category A to D

• Should not be used for more than 5-7 days to stop preterm labor

• ACOG recommends limiting to <48 hours for PTL between 24 - 34 weeks
Magnesium for Neuroprophylaxis

- 1990s observational studies showed possible correlation between prenatal magnesium sulfate administration and less frequent neonatal morbidities.

  
  - Trial of magnesium for prevention of cerebral palsy
  - Increased incidence of neonatal mortality in magnesium group
  - Early termination of trial

Magnesium for Neuroprophylaxis

- Crowther, et al. 2003
  - Delivery at less than 30 weeks
  - No significant reductions in the occurrences of infant death or cerebral palsy or both
  - Secondary analysis showed less frequent “substantial gross motor dysfunction” or death or both

- Marret, et al. 2007
  - Delivery before 33 weeks
  - No significant differences in total infant death or severe white matter injury or both
  - Follow-up evaluation showed no significant reductions in death or “gross motor dysfunction” or both
  - and death or “motor or cognitive dysfunction” or both

- Rouse, et al. 2008
  - Delivery before 32 weeks
  - No significant reduction in total stillbirth or infant death by 1 year or moderate to severe cerebral palsy at or beyond 2 years
  - Secondary analysis showed less frequent overall cerebral palsy

Magnesium for Neuroprophylaxis

  - Meta-analysis
  - Neuroprotective intent
    - Prenatal administration reduces occurrence of cerebral palsy
    - Reduced total occurrences of death and cerebral palsy

Magnesium for Neuroprophylaxis

- Reduces severity and risk of cerebral palsy when birth is anticipated before 32 weeks

<table>
<thead>
<tr>
<th>Treatment Regimens</th>
<th>Dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crowther</td>
<td>4g load</td>
<td>Up to 24 hours</td>
</tr>
<tr>
<td></td>
<td>1 g/hr</td>
<td></td>
</tr>
<tr>
<td>Marret</td>
<td>4g load</td>
<td>Load only</td>
</tr>
<tr>
<td>Rouse</td>
<td>6g load</td>
<td>Up to 12 hours; trmt resumed with imminent delivery</td>
</tr>
<tr>
<td></td>
<td>2g/hr</td>
<td></td>
</tr>
</tbody>
</table>
Antenatal Steroids

- Promotes fetal lung development
- Reduces
  - Neonatal mortality
  - Respiratory distress syndrome
  - Intraventricular hemorrhage
  - Necrotizing enterocolitis

Antenatal Steroids

- 24 0/7 and 33 6/7 weeks and at risk for delivery within 7 days
  - Includes ruptured membranes and multiple gestations
- Consider at 23 0/7 weeks and at risk for delivery within 7 days
- 34 0/7 and 36 6/7 weeks and at risk for delivery within 7 days and who have NOT received a previous course*
- Single repeat course -
  - Consider if < 34 0/7 weeks who have imminent risk for delivery and prior course was >14 days previously
  - Regular scheduled repeat courses or more than 2 courses are not currently recommended by ACOG

Antenatal Steroids

- The New England Journal of Medicine - Antenatal Betamethasone

- Singleton pregnant 34 0/7 to 36 5/7

- High probability of delivery -
  - Preterm labor with intact membranes with at least 3cm cervical dilation or 75% cervical effacement
  - Spontaneous rupture of membranes
  - Preterm delivery for any other indication as determined by provider

- Decreased rate for respiratory complications in newborns

- Increased rate of neonatal hypoglycemia but not the rates of other maternal or neonatal complications

Antenatal Steroids

- Betamethasone
  - 12mg IM Q 24 hours x 2 doses
  - 12mg betamethasone = 100mg prednisone = 400mg hydrocortisone
- Dexamethasone
  - 6mg IM Q 12 hours x 4 doses
  - 6mg dexamethasone = 40mg prednisone = 160 mg hydrocortisone
## Antenatal Steroids

<table>
<thead>
<tr>
<th>Pregnancy Category</th>
<th>Maternal Side Effects</th>
<th>Fetal Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>• Betamethasone – C</strong>&lt;br&gt;<strong>• Dexamethasone – C</strong>&lt;br&gt;<strong>• Placental Passage</strong></td>
<td><strong>• Hyperglycemia</strong>&lt;br&gt;<strong>• Increased white blood cells count</strong>&lt;br&gt;<strong>• Possible pulmonary edema with tocolytic therapy??</strong></td>
<td><strong>• Transient fetal heart rate changes</strong>&lt;br&gt;<strong>• Transient improvement in end-diastolic flow</strong></td>
</tr>
</tbody>
</table>

Prevention
Progesterone

- Mechanism of action
  - Local increase in progesterone in gestational tissue
  - Relaxation of myometrial smooth muscle
  - Blocking of the action of oxytocin
  - Inhibition of the formation of gap junctions

- Clinical considerations
  - Cervical length
  - Prior spontaneous preterm birth
  - Singleton vs multiple gestation

Prevention Progesterone

Singleton

History of Spontaneous Preterm Birth
(20 0/7 - 36 6/7 weeks)

17-HP
250 mg IM weekly
(Starting at 16-20 6/7 weeks until 36 weeks)
(Starting at 16-24 weeks per ACOG)

No Prior Spontaneous Preterm Birth

Short Cervix ≤ 20 mm at ≤ 24 weeks

Vaginal Progesterone
90mg gel or 200mg suppository PV daily
(from diagnosis until 36 weeks)

Prevention
Progesterone

• **Formulations**
  - Insufficient evidence that any of the vaginal preparations or doses are superior

<table>
<thead>
<tr>
<th>Injectable</th>
<th>Vaginal</th>
</tr>
</thead>
<tbody>
<tr>
<td>17-Hydroxyprogesterone caproate</td>
<td>Micronized progesterone</td>
</tr>
<tr>
<td>250mg/mL</td>
<td>100mg, 200mg</td>
</tr>
<tr>
<td>Contains castor oil</td>
<td>Contains peanut oil</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Progesterone in oil</td>
<td>Progesterone vaginal gel</td>
</tr>
<tr>
<td>50mg/mL</td>
<td>4% (45mg), 8% (90mg)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Progesterone insert</td>
</tr>
<tr>
<td></td>
<td>100mg</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Progesterone suppository compounding kit</td>
</tr>
<tr>
<td></td>
<td>25mg, 50mg, 100mg, 200mg, 400mg</td>
</tr>
</tbody>
</table>

Prevention
17-HP

- Meis, et al., 2003

- Substantial reduction in the rate of preterm delivery (37, 35, 32 weeks) in high-risk women with a history of preterm delivery

- Delivery before 37 weeks GA, 36.3% in 17-HP group vs 54.9% in placebo (p<0.001)

- Reduced rate of NEC, need for supplemental oxygen, and IVH in neonate

Prevention
17-HP

• 17-Hydroxyprogesterone

  • FDA approved indication

  • 250 mg IM weekly

  • Indicated in women with singleton gestation and a history of spontaneous preterm birth <37 weeks

  • Begin at 16-24 weeks regardless of transvaginal ultrasound cervical length

***Note – Injectable progesterone doses and indications are different

Prevention
Vaginal Progesterone

- Vaginal progesterone is associated with reduction in preterm birth and composite perinatal morbidity and mortality for women with singleton gestation, no prior spontaneous preterm birth, and short cervix.

- OPPTIMUM study, Feb 2016
  - 1228 women; Vaginal progesterone was not associated with reduced risk of preterm birth or composite neonatal adverse outcomes, and had no long-term benefit or harm on outcomes in children at 2 years of age.

- Romero R, et al., meta-analysis, July 2016
  - 5 trials, including OPPTIMUM
  - Reaffirms that vaginal progesterone reduces the risk of preterm birth and neonatal morbidity and mortality for women with singleton gestation and short cervix.

Prevention
Progesterone

• Contraindications

• Hypersensitivity to progesterone products
• History of venous or arterial thrombosis
• Carcinoma of breast or genital tract
• Undiagnosed abnormal vaginal bleeding unrelated to pregnancy
• Hepatic disease

Patient Case

- PT is a 34 y.o. female, G2P1, at 25 weeks gestation who presents with contractions. She is found to be 3 cm dilated and has 100% cervical effacement. Her pregnancy is complicated by gestational diabetes current mellitus requiring insulin. She has a history of PTL with her last pregnancy and delivered at 32 weeks. She is currently on 17-hydroxyprogesterone.

- What pharmacologic therapy should PT receive?
Group B Strep

- Group B Streptococcus (GBS) is the leading infectious cause of infant morbidity and mortality in the US.

- Acquired by exposure to GBS from the vagina of a colonized woman

- Ascends from the vagina to the amniotic fluid after onset of labor or rupture of membranes
  - Can also occur with intact membranes

- Exposure can also occur in the birth canal

## Group B Strep Prophylaxis Indications

- Universal Screening for GBS at 35-37 weeks

<table>
<thead>
<tr>
<th>GBS Prophylaxis Indicated</th>
<th>GBS Prophylaxis NOT Indicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous infant with invasive GBS disease</td>
<td>Colonization with GBS in previous pregnancy</td>
</tr>
<tr>
<td>GBS bacteriuria during any trimester of current pregnancy</td>
<td>GBS bacteriuria during previous pregnancy</td>
</tr>
<tr>
<td>Positive GBS screening during current pregnancy</td>
<td>Negative GBS screening during current pregnancy</td>
</tr>
<tr>
<td>Unknown GBS status at labor onset plus:</td>
<td>Cesarean delivery performed before the onset of labor and intact amniotic membranes, regardless of GBS colonization status or gestational age</td>
</tr>
<tr>
<td>- Delivery at &lt;37 weeks</td>
<td></td>
</tr>
<tr>
<td>- Amniotic membrane rupture ≥ 18 hours</td>
<td></td>
</tr>
<tr>
<td>- Intrapartum temperature ≥ 100.4F</td>
<td></td>
</tr>
<tr>
<td>- Intrapartum NAAT positive for GBS</td>
<td></td>
</tr>
</tbody>
</table>

**Group B Strep Prophylaxis Regimens**

- Adequate prophylaxis ≥ 4 hours of IV penicillin, ampicillin, or cefazolin before delivery

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>5 million units IV, then 2.5-3 million units IV Q 4 hours</td>
<td></td>
</tr>
<tr>
<td>Ampicillin</td>
<td>2 g IV, then 1 g IV Q 4 hours</td>
<td></td>
</tr>
<tr>
<td>Cefazolin</td>
<td>2 g IV, then 1 g IV Q 8 hours</td>
<td>Use if PCN allergy without: anaphylaxis, angioedema, respiratory distress, urticaria</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>900 mg IV Q 8 hours</td>
<td>Perform susceptibility testing to clindamycin and erythromycin</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1 g IV Q 12 hours</td>
<td></td>
</tr>
</tbody>
</table>

Group B Strep
Preterm Labor Prophylaxis

For < 37 weeks
Group B Strep
PPROM Prophylaxis

For < 37 weeks
PPROM

• Preterm Premature Rupture of Membranes

  • Before 37 weeks

• Birth within 1 week occurs in ≥ 50% of patients with PPROM.

• Clinically evident intraamniotic infection occurs in 15-25% of these patients.

• Postpartum infection occurs in 15-20% of these patients.

# PPROM Management

<table>
<thead>
<tr>
<th>Gestational Age</th>
<th>Management Recommendations</th>
</tr>
</thead>
</table>
| ≥ 37 weeks      | - Proceed to delivery  
                  - GBS prophylaxis as indicated |
| 34 0/7 weeks to 36 6/7 weeks | - Proceed to delivery  
                                   - GBS prophylaxis as indicated |
| 24 0/7 weeks to 33 6/7 weeks | - Expectant management  
                                   - Antibiotics to prolong latency if no contraindications  
                                   - Single-course of corticosteroids  
                                   - GBS prophylaxis as indicated |
| < 24 weeks      | - Patient counseling  
                  - Expectant management or induction of labor  
                  - Antibiotics may be considered at 20 0/7 weeks  
                  - GBS prophylaxis not recommended before viability  
                  - Steroids not recommended before viability  
                  - Tocolysis not recommended before viability  
                  - Neuroprophylaxis not recommended before viability |

PPROM

Latency Antibiotics

- Administration of broad-spectrum antibiotics prolongs pregnancy, reduces maternal and neonatal infections, and reduces gestational age-dependent morbidity.

- < 34 weeks

<table>
<thead>
<tr>
<th>Ampicillin 2 g IV Q 6 hours x 48 hours</th>
<th>Amoxicillin 250 mg PO Q 8 hours x 5 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythromycin 250 mg IV Q 6 hours x 48 hours</td>
<td>Erythromycin base 333 mg PO Q 8 hours x 5 days</td>
</tr>
</tbody>
</table>

PPROM
Alternative Regimen

• Azithromycin
  • May be used in place of erythromycin
  • Ease of administration, improved GI tolerance, presumed equivalency, and favorable cost
• Dosing?
  • Azithromycin $t^{1/2}$=68 hours       Erythromycin $t^{1/2}$=2 hours
• Pierson RC, Gordon SS, Haas DM.
  • Compared Ampicillin + Erythromycin vs Ampicillin + Azithromycin
  • Similar rates of chorioamnionitis, cesarean delivery, APGAR scores, birth weight, neonatal death, neonatal sepsis, and neonatal respiratory distress syndrome
• Similar length of latency period

Patient Case

- PP is a 28 y.o. G1P0 who presents at 28 weeks with ruptured membranes. She has NKDA. What antibiotic regimen should she be started on?

- PP’s Group B strep test results as negative. How would you alter her antibiotic regimen?
Induction of Labor

• Indicated or elective

• Risks
  • Chorioamnionitis, cesarean delivery, iatrogenic prematurity, and respiratory morbidities in the newborn

• Cervical ripening - Bishop Score
  • Prostaglandins
    • Laminaria japonicum

• Labor inducing
  • Oxytocin

## Induction of Labor

### Prostaglandin E2

<table>
<thead>
<tr>
<th>Drug Form</th>
<th>How supplied</th>
<th>Indication</th>
<th>Dosing</th>
<th>Time before Initiation of Pitocin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal Gel</td>
<td>0.5g/3g (2.5 mL)</td>
<td>Cervical ripening</td>
<td>Intracervical; 0.5mg x1, may repeat Q 6-12 hours for max dose of 1.5mg (3 doses) within 24 hours</td>
<td>6-12 hours</td>
</tr>
<tr>
<td>Vaginal Insert</td>
<td>10mg</td>
<td>Cervical ripening</td>
<td>Posterior vaginal fornix; Releases 0.3mg/hour x 12 hours</td>
<td>30-60 mins</td>
</tr>
<tr>
<td>Vaginal Suppository</td>
<td>20mg</td>
<td>Termination</td>
<td>20mg vaginally Q 3-5 hours; administration &gt;2 days not advisable</td>
<td>N/A</td>
</tr>
</tbody>
</table>

## Induction of Labor

### Prostaglandin E1

<table>
<thead>
<tr>
<th>How supplied</th>
<th>Induction</th>
<th>Dosing</th>
<th>Time before Initiation of Pitocin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Misoprostol</td>
<td>100 mcg, 200 mcg tablets</td>
<td>Cervical ripening Labor Induction</td>
<td>PO or Vaginal; Initial dose of 25 mcg; Q 3-6 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Higher doses associated with an increased risk of complications (uterine tachysystole and fetal heart rate decelerations)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fetal Demise: 200-400 mcg vaginally Q 4-12 hours at &lt;28 weeks</td>
</tr>
</tbody>
</table>

Induction of Labor
Seaweed?

- *Laminaria japonicum*
  - Mechanical method that works via osmosis
  - Made from stems of brown seaweed that have been cut, dried, and sterilized
  - Possible risk for infection
  - Thin, medium, thick, extra thick
  - Remove insert within 24 hours

Induction of Labor

Oxytocin

- Uterine response depends on duration of pregnancy
- Steady state is reach at ~ 40 minutes
- Develop guidelines for use

<table>
<thead>
<tr>
<th></th>
<th>Starting Dose (milliunits/min)</th>
<th>Increase (milliunits/min)</th>
<th>Interval (mins)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-Dose</td>
<td>0.5-2</td>
<td>1-2</td>
<td>15-40</td>
</tr>
<tr>
<td>High-Dose</td>
<td>6</td>
<td>3-6</td>
<td>15-40</td>
</tr>
</tbody>
</table>

Induction of Labor Precautions

- Uterine tachysystole with or without fetal heart rate decelerations
- Uterine rupture
- Prostaglandins
  - Headache, nausea, vomiting, fever, diarrhea
- Misoprostol - avoid 3rd trimester use if prior uterine scar
- Oxytocin
  - Excessive doses can lead to water intoxication and hyponatremia
  - Hypotension when given by rapid infusion

Conclusions

- Consider gestational age and risk vs benefits when selecting appropriate tocolytic therapy.

- Betamethasone and magnesium are both interventions that can be performed for neonatal benefit. Betamethasone may now be considered up to <37 weeks.

- 17-HP is for prevention of preterm labor in a women with a previous spontaneous preterm birth, and vaginal progesterone is for prevention of preterm birth in a woman with a short cervix.

- Administer appropriate antibiotics per CDC guidelines for GBS prophylaxis.

- Ampicillin + erythromycin/azithromycin are preferred PPROM latency antibiotic regimens.

- Consider cervical status when selecting labor induction agents as well as adverse effects of agents. Institutions should have protocols guiding use.
Learning Assessment
Question #1

• True or False. Adequate intrapartum antibiotic prophylaxis is greater than or equal to 4 hours of IV penicillin, ampicillin, cefazolin, or clindamycin before delivery.
Learning Assessment

Question #2

Which of the following is TRUE about betamethasone:

A. Is administered to promote fetal lung maturity

B. Is recommended for women at 24 to 34 weeks gestation at risk for delivery within 7 days

C. May be considered in women with a singleton pregnancy between 34 0/7 and 36 6/7 weeks gestation at imminent risk of preterm birth within 7 days

D. All of the above
Learning Assessment

Question #3

- Which of the following is a labor induction agent?
  
  A. Methergine
  
  B. Misoprostol
  
  C. Indomethacin
  
  D. 17-hydroxyprogesterone
Questions

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