Preterm Birth

Grand Rounds
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The Basics

- Preterm birth (PTB): includes all non-indicated births (PTL, PPROM, cervical insufficiency) between 20-37 WGA
  - 50% preceded by preterm labor
- PTB is leading cause of neonatal mortality in US
  - 70% neonatal deaths (1st 28 days)
  - 36% infant deaths (up to 1 year)
  - 25-50% long-term neurologic impairment
- NICU care:
  - Improved survival rate
  - Increased proportion of survivors with disabilities
- 20% increase 1990-2006, 12.3% decrease 08-09, current 12%
  - 8.49% 34-36 WGA, 1.53% 32-33 WGA, 1.97% <32 WGA
Risk Factors

- Strongest: prior preterm birth – 1.5-2x increased risk
  - Order matters! PT, then T with decreased risk
  - Number of priors:
    - One prior: 14-22%
    - Two priors: 28-42%
    - Three priors: 67%
  - Twin, then singleton: up to 40% if <30 WGA; 67.3% for reverse

- Short cervical length (<25 mm) at <24-28 WGA measured by TVUS; shorter cervix = greater risk
- Low maternal pre-pregnancy weight (BMI <20) or maternal obesity
- Smoking: dose-dependent
- Short interpregnancy interval <18-23 months
Risk Factors (cont’d)

- Occupational issues: prolonged standing, physical exertion
- Uterine distention: multiple gestations, polyhydramnios
- Demographic characteristics: younger or more advanced age, African American, low SES
- Infections: UTI/pyelo, genital infections, pneumonia, appendicitis
- VB, abruption, placental abnormalities
- Periodontal disease: PTB unaffected by care
- Prior cervical surgery
- Substance abuse
Evaluation / Treatment

• Prior preterm with current singleton:
  • Progesterone starting 16-24 WGA until 37 WGA
    • 250 mg weekly 17α-hydroxyprogesterone caproate
    • 90-100 mg daily vaginal progesterone
    • 200 mg daily vaginal micronized progesterone gel capsule
  • Insufficient evidence for combo therapy or multiple methods
• Serial TV cervical length screening 16-23 WGA
  • >3 cm: Q2 weeks
  • 2.5-2.9 cm: Q1 week
  • <2.5 cm: offer cerclage placement
TVUS of cervix: safe, reliable, reproducible assessment of CL, & more predictive
TV vs abdominal US: Not affected by maternal obesity, cervix positioning, or shadowing from fetal positioning
Versus digital exam: Can identify other risk factors
  - Intraamniotic debris: possible intrauterine microbial colonization
  - Choriodecidual separation
Procedure

- Probe placed in anterior fornix with empty maternal bladder
- Shortest of 3 measurements
  - 60% of women with CL <15 mm delivered within 7 days
- Inter-observer variation of 5-10%
- Funneling does not add to preterm delivery risk
Cerclage Placement

- Population
  - Singleton
  - Hx prior delivery at <34 WGA
  - Cervix <25 mm at <24-28 WGA
- Significant decreases in preterm birth outcomes, decrease in perinatal morbidity and mortality
Multifetal Gestations

- Do not support use of progesterone or cerclage placement
  - Not affected by h/o prior PTB

- Cerclage may cause 2x increase in PTB

- No benefit of progesterone
Incidental Short Cervical Length
Screening Populations

- No hx prior preterm:
  - Routine screening not recommended, but may be considered/ Recommend CL measurement be performed at anatomy scan 18-22 WGA
  - Incidental short cervix, f/u TVUS
  - 0.2-0.8 % risk of PTB

- Decision and economic analyses: universal US screening for short CL, initiation of treatment was cost-effective
Incidentally Diagnosed

- Screening: FFN and BV screening, home uterine activity monitoring not recommended for screening asymptomatic women

- Therapy: Indomethacin, antibiotics, restriction of activity, omega-3 fatty acids lack clinical trials, not recommended for incidentally diagnosed short CL
Short CL, No h/o prior PTD

- Cerclage: for <25 mm at 16-24 WGA not assoc with sig reduct in PTB <34 WGA

- Progesterone
  - Vaginal micronized, 200 mg daily: 44% decrease in PTB at <34 WGA in women with asympt CL of <15mm at 20-25 WGA
  - Vaginal gel, 90 mg daily: 45% decrease in PTB at <33 WGA and 43% decrease in neonatal M&M among asympt CL of 10-21 at 19-<24 WGA
Acute Treatment
Preterm Labor

- Clinically, regular uterine contractions with change in cervical dilation, effacement, or both
  - 4 every 20 minutes, 8 every 60 minutes
  - Minimum of 2 cm dilation, effacement >80%
- Over-diagnosis common
- Less than 10% of women dx with PTL give birth within 7 days
  - 30% resolves
  - 50% give birth at term
- Should not rely on FFN or CL alone for management
Tocolytics

- In general, not indicated for use prior to viability – upper limit of use is 34 WGA
- Contraindicated when maternal and fetal risks of prolonging pregnancy or risks associated with tocolytics greater than risks assoc with PTB
- Intended for short-term prolongation (up to 48 hrs) of pregnancy: ANCS, NP mag, transport
- Should not be given to women with preterm contractions but no cervical change, especially with dilation <2 cm
Tocolytic Contraindications

- IUFD
- Lethal anomaly
- Nonreassuring fetal status
- Severe pre-eclampsia or eclampsia
- Maternal bleeding with hemodynamic instability
- Chorio
- PPROM: without infection, may be considered for transport, steroid administration, or both
- Maternal contraindications to tocolysis
<table>
<thead>
<tr>
<th>Agent or Class</th>
<th>Maternal Side Effects</th>
<th>Fetal or Newborn Adverse Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium channel blockers</td>
<td>Dizziness, flushing, and hypotension; suppression of heart rate, contractility, and left ventricular systolic pressure when used with magnesium sulfate; and elevation of hepatic transaminases</td>
<td>No known adverse effects</td>
<td>Hypotension and preload-dependent cardiac lesions, such as aortic insufficiency</td>
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<tr>
<td>Nonsteroidal anti-inflammatory drugs</td>
<td>Nausea, esophageal reflux, gastritis, and emesis; platelet dysfunction is rarely of clinical significance in patients without underlying bleeding disorder</td>
<td>In utero constriction of ductus arteriosus*, oligohydramnios*, necrotizing enterocolitis in preterm newborns, and patent ductus arteriosus in newborn¹</td>
<td>Platelet dysfunction or bleeding disorder, hepatic dysfunction, gastrointestinal ulcerative disease, renal dysfunction, and asthma (in women with hypersensitivity to aspirin)</td>
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<tr>
<td>Beta-adrenergic receptor agonists</td>
<td>Tachycardia, hypotension, tremor, palpitations, shortness of breath, chest discomfort, pulmonary edema, hypokalemia, and hyperglycemia</td>
<td>Fetal tachycardia</td>
<td>Tachycardia-sensitive maternal cardiac disease and poorly controlled diabetes mellitus</td>
</tr>
<tr>
<td>Magnesium sulfate</td>
<td>Causes flushing, diaphoresis, nausea, loss of deep tendon reflexes, respiratory depression, and cardiac arrest; suppresses heart rate, contractility and left ventricular systolic pressure when used with calcium channel blockers; and produces neuromuscular blockade when used with calcium-channel blockers</td>
<td>Neonatal depression¹</td>
<td>Myasthenia gravis</td>
</tr>
</tbody>
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*Greatest risk associated with use for longer than 48 hours.
¹Data are conflicting regarding this association.

Indomethacin

- Nonspecific COX inhibitor: stops conversion of arachidonic acid to prostaglandins, critical step in parturition
- GI side effects seen in 4% of patients
- Primary tocolytic in 24-32 WGA
- Not recommended after 32 WGA: constriction of ductus arteriosus → pulmonary HTN, tricuspid regurg, persistent fetal circulation
  - Gestational age, duration of use
Indomethacin (cont’d)

- Contraindications: platelet dysfunction or bleeding DO, hepatic or renal dysfunction, GI ulcer, asthma
- Dosing:
  - Loading: 50-100 mg
  - Maintenance: 25 mg PO Q4-6 hrs
- Half-life:
  - Maternal 2.2 hrs
  - Fetal 15 hrs
- If >48 hrs, fetal echo: tricuspid regurg, RV dysfunction, pulsatility index <1.9, oligohydramnios
Nifedipine

- Calcium channel blockers: block calcium movement into cells, increase movement out of cells, block calcium release from sarcoplasmic reticulum → inhibition of myosin phosphorylation → myometrial relaxation

- Peripheral vasodilator: nausea, flushing, dizziness, palpitations, HA

- Primary 32-34 WGA tocolytic
Nifedipine (cont’d)

• Contraindicated with hypotension, preload-dependent cardiac lesions
  • Potential for synergistic effects with magnesium sulfate → respiratory depression

• Dosing
  • Loading: 30 mg PO
  • Maintenance
    • 10 mg PO Q4 hrs x up to 48 hrs
    • 20 mg PO Q6 hrs x up to 48 hrs
  • Half-life: 2-3 hrs
Terbutaline

- Beta-adrenergic receptor agonists: receptor binding $\rightarrow$ decreased intracellular calcium $\rightarrow$ inhibition of actin/myosin interaction $\rightarrow$ decreased myometrial contractility
- Desensitization with prolonged use (tachyphylaxis)
- Side effects: tachycardia, palpitations, lower BP, pulmonary edema (rare<0.3%), hypokalemia, hyperglycemia, lipolysis, myocardial ischemia (rare)
- Contraindications: tachycardia-sensitive cardiac disease, poorly-controlled hyperthyroidism or diabetes (hourly monitoring, IV insulin)
Terbutaline (cont’d)

- Injectable not be used >72 hrs due to risk of maternal heart problems, death; oral should not be used

- Dosing: variable
  - 0.25 mg IM Q20-30 min or up to 4 doses or until tocolysis achieved
  - 0.2 mg IM Q3-4 hrs
Magnesium Sulfate

- Precise mechanism not entirely understood: competes with calcium at level of plasma membrane voltage-gated channels $\rightarrow$ hyperpolarization of plasma membrane $\rightarrow$ interferes with myosin activity and reduces myometrial contractility

- Neither more nor less effective than other tocolytics

- Side effects: flushing, diaphoresis, slight decrease in fetal baseline and variability
Magnesium Sulfate

- Contraindicated in myasthenia gravis, known myocardial compromise, cardiac conduction defects

- Dosing
  - Load: 6 gram IV dose over 20 minutes
  - Maintenance: 2 grams / hr IV
**ANCS**

- Most beneficial intervention for improvement of neonatal outcomes
- Significantly lower RDS, intracranial hemorrhage, necrotizing enterocolitis, death
- Single course recommended if anticipated delivery in 7 days and 24-34 WGA
  - Betamethasone 12 mg IM Q24 hrs x2 doses
  - Dexamethasone 6 mg IM Q12 hrs x4 doses
Steroid Dosing

- Should give first dose even if unlikely that second dose will be able to be achieved

- No proven benefit of accelerated dosing for ANCS

- Rescue dose:
  - Intact membranes with prior ANCS given 2+ weeks prior, gestational age <33 WGA, anticipated delivery in 1 week or less
  - Dosing same as standard ANCS
  - More than 2 courses not recommended
Mg for Neuroprotection

- Administered to reduce occurrence and / or severity of CP when delivery anticipated prior to 32 WGA
- Not intended for pregnancy prolongation
- 6 g load, 2 g / hr x 12 hours
Most studies have failed to prove benefit of antibiotic administration for infection / inflammation associated with ctxns

Should still give prophylactic antibiotic administration for GBS or for PPROM
Multifetal Gestation

- Use of tocolytics not recommended due to greater risk of maternal complications.
- Inadequate data regarding use of ANCS, but due to clear benefit in singleton, recommended for multifetal.
- NP mag recommendations similar to those for ANCS.
Summary

- Preterm labor and delivery relatively common with long-term implications
- Hx prior: progesterone, serial CL, cerclage
- No prior hx: progesterone
- Acute tx: tocolytics for short-term prolongation of pregnancy
- Mag for NP, ANCS, GBS Abx
- Multifetal: no cerclage or progesterone, ANCS and NP mag recomm
Sources

Sources (cont’d)

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- Simhan, HN, MD, MS, Caritis, S, MD. Inhibition of Acute Preterm Labor. In: *UpToDate*, Barss, VA (Ed), UpToDate, Waltham, MA 2013.