Preterm Birth: Prevention & Management

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Maternal & Obstetric Complications Conference
October 11, 2019

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Disclosure

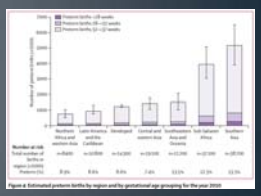
- I have no financial disclosures or conflicts of interest.

Objectives

- Identify risk factors for preterm birth
- Review management of spontaneous preterm labor, including strategies to decrease neonatal morbidity
- Discuss prevention of recurrent preterm birth

Preterm Birth - Definitions

- Preterm birth = delivery before 37 completed weeks of gestation
  - Extreme preterm <28 weeks
  - Very preterm 28-31 6/7 weeks
  - Moderate preterm 32-33 6/7 weeks
  - Late preterm 34-36 6/7 weeks

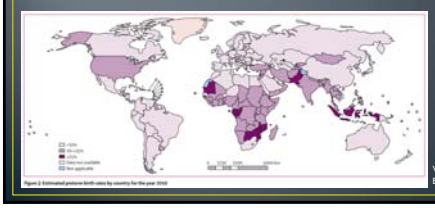


- Preterm, premature rupture of membranes (PPROM) = rupture of membranes <37 weeks prior to the onset of labor

Blencowe et al, Lancet, 2012

The Scope of the Problem

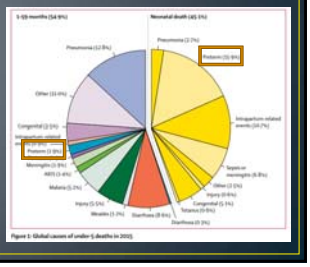
- 15 million babies worldwide are born preterm every year
  - More than 1 in 10
- Rate of preterm birth worldwide ranges from 5-18%
- In almost all countries with reliable data, preterm birth rates are INCREASING



World Health Organization, 2018
Blencowe et al, Lancet, 2012

Why Does Preterm Birth Matter?

- Leading cause of death <5 years of age
  - 2015 = 1 million deaths from prematurity-related complications
  - Survival rates vary dramatically by low-income vs. high-income settings
- ¾ of deaths are preventable
  - Childbirth & postnatal care
  - Steroid injections
  - Kangaroo maternal care
  - Antibiotics
- Survivors face lifelong disability
  - Intellectual
  - Sensory



World Health Organization, 2018
Liu et al, Lancet, 2016

Risk Factors for Preterm Birth

Category	Risk Factors
Historical	Hx prior PTB, hx 2nd trimester abortion, hx cervical surgery
Obstetric	Multiple gestations, polyhydramnios, IVF, PPROM, positive FFN
Infectious	STIs, systemic infections, bacteriuria, periodontal disease, Malaria
Placental	Previa, abruption
Fetal	Fetal anomaly, fetal growth restriction
Structural	Uterine anomaly, short cervix, advanced cervical dilation, abdominal surgery
Maternal	Chronic medical illness (HTN, chronic kidney disease, T1DM, autoimmune disease)
Psychological	Anxiety, depression
Hematologic	Vaginal bleeding in any trimester, severe anemia
Social	No partner, low SES, life stressors, extremes of age, non-Hispanic black race, low maternal education, inadequate prenatal care
Toxin	Substance use (cocaine, alcohol), tobacco use (dose dependent)
Behavioral	Short interpregnancy interval, occupational physical activity
Genetic	"PTB-susceptibility genes," hx of 1st degree relative with spontaneous PTB
Nutritional	Poor nutritional intake, low BMI

Counseling the Patient with Risk Factors for Preterm Birth

- Challenging for many reasons
  - 2/3 of PTBs occur among women with NO risk factors
  - Causality is hard to prove
  - No animal models exist for spontaneous PTB
- No adequate risk scoring systems
- Biomarkers
  - Fetal fibronectin – qualitative vs. quantitative (not available in USA)
    - Positive predictive value alone is poor
    - Should not be used exclusively to guide management[1]
    - May be beneficial in conjunction with short cervical length – controversial[2]

[1]ACOG Practice Bulletin #171, 2016
[2]NICE Guideline, Preterm Labour and Birth, 2015

Acute Management of Preterm Labor

Management of Preterm Labor

- 30% of preterm labor spontaneously resolves
  - 50% will ultimately deliver at term
- Acute preterm labor defined as:
  - Regular contractions leading to cervical dilation, effacement or both
  - Regular contractions and cervical dilation >2 cm

Management of Preterm Labor

- Interventions to reduce delivery are useful at a GA where delay will provide benefit to the newborn
- Mainstays of treatment include:
  - Tocolytic medication
  - Antenatal corticosteroids
  - Magnesium sulfate
  - Intrapartum antibiotics

Tocolysis

- Reduces strength & frequency of uterine contractions
  - Not indicated before fetal viability
  - Upper limit of use generally 34 weeks
  - Not indicated for CTX without cervical change
- Contraindications
  - IUFD
  - Non-reassuring fetal status
  - Severe preeclampsia
  - Hemorrhage with hemodynamic instability
  - Chorioamnionitis
  - PPROM*
  - Maternal medical contraindications (agent-specific)
- Tocolytics discontinued after 48 hours

*May consider for steroid administration in absence of infection

Tocolysis

- 2009 meta-analysis of 58 studies on tocolytic efficacy
  - 75-93% effective delaying delivery 48 hours vs. 53% with placebo[1]
  - Prostaglandin inhibitors were best
  - Betamimetics had the most side effects leading to discontinuation
- Regimens typically used
  - 24-32 weeks: indomethacin 50-100mg PO or PR x1 → 25mg PO Q4-6h
    - Contraindications: platelet dysfunction/bleeding disorder, hepatic dysfunction, PUD, renal disease
    - Theoretical fetal risks: DA constriction, oligohydramnios
    - Potential neonatal risks: Severe IVH, NEC, PVL[2]
  - 32-34 weeks: nifedipine 30mg PO x1 → 10-20mg PO Q4-6h
    - Contraindications: hypotension, preload-dependent cardiac lesions, LV dysfunction or CHF
  - Regimens recommended by NICE Guideline for Preterm Labour & Birth are different[3]
    - Nifedipine or oxytocin receptor antagonists

[1]Haas et al, Obstet Gynecol 2009
[2]Hammers et al, AJOG 2015
[3]NICE Guidelines, Preterm Labour and Birth, 2015

Corticosteroids for Fetal Lung Maturity

- Initial studies in lambs to accelerate lung maturation confirmed in humans in 1972 by Liggins & Howie
  - Blinded & randomized trial, IV ethanol or salbutamol for tocolysis
  - 213 pts in spontaneous PTL 24-36 weeks' EGA
  - Betamethasone 12mg vs. cortisone 6mg (control) x2 doses 24h apart
- Infants treated with betamethasone
  - Fewer early neonatal & perinatal deaths
  - Of liveborns, less RDS, all <32 weeks (11.8% vs 69.6%)
  - Of infants who died → no cases of hyaline membrane disease, no IVH

Liggins & Howie, Pediatrics, 1972

Prevention of RDS by Steroids

TABLE V

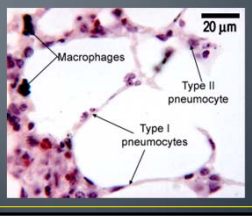
OCCURRENCE OF RDS IN LIVEBORN INFANTS RELATED TO ENTRY-DELIVERY INTERVAL IN INFANTS DELIVERED AFTER UNPLANNED PREMATURE LABOR

Entry-Delivery Interval	*Betamethasone-Treated Group*			*Control Group*			
	No.	*RDS*	*% RDS*	*No.*	*RDS*	*% RDS*	*p*
Under 24 hours	29	7	24.1	22	7	31.8	NS
24 and under 48 hours	20	2	10.0	19	7	36.8	NS
2 and under 7 days	28	1	3.6	24	8	33.3	.05
7 days and over	45	1	2.2	32	3	9.4	NS
All live births	122	11	9.0	97	25	25.8	.003
All infants born alive over 24 hours after entry to trial	93	4	4.3	75	18	24.0	.002

Liggins & Howie, Pediatrics, 1972

Physiology of Steroids for FLM

- Accelerates development of Type 1 & Type 2 pneumocytes
  - Improved lung compliance & volume
  - Improved gas exchange
  - Increased surfactant production
  - Induction of enzymes/receptors to enhance absorption of lung fluid



Benefits of Betamethasone

- Multiple studies worldwide have demonstrated benefit[1]
  - 34% Reduction in respiratory distress syndrome (RDS)
    - 41% Reduction in moderate/severe RDS (41%)
    - 32% Reduction in mechanical ventilation
  - 45% Reduction in interventricular hemorrhage (IVH)
  - 50% Reduction in necrotizing enterocolitis (NEC)
  - 40% Reduction in systemic infection
  - 31% Reduction in neonatal mortality
- Benefits independent of race, fetal sex
- Unlikely benefit on lung function <22 weeks[2]

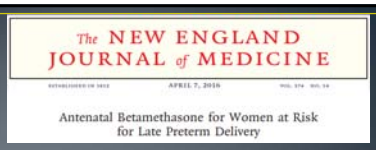
[1]Cochrane Database, 2017
[2]Deshmukh & Patole, Arch Dis Child Fetal Neonatal Ed, 2017

Corticosteroids for Fetal Lung Maturity

- When to consider antenatal corticosteroids:
  - Pregnancies 24 0/7-33 6/7 with risk of PTB within 7 days
    - Includes PPROM, multiple gestations
  - Pregnancies >23 0/7 with risk of PTB within 7 days
    - Based on family's decision on resuscitation
- When to give "rescue" steroids
  - Single repeat course if <34 0/7 weeks and risk of PTB within 7 days
  - >14 days has passed since first course
  - >2 courses is NOT recommended
- Regimens:
  - Betamethasone 12mg IM Q24h x2 doses
  - Dexamethasone 6mg IM Q12h x4 doses

ACOG Committee Opinion #713, 2017

What About Steroids AFTER 34 Weeks?


The NEW ENGLAND JOURNAL of MEDICINE

Antenatal Betamethasone for Women at Risk for Late Preterm Delivery

- ALPS Trial, 2016
  - Multicenter randomized placebo-controlled trial
  - 2831 women randomized
  - Inclusion: 34-36 5/7 weeks, high risk of delivery in 24h-7d (PTL with 3cm dilation, 75% effacement or PPROM), singleton gestations
  - Exclusion: multiple gestations, expected delivery within 12h, chorio, prior BMZ administration, dilation >8cm, NRFHT, pregestational diabetes, fetal anomalies
- Respiratory morbidity significantly lower w steroids
  - Particularly: TTN (6.7% vs 9.9%), need for CPAP (6.5% vs 10.5%), need for resuscitation at birth (14.5% vs 18.7%), surfactant use (1.8% vs 3.1%)
  - Significantly higher incidence of neonatal hypoglycemia (24% vs 15%)
  - No difference in length of hospital stay

Late Preterm Steroids 34-36 6/7 weeks

- Betamethasone for fetal lung maturity recommended for:[1]
  - Singleton gestations
  - High risk for delivery within 24 hours - 7 days
  - No history of betamethasone administration
- NOT recommended in the setting of:
  - Multiple gestations
  - Pre-gestational diabetics
  - Likely delivery in <12 hours
  - Chorioamnionitis
  - Anomalous fetus
  - Prior betamethasone in the pregnancy
- Administration remains controversial[2]
  - Clinical importance of outcomes studied
  - Longterm impact of high-dose steroids on the developing fetal brain

[1]ACOG Committee Opinion #713, 2017
[2]Lee & Guinn, UpToDate, 2018

Magnesium for Neuroprotection

- Beneficial Effects of Antenatal Magnesium Sulfate (BEAM Trial)[1]
  - 2008 multicenter double-blinded placebo-controlled RCT
  - N=2241 women at imminent risk for delivery 24-31 wk GA
  - Regimen: 6g magnesium sulfate bolus → 2g/hr infusion
  - Primary outcome: composite stillbirth or infant death by 1 year CGA or moderate/severe cerebral palsy at 2 years CGA
- Preterm exposure to magnesium
  - Decreased diagnosis of cerebral palsy (4.2% vs 7.3%, p=0.004)
  - Decreases in all grades of CP (p=0.004)
    - Mild 2.2% vs 3.7%
    - Moderate 1.5% vs 2.0%
    - Severe 0.5% vs 1.6%
- Overall 30% decreased risk of CP when magnesium is given <32 weeks[2]

[1]Rouse et al, NEJM 2008
[2]ACOG Committee Opinion #455, 2010

Antibiotics

- Preterm labor with intact membranes
  - Intrauterine infection = important cause of PTL[1]
  - ORACLE II: RCT of 6295 women, PTL with intact membranes[2]
    - Randomized to erythromycin vs amoxicillin-clavulanate vs placebo
    - No difference in composite primary outcome (neonatal death, CLD, cerebral abnormality)
  - Cochrane meta-analysis: no demonstrated benefit of antibiotic prophylaxis for prolongation of pregnancy or neonatal morbidity[3]
- Additional potential for longterm harm[3]
  - Secondary analysis of ORACLE II → increased neonatal death, functional impairment, cerebral palsy

[1]Hillier et al, Obstet Gynecol, 1993.
[2]ORACLE Collaborative Group, Lancet, 2001
[3]Cochrane Systematic Review, 2013

Antibiotics in PTL – GBS Prophylaxis

- GBS prophylaxis IS recommended if status is unknown
  - For patients progressing in PTL

ACOG Committee Opinion #485, reaffirmed 2016

A Word about PPROM

- At least 50% of women will deliver within 1 week
  - Latency inversely correlated to GA at time of membrane rupture
- Risks include:
  - 15-25% intraamniotic infection, 15-25% postpartum infection
  - 2-5% placental abruption
  - 1-2% IUFD
  - Other neonatal risks relate to complications of prematurity
- Indications for delivery:
  - Non-reassuring fetal status
  - Chorioamnionitis
  - Abruptio placentae

ACOG Practice Bulletin #188, 2018

Expectant Management of PPROM

- Inpatient hospitalization with periodic fetal assessment
- Latency antibiotics
  - Improves latency 7-10d
  - Reduces maternal & neonatal infectious morbidity
  - NICHD/MFMU regimen:[1]
    - Ampicillin 2g IV Q6h + Erythromycin 250mg IV Q6h x48 hours
    - **I**
    - Amoxicillin 250mg PO Q8h + Erythromycin 333mg PO Q8h x5 days
- Antenatal corticosteroids x1 course if <34 weeks
- Magnesium for neuroprotection if delivery imminent <32 weeks
- Tocolysis controversial – typically not recommended
- Delivery is recommended at 34 weeks[2]
  - Studies of expectant management >34 weeks → increased infectious risk

[1]Mercer et al, JAMA 1997
[2]ACOG Practice Bulletin #188, 2018

What About Late Preterm Birth?

- Preterm labor between 34 - 36 6/7 weeks
  - Tocolysis not recommended
  - Magnesium sulfate not recommended
  - GBS prophylaxis recommended if status unknown
  - Betamethasone use is typically recommended but controversial

Anticipatory Guidance for the Next Pregnancy

What about next time?

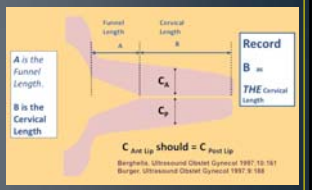
Prevention of Preterm Birth

- Maternal history of PTB → 1.5-2 fold increased risk of recurrent PTB[1,2]
  - Number of prior PTBs
  - GA at prior delivery
  - Prior twin PTB <30 weeks → 40% risk of PTB with subsequent singleton
- Screening and treating women at increased risk of PTB is recommended
  - Detailed medical history
  - Obstetric history: prior spontaneous vs. indicated PTB? Placental pathology?
  - Evaluate candidacy for progesterone, cerclage, or both

[1]ACOG Practice Bulletin #130, 2012
[2]McManemy et al, AJOG 2007

Cervical Length Screening

- Transvaginal cervical ultrasonography
  - Reliable and reproducible
  - Inter-observer variation 5-10%
  - Shortest of 3 measurements
  - Performed between 16-24 wks
- "Short" typically defined as 20-30mm
- Screening beyond 24 weeks not recommended[1]
  - Studied interventions use 24 wk as upper limit



CLEAR guidelines for transvaginal measurement of cervical length

[1]SMFM Consult Series #40 "The role of routine cervical length screening in selected high-and low-risk women for preterm birth prevention"

Progesterone Supplementation

- Progesterone supplementation reduces the risk of recurrent spontaneous PTB[1]
  - NICHD/MFMU Trial of 463 women randomized to IM 17OHP vs. placebo
  - Demonstrated 34% reduction in recurrent PTB <37 wk
  - Trial was stopped early due to demonstrated benefits[2]
- Vaginal progesterone 100mg daily has also demonstrated benefit[3]
  - Subsequent studies have shown no difference from placebo[2]

[1]Meis et al, NEJM, 2003
[2]SMFM Statement, 2017
[3]da Fonseca et al, AJOG, 2003

Progesterone for Prevention of Recurrent PTB

- Indications: Prior spontaneous PTB <37 weeks
- SMFM-Recommended Regimen: 17 α-hydroxyprogesterone caproate (Makena®)
  - 250mg IM weekly
  - Treatment initiated between 16-20 weeks until 36 weeks

SMFM Statement, March 2017

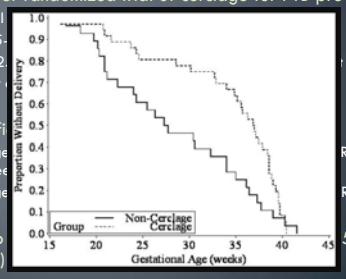
Cerclage

- History indicated
  - Typically offered after ≥1 PTBs or 2nd trimester losses in the absence of labor or placental abruption
  - Placed between 12-14 weeks
- Ultrasound indicated
  - Recommended for women with h/o PTB and CL <25 mm
- McDonald or Shirodkar technique is acceptable
  - No head-to-head data to suggest one is superior
  - Surgeon preference
- After cerclage, continued US is not recommended[1]
  - Neither overall length nor distal length correlate with outcomes
  - No additional treatment options – reinforcement does not improve outcome

[1]SMFM Consult Series #40 "The role of routine cervical length screening in selected high-and low-risk women for preterm birth prevention"

Cerclage for Prevention of Preterm Birth

- Multicenter randomized trial of cerclage for PTB prevention[1]
  - Cervical
  - If CL 25-
  - If CL <2
  - Primary
- No signifi
  - Cerclage <37 wee R 0.44) and
  - Cerclage R 0.54)
- If pre-op (RR 0.23) 5 weeks



[1]Owen et al, AJOG, 2009

Cerclage for Prevention of Preterm Birth

- Ultrasound-indicated cerclage is recommended for:[1]
  - Women with prior PTB <34 weeks
  - Current singleton gestation
  - Short cervical length <25mm
- Overall risk reductions:
  - 30% decreased risk of preterm birth <35 weeks
  - 36% reduction in perinatal morbidity & mortality
- No evidence to suggest additive benefit of progesterone + cerclage for high risk women

[1]ACOG Practice Bulletin #130, 2012

Special populations

But that's not all!

Multiple Gestations

- 6x increased risk of PTB, 13x increased risk of PTB <32 weeks[1]
- Differences in management of PTL:
  - Tocolytics → increased maternal risk
  - Still no role for prophylactic tocolysis
  - Steroids & magnesium → no studies
- Cervical length screening is not supported by SMFM[2]
- Short cervix:
  - Limited data to support vaginal progesterone
  - Limited data to support US-indicated cerclage,[3] though cerclage may be beneficial with cervical dilation[4]

Table 1. Morbidity and Mortality in Multifetal Gestations

Characteristic	Singleton	Twins	Triplets	Quadruplets
Mean birth weight*	3,296 g	2,336 g	1,660 g	1,291 g
Mean gestational age*	38.7 weeks	35.3 weeks	31.9 weeks	29.5 weeks
Percentage less than 32 weeks of gestation*	1.6	11.4	36.8	64.5
Percentage less than 37 weeks of gestation*	10.4	58.8	94.4	98.3
Rate of cerebral palsy (per 1,000 live births)†	1.6	7	28	—
Infant mortality rate† (per 1,000 live births)	5.4	23.6	52.5	96.3‡

[1]ACOG Practice Bulletin #169, 2016
[2]SMFM Consult Series #40, 2016
[3]Rafael, Berghella & Alfirevic. Cochrane Database, 2014
[4]Rebarber et al, Eur J Obstet Gynecol Reprod Biol, 2014

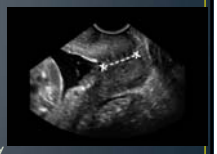
History of Cervical Excision

- Theoretic risk with scarring of stroma & destruction of cervical glands
  - Risk of PTB <32-34 weeks only significant after cold knife conization in a meta-analysis of >12,000 deliveries (RR 2.8, 95% CI 1.7-4.5)[1]
  - No randomized trials
- Data does not support serial cervical length monitoring[2]
- Reasonable to perform CL screen at 18-24 weeks
  - If CL <20mm, vaginal progesterone supplementation
    - If continued shortening to <10mm, cerclage increases duration of pregnancy (34w3d vs. 27w2d, p<0.001)[3]

[1]Arbyn et al, BMJ 2008
[2]SMFM Consult Series #40, 2016
[3]Enakpene et al, AJOG 2018

Short Cervical Length

- Transvaginal ultrasound CL <25mm associated with PTB[1,2]
  - Shorter CL = greater risk of PTB, particularly <15mm
- Vaginal progesterone supplementation
  - Indications: singleton gestation, asymptomatic, CL <20mm, <24 weeks GA
  - 200mg progesterone suppository
  - 44% decrease in spontaneous PTB <34 weeks[3]
- Cerclage placement
  - Has not significantly decreased rate of PTB
- Pessary
  - Randomized trial of 385 women CL <25mm[4]
    - 82% reduction in PTB <34 weeks with pessary
  - Multinational trial of 924 women CL <25mm[5]
    - All had vaginal progesterone
    - Rate of PTB <34 weeks was similar



[1]Mella & Berghella, Semin Perinatol, 2009
[2]Iams et al, NEJM, 1996
[3]Fonseca et al, NEJM, 2007
[4]Goyo et al, Lancet, 2012
[5]Nicolaides et al, NEJM, 2016

Short Cervical Length

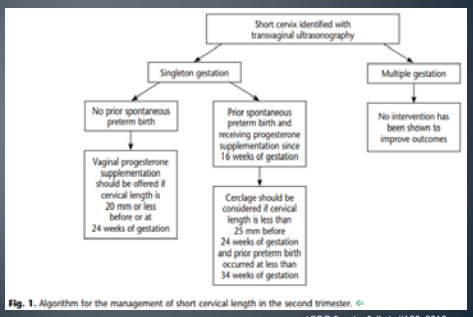


Fig. 1. Algorithm for the management of short cervical length in the second trimester.

ACOG Practice Bulletin #130, 2012

In Summary

Summary

- PTB remains a major cause of neonatal morbidity & mortality worldwide.
  - Risk factors are broad and predictive models remain limited
- Mainstays of treatment for acute PTL include:
  - Tocolysis x48 hours + corticosteroids if <34 weeks,
  - Magnesium for neuroprotection if <32 weeks
  - GBS prophylaxis
- Progesterone supplementation and cervical length screening is recommended for a history of PTB.

Thank you!

- Joanne Stone, MD
- Fundación Vida & Clínica de Maternidad Rafael Calvo, Cartagena, Colombia
- Heidi Thorson, MD
- Susan Gordon
- Minnesota Perinatal Physicians

Other Tocolytic Regimens

- Betamimetics (terbutaline, ritodrine)
  - Systematic review of placebo-controlled RCTs of ritodrine, 32% reduction in PTB within 48 hours[1]
  - Maternal SEs: Tremor, palpitations, SOB, chest discomfort, rarely pulmonary edema 0.3%
  - Fetal/neonatal SEs: Tachycardia, hypoglycemia, ?risk of IVH
  - Contraindications: tachycardia-sensitive cardiac disease, poorly controlled HTN or DM
  - Dose: terbutaline 0.25mg SC Q20-30min x4, then 0.25mg SC Q3-4h
    - Monitoring: strict I/O, maternal HR, glucose & potassium levels

[1]Cochrane Database Syst Rev 2014

Other Tocolytic Regimens

- Magnesium Sulfate
  - No statistical reduction in PTB compared to no treatment/placebo
  - Contraindications: myasthenia gravis, myocardial disease, conduction defects, renal failure
  - Dose: 6g IV x1 over 20 mins → 2g/h IV infusion
    - Monitoring: patellar reflexes, respirations, UOP
- Oxytocin-receptor antagonists (Atosiban)
  - No demonstrated efficacy in placebo-controlled trials
  - No contraindications
  - Dose: 6.75mg IV x1 → 300mcg/min infusion x3h → 100mcg/min x45h

Adverse Neurodevelopmental Outcomes from Steroids

- Neonatal dexamethasone for BPD & increased cerebral palsy
- Serial courses of betamethasone
  - RCT of serial weekly courses vs single course → decreased BW, increased SGA, decreased head circumference
  - Deleterious effects on:
    - Cerebral myelination
    - Lung growth
    - Hypothalamic-pituitary-adrenal axis
  - Possible increased risk of cerebral palsy (4+ courses)