PRETERM BIRTH

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Preterm Birth

- More than 500,000 live preterm births annually
  - Births <37 weeks and > 20 weeks
  - In the US, preterm delivery rate is 9.6% in 2015
    - Slight increase from 2014
  - In Europe, preterm delivery rate is 5-7%
  - Decrease rate of PTD since 2006 (12+%)
    - 11.7% in 2011
    - Early PTD < 34 weeks and late PTD 34-37 weeks

Preterm Birth Outcomes

- Neonatal mortality rates continue to decrease
  - 20-30% survival at 22-23 weeks
  - 50% survival at 24 weeks
  - 90% survival at 28 weeks
- Short term morbidities
  - RDS, IVH, PVL, NEC, BPD, sepsis, PDA
- Long term morbidities
  - Cerebral palsy, mental retardation, ROP
  - Risk directly related to gestational age
    - CP risk 2/1000 live births overall
    - CP risk 8-10% survivors BW < 1000g
Percentage Survival by Gestational Age

Percentage with severe or moderate disability by gestational age among surviving newborns

Preterm Birth
- Leading cause of neonatal mortality in US
  - Responsible for 75% of neonatal mortality
  - 36% of deaths within first year of life
  - 50% of long-term neurologic impairment
- Preterm birth financial costs
  - 30% of US health care spending for infants
  - 10% of US health care spending for all children
  - Cost of preterm birth $26.2 billion in 2005
  - $51,600 per infant born preterm
- Remains single largest challenge for obstetrician
  - Screening strategies
  - Importance of effective measures
  - Corticosteroids, GBS prophylaxis
  - Magnesium sulfate (neuroprotection), atraumatic delivery, NICU
Preterm Delivery Risk Factors

- History of prior preterm delivery
  - 17%-40% recurrence risk
  - The earlier the prior delivery, the greater the recurrence risk
- Short CL
  - Commonly defined as < 25 mm at < 24 weeks
  - Shorter the cervix, the greater the risk of PTD
- African-American race
  - 18% vs. 8% for white patients
- Multiple gestations
  - Twins 36 wks, Triplets 33 wks, Quads 31 wks
- Additional risk factors
  - Age <17 or >35
  - Low socioeconomic status
  - Tobacco use
  - Poor or excessive weight gain/low BMI/high BMI
  - Prior cervical surgery, uterine instrumentation
  - Vaginal bleeding, UTI, periodontal disease

Preterm Birth Screening Strategies

- Transvaginal CL measurement
  - Reliable and reproducible
  - "Universal screening may be considered"
- Technique
  - Empty bladder
  - Identify echodense line between internal and external os
  - CL is shortest of 3 measurements
- Other tests or interventions not helpful in asymptomatic patient
  - fFN
  - Screening for BV
  - HJAM
  - Antibiotics, indomethacin, omega-3 fatty acids, vitamin C, vitamin E

CL and Risk of PTD < 35 weeks

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<th>Cervical length (mm)</th>
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Table 2. Predicted Probability of Preterm Delivery Before Week 35, by Cervical Length and Time of Measurement (Week of Pregnancy)

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Transvaginal ultrasound with cervical funneling

Cervical Length in Women Enrolled in Studies of the Use of Progestogens as Prophylaxis against Preterm Birth.


Vaginal Progesterone Sonographic Short Cervix

- Safety and efficacy of vaginal progesterone gel reducing PTD < 33 weeks with short CL
  - Asymptomatic patients screened 19-23 weeks
  - Transvaginal CL 16-20 mm
  - Multicenter, randomized, double-blind, placebo-controlled trial of progesterone gel (Prochieve 8%); > 200 patients in each arm
- Treated patients
  - Significantly lower rate PTD < 28, < 33, and < 35, weeks
    - 8.9% v. 16.1%; RR, 0.55; P=0.02 (< 33 weeks)
    - Significantly lower rate RDS (3.0% v. 7.6%; RR, 0.39; P=0.03)
    - Significantly lower rate 'any neonatal morbidity/mortality'
    - 7.7% v. 13.5%; RR, 0.57; P=0.04
  - 14 patients need Rx to prevent one PTD < 33 weeks
  - 22 patients need Rx to prevent one case RDS
Vaginal Progesterone in Patients with Asymptomatic Short Cervix: Systematic Review and Metaanalysis

- 5 placebo-controlled trials
  - Rate PTD < 33 wks: 12.4% vs. 22.0%
  - Neonatal outcomes significantly improved
    - RDS RR, 0.50
    - Composite neonatal mortality/mortality RR, 0.57
    - BW < 1500 g RR, 0.55
    - NICU adm RR, 0.75
  - Beneficial effects of progesterone
    - Similar in subgroups 21-25 mm v. 10-20 mm v. < 10 mm
    - Similar regardless of prior history of PTD
    - Similar whether dose was 90-100 mg/day or 200 mg/day
    - Did not depend on age, BMI, or race/ethnicity
- With twins, therapy associated with significant reduction of neonatal mortality but not necessarily PTD

Vaginal Progesterone Rx Short CL
ACOG
Reaffirmed 2016

- Singleton gestation without prior PTD with CL less than 20 mm before 24 weeks, vaginal progesterone recommended as management option
  - Cerclage in this population of no benefit
- With twins or triplets, vaginal progesterone is not recommended to prevent PTD as no benefit has been demonstrated
  - Meta-analysis 2017 Vaginal progesterone for asymptomatic patients with twin gestation and short CL reduces risk of PTL at < 30 to < 35 weeks gestation with improved neonatal outcomes
- Vaginal progesterone preparations
  - Vaginal progesterone 90 mg daily
  - Micronized progesterone gel 200 mg daily
  - Vaginal progesterone gel 90 mg daily

Management of Patients with Prior PTD

- Evolving concept of ‘contractions’ as cause preterm birth
  - Cervical ripening and decidual activation key
  - Progesterone impacts inflammation-driven process
  - Cerclage may benefit some patients by preventing membrane prolapse and bacterial invasion
    - Process starts before 20 weeks in many women
- Important to better identify women with prior preterm birth
- Document history and clinical facts of prior PTD
Management of Patients with Prior PTD
17 alpha-hydroxyprogesterone caproate (17P)

- Preterm labor prophylaxis
  - Trials from 1980’s demonstrated efficacy
  - FDA approved 1996
  - Not employed as acute therapy
  - Not widely adopted in practice
- NEJM trial NIH-MFMU ‘rediscovered’ Delalutin
  - NEJM 348:2379-85, 2003
  - Prospective, randomized, double-blinded, placebo-controlled trial
  - Women between 16-20 wks with history prior preterm birth
  - Study patients received 250mg 17P weekly until 36 wks

Management of Patients with Prior PTD
17 alpha-hydroxyprogesterone caproate (17P)

- Study patients had significantly reduced risk:
  - Preterm birth at < 37, < 35, and < 32 wks
- Neonatal outcomes also significantly improved:
  - Reduced risk of NEC, IVH, and oxygen therapy duration
- Still, not a “magic bullet”
  - Risk of preterm birth ranged from 11% to 36%

Management of Patients with Prior PTD
ACOG
Reaffirmed 2016

- ‘Patients with a singleton gestation and prior history of PTD should be offered progesterone supplementation starting at 16-24 weeks’
  - 17P 250 mg IM weekly 16-36 weeks
  - TV CL assessment q 2 weeks 16-24 weeks
- ‘Cerclage should be considered if CL < 25 mm noted before 24 weeks and prior PTD occurred < 34 weeks’
  - Role of vaginal progesterone?
- Multiple gestations
  - Progesterone Rx does not reduce risk of PTD
  - Cerclage may increase risk of PTD in twins with CL < 25 mm
  - Neither intervention is recommended
Management of Patients with **Prior PTD**

*Role for Vaginal Progesterone?*

- Vaginal progesterone vs cervical cerclage for the prevention of preterm birth in women with a sonographic short cervix, previous preterm birth, and singleton gestation: a systematic review and indirect comparison metaanalysis*
  - Agustin Conde-Agudelo, MD, MPH; Roberto Romero, MD, DMinSci; Kypros Nicolaides, MD

- Based on state-of-the-art methods for indirect comparisons, either vaginal progesterone or cerclage are equally efficacious in the prevention of preterm birth in women with a sonographic short cervix in the mid trimester, singleton gestation, and previous preterm birth. Selection of the optimal treatment needs to consider adverse events, cost and patient/clinician preferences.
Cerclage for Cervical Insufficiency
ACOG Recommendations

- Good/consistent evidence (Level A)
  - Prior PTD, singleton, short CL < 24 weeks
    - Decreased PTD, improved neonatal outcomes
      - No improvement in patients without prior PTD and short CL
  - Limited/inconsistent evidence (Level B)
    - Activity restriction, pelvic rest not effective
    - No suture type or technique more effective
    - Cerclage may increase risk PTD in twins with short CL
    - Antibiotics/tocolytics not shown to improve outcomes
      - But, frequently used
    - History-indicated cerclage may be considered
      - Prior second trimester painless cervical dilation

Cerclage for Cervical Insufficiency
ACOG Recommendations

- Consensus/expert opinion (Level C)
  - Cerclage placement before fetal viability
  - Physical-exam indicated cerclage may be beneficial in singletons with cervical change of the internal os: ‘emergency or rescue cerclage’
    - Rule out infection or labor first
  - Removal recommended at 36-37 weeks

Preterm Labor

- Uterine contractions < 37 wks with cervical change
- Causes of preterm labor numerous
- Preterm labor is not the only etiology for PTD
  - Spontaneous PTL (40-50%)
  - Preterm PROM (25-40%)
  - Indicated delivery (20-25%)
Pathogenesis Preterm Labor

- Not well understood
- Numerous theories abound
  - Progesterone withdrawal
  - Oxytocin initiation
  - Premature decidual activation
- Many potential pathways
  - Inflammation
  - Intra-amniotic infection
  - Decidual hemorrhage
  - Uterine over-distension
  - Premature activation of normal labor

Preterm Labor Interventions*

- Single most beneficial intervention is administration of corticosteroids for women at risk for delivery between 24 and 34 wks gestation (consider at 23 weeks)
  - Decreased risk neonatal mortality, RDS, IVH, NEC
    - Betamethasone 12 mg IM q24 hours for 2 doses
    - Dexamethasone 6 mg IV q6 hours for 4 doses
- Magnesium Sulfate reduces severity and risk of cerebral palsy in surviving infants delivered before 32 weeks
- Antibiotics with intact membranes not effective
- Non-pharmacologic therapy of no proven benefit
  - Bed rest, hydration, “pelvic rest”

Preterm Labor
Risk Stratification Tools: Symptomatic Patients

- Cervical length
  - Median length is 35 mm
  - Range 25-45 mm
- Fetal Fibronectin (fFN)
  - “Glue” that attaches fetal membranes to decidua
  - Normally present in cervico-vaginal secretions
    - Before 16-18 wks and at term
    - Not normally present between 22 and 37 wks
  - Presence of fFN after 22 wks is marker of disruption of decidual-chorionic interface
    - Positive fFN (> 50 ng/ml)
      - 6x increase risk delivery <35 wks
      - 14x increase risk delivery <28 wks
Preterm Labor
Risk Stratification Tools: Symptomatic Patients

- Current strategies: 40% false positive diagnosis of preterm labor
- Powerful clinical characteristic of fFN is negative predictive value
  - Symptomatic patient with negative fFN
  - Risk of delivery within 7-14 days reported as < 1%
  - Null PPV of delivery within 14 days < 20%
- CL > 30 mm reliably excludes preterm labor
- Clinical value of fFN and CL rests primarily in negative tests
  - Management of patients with positive tests remains uncertain
  - PPV for PTD < 35 wks with positive fNN and CL < 25 mm only 50%
- Routine screening of low-risk, asymptomatic patients not indicated
  - For symptomatic patients, may avert interventions if negative

Tocolytic Therapy: Summary

- Evidence supports use of first-line tocolytic treatment for short-term pregnancy prolongation to allow:
  - Administration of steroids
  - Magnesium sulfate for neuroprotection
  - Transfer to tertiary facility
- Typically not employed > 34 wks
- Maintenance therapy ineffective
  - Does not prevent PTD or improve neonatal outcome
- Multiple gestations
  - Inadequate data
    - Increased risk maternal complications
  - Most experts recommend use

Tocolytic Therapy: Meta & Decision Analysis

- Quantitative analysis of RCT’s of tocolytics
- All tocolytics superior to placebo
  - No difference in RDS or neonatal death
- Decision analysis demonstrated
  - Prostaglandin inhibitors may be superior first line agent before 32 weeks to delay delivery for 48 hrs and 7 days
  - Calcium channel blockers may be superior first line agents to delay delivery until 37 weeks
- These agents seem to have best combination of tolerability and efficacy
Tocolytic Therapy: Indomethacin

- Prostaglandin synthetase inhibitor
- First prospective trial 1980
  - Few maternal side effects
- Administered orally/rectally
  - Loading dose: 50-100 mg
  - Duration of therapy: 48 hours
- Potential fetal effects:
  - Decreased urine output
  - Oligohydramnios
  - Constriction of ductus arteriosus
- Due to risks of long term therapy
  - Limit duration to < 48 hours
  - Limit use to < 32 wks

Tocolytic Therapy: Calcium Channel Blockers

- Nifedipine most widely studied
- Loading dose of 20mg orally
  - Followed with 10-20 mg q 6-8 hrs
- Sublingual route hazardous
  - Risk of acute/severe hypotension
- Systematic review and metaanalysis
  - Significant reduction in PTD within 7 days v. β₂ agonists
  - No difference efficacy/adverse outcomes v. MgSO₄
  - Fewer maternal side effects v. MgSO₄ and β₂ agonists
  - Maintenance tocolysis with nifedipine ineffective

Tocolytic Therapy: Magnesium Sulfate

- First described as tocolytic 1977
- Initial bolus of 4-6 g over 30min
  - Maintenance infusion 1-3 g/hr
- Common side effects
  - Nausea, flushing, lethargy, blurred vision
  - Deep tendon reflexes lost > 12 mg/dL
  - Respiratory depression > 14 mg/dL
  - Cardiac arrest > 18 mg/dL
- Reversal with 1g calcium gluconate
Tocolytic Therapy: Magnesium Sulfate

- Absolute contraindications
  - Myasthenia gravis; heart block
- Relative contraindications
  - Renal disease; recent MI; concurrent calcium channel blockers
- Pulmonary edema occurs 1%
  - Monitoring I/O’s essential
- Widely employed first-line tocolytic
- Controversy in literature
  - Grimes Obstet Gynecol March 2006
    - “Magnesium Sulfate Tocolysis: Time to Quit”
  - Cochrane review: ineffective tocolytic
    - “Clinicians should feel comfortable continuing to use MgSO4 as a first-line tocolytic drug to treat their patients presenting in preterm labor.”

Tocolytic Therapy: Beta Mimetics

- Ritodrine
  - Only medication “approved” by FDA for treatment of PTL
  - Beta agonist side effects
    - Pulmonary edema, myocardial ischemia, arrhythmia, hyperglycemia, maternal death, fetal cardiac effects
  - Due to maternal/fetal complications, ritodrine not widely used
- Terbutaline
  - Most commonly used beta mimetic
  - Administered via intravenous, or subcutaneous routes
  - FDA issued warning 2011 regarding oral terbutaline therapy
  - Parenteral terbutaline may be used only for inpatient, monitored patients for less than 72 hours
  - Subcutaneous terbutaline pump not effective

Antibiotic Therapy
ACOG Committee Opinion

- “The utility of antibiotics to prolong pregnancy and reduce neonatal mortality in women with preterm labor and intact membranes has been evaluated in numerous randomized clinical trials. Antibiotic use intended only for pregnancy prolongation in women with preterm labor with intact membranes does not have short-term neonatal benefits and may be associated with long-term harm.”
- Patients in preterm labor should receive GBS prophylaxis unless proven GBS negative
Corticosteroid Therapy

- Single most effective intervention to improve neonatal outcome
- Administered between (23?) 24-34 wks
- First line agent: betamethasone
  - 12 mg IM q 24 hours for 2 doses
- Alternative agent: dexamethasone
  - 6 mg IV q 6 hours for 4 doses
- May be less effective reducing IVH/PVL
- Multiple gestations
  - Inadequate data, but most experts recommend use

Corticosteroid Therapy: Rescue Course

- Multicenter RCT May 2003-February 2008
  - Single course ACS < 30 wks & 14 day window
  - 223 single rescue steroid course; 214 placebo
- Significant reduction neonatal morbidity < 34 wks
  - 43.9% v. 63.6%; OR 0.45; 95% CI 0.27-0.75)
- Composite defined as one or more
  - RDS, BPD, severe IVH, PVL, sepsis, NEC, death
  - No difference in perinatal mortality

Corticosteroid Therapy: Rescue Course


- 'A single rescue course of antenatal corticosteroids may be considered if the antecedent treatment was given more than 2 weeks prior, the gestational age is less than 32 6/7 weeks, and the women are judged by the clinician to be likely to give birth within the next week. However, regularly scheduled repeat courses or multiple courses (more than two) are not recommended. Further research regarding the risks and benefits, optimal dose, and timing of a single rescue course of steroid treatment is needed.'
- Rescue course should be considered when prior course was administered at least 7 days previously
  - ACOG Practice Bulletin #127; June 2012
- Rescue course should be considered when prior course was administered > 14 days previously. Rescue course could be provided as early as 7 days from prior dose, if indicated by clinical circumstances
  - ACOG Practice Bulletin # 171; October 2016
Late Preterm Corticosteroids
ACOG Committee Opinion #677
October 2016

- A single course of betamethasone is recommended for patients at 34\(\frac{0}{7}\) to 36\(\frac{6}{7}\) weeks at risk of PTD within 7 days who have not received a previous course.
- In women with preterm labor symptoms, recommend waiting for evidence of preterm labor, such as a cervical dilation of at least 3 cm or effacement of at least 75%, before treatment with betamethasone.
- Tocolysis should not be used in an attempt to delay delivery in order to administer betamethasone in the later preterm period.
- In women with late preterm pregnancies, recommend betamethasone be given unless there is a definitive plan for late preterm delivery.
- Treatment with betamethasone should not be given for pregestational diabetics or patients diagnosed with chorioamnionitis in the late preterm gestational age period.
- We recommend that institutions utilize standard guidelines for the assessment and management of neonatal hypoglycemia in late preterm newborns.

Magnesium Sulfate for Neuroprotection

- Systematic review of Cochrane database
  - Identified 5 eligible RCTs
    - In 4, primary intent was neuroprotection
  - Magnesium sulfate reduced risk of cerebral palsy
    - RR 0.69 (95% CI 0.54-0.87); 5 trials; 6145 infants
    - Need to treat 63 to prevent one case CP
  - Significant reduction gross motor dysfunction
    - RR 0.61 (95% CI 0.44-0.85); 4 trials; 5980 infants
  - No evidence of increased pediatric mortality

ACOG Practice Bulletin #171, October 2016

Committee on Obstetric Practice and the Society for Maternal-Fetal Medicine recognize that none of the individual studies found a benefit with regard to their primary outcome. However, the available evidence suggests that magnesium sulfate given before anticipated early preterm birth reduces the risk of cerebral palsy in surviving infants. Physicians electing to use magnesium sulfate for fetal neuroprotection should develop specific guidelines regarding (use) in accordance with one of the larger trials.

Multiple gestations
- Inadequate data, but most experts recommend use
  - ACOG Practice Bulletin #171, October 2016

ACOG Practice Bulletin #171, October 2016
Magnesium Sulfate for Neuroprotection
Sample Protocol

- Gestational age greater than or equal to 23 weeks gestation and less than 32 weeks gestation at the time of magnesium sulfate initiation
- Clinical suspicion for imminent PTD
  - If the patient remains undelivered after 12 hours, a provider must reassess and document clinical suspicion for imminent PTD
  - If PTD remains imminent, then magnesium sulfate maintenance should continue and this decision be reassessed every 12 hours until delivery occurs or therapy is discontinued.
- Magnesium sulfate therapy should not be continued for more than 48 consecutive hours.
  - If PTD is no longer imminent, then the magnesium sulfate infusion should be discontinued.
  - This infusion can be restarted if delivery is again deemed to be imminent and the prior eligibility requirements are again satisfied.
- If more than 6 hours have elapsed between discontinuation and restarting of magnesium, a repeat loading dose should be administered prior to maintenance infusion, as described above. If less than 6 hours have elapsed, maintenance infusion should be resumed without a repeat loading dose.

Preterm Birth: Delivery Issues

- Discuss cesarean birth for fetal indications at +/- 24 wks
  - Extensive counseling critical
  - Neonatal outcomes
  - Future obstetric implications
- Preterm cephalic infants delivered via cesarean section for same indications as term infants
  - No benefit demonstrated for cesarean section
- Preterm breech birth infants typically delivered via cesarean section
  - Particular attention to avoiding traumatic delivery
    - Risks of vacuum extraction
    - Intact membranes may protect
    - In caul delivery for borderline viable breech neonates
Preterm Birth: Summary

- Focus on **effective** interventions
  - ? Universal CL screening mid-trimester?
  - Vaginal progesterone asymptomatic short CL
  - 17P therapy patients prior spontaneous PTD
  - Delivery at site where NICU available
  - Corticosteroid administration
  - Magnesium sulfate for neuroprotection
  - GBS prophylaxis
  - Avoid trauma/hypoxemia

ACOG Practice Bulletin #171, October 2016

Questions