Objectives

Following this lecture the participant will be able to:
1. Define preterm labor (PTL) and preterm birth (PTB)
2. Discuss PTB rates and impact on healthcare costs
3. Describe the various etiologies.
4. Discuss the general management of PTL
5. Discuss pros and cons of MgSO₄ vs. No MgSO₄
   - Tocolysis
   - Prevention of cerebral palsy
**PTL & PTB**

*Definitions*

**PTL:** Regular uterine contractions prior to 37 0/7 weeks that results in cervical change

**PTB:** Birth prior to 37 weeks gestation

---

**Background**

- Preterm birth is the major determinant of infant mortality in developed countries
- The rates of preterm birth in the US have increased in the last decades

---

**Ten Leading Causes of Infant Mortality**

*United States, 1997*

<table>
<thead>
<tr>
<th>Cause</th>
<th>Rate per 100,000 live births</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth defects</td>
<td>159.2</td>
</tr>
<tr>
<td>Preterm/LBW</td>
<td>84.1</td>
</tr>
<tr>
<td>Sepsis</td>
<td>77.1</td>
</tr>
<tr>
<td>Respiratory Distress</td>
<td>33.1</td>
</tr>
<tr>
<td>Preeclampsia/Eclampsia</td>
<td>31.7</td>
</tr>
<tr>
<td>Infections</td>
<td>28.3</td>
</tr>
<tr>
<td>Congenital anomalies</td>
<td>20.0</td>
</tr>
<tr>
<td>Hypomature Infants</td>
<td>19.7</td>
</tr>
<tr>
<td>Neonatal sepsis</td>
<td>18.7</td>
</tr>
<tr>
<td>Prematurity</td>
<td>18.1</td>
</tr>
<tr>
<td>Other Neonatal diseases</td>
<td>11.6</td>
</tr>
</tbody>
</table>

Preterm Births
United States: 1985-1998

Note: Preterm is less than 37 weeks gestation.

In an Average Week in the U. S.

• 78,058 babies are born
• 8,985 babies are born preterm
• 538 babies will die before their first birthday

• In 2001: 476,000 babies were born preterm

Financial Impact of Preterm Birth
Of 23,000 Preterm babies in 2000

- Prematurity related infant stays resulted in costs of $1,200,000,000
- The average hospital charge is approximately $58,000 per baby

NIH MFMU Network

Comparative Costs

- Infants born at 25-27 weeks cost 28 times the cost of those born at 39-42 weeks gestation
  
  $280,146 vs. $9,803

Comparative Costs

- At 25 weeks:
  
  Birth vs. inpatient antepartum care for mother until 34 weeks
  
  $280,146 vs. $16,820
- Long-term burden on family

PTL-MgSO₄, Galan, 2009
**Patient Characteristics**

**Predisposing Factors**
- Low socioeconomic status
- Nonwhite race
- Maternal age <18 or >40 years
- Low prepregnancy weight
- Multiple gestation
- Prior preterm birth
- Prior TOP
- Substance abuse
- No PNC
- Smoking


---

**Etiologies of Preterm Labor**

- Anatomic
  - Cervical incompetence
  - Uterine anomalies
  - Uterine overdistention
- Infectious
  - Chorioamnionitis
- PPROM
- Cause unknown for most cases


---

**Management Goal?**

**Prolong Pregnancy**

**Survival According to Gestational Age**


---
**Management Goals**

- Prolong Pregnancy
  - Administration of corticosteroids
  - MFT to Level III nurseries
  - When there are underlying reversible causes:
    - Acute pyelonephritis
    - Abdominal surgery
    - Polyhydramnios

**Prevention Strategies**

- Antibiotic Therapy
- Social support
- Bed rest
- Home uterine monitoring
  - Cervical cerclage
  - Progesterone
  - Tocolytic drugs

**Prediction Strategies**

- Cervical length
- Fetal fibronectin
Tocolytics

- Ethanol
- Sedation & Hydration
- β-agonists
  - Ritodrine; Terbutaline
- NSAIDS
  - Indomethacin; COX-2 inhibitors; Sulindac
- Oxytocin receptor antagonists
- Calcium channel blockers
- Magnesium Sulfate

MgSO₄

- Seizure Prophylaxis
- Tocolysis
- *Neuroprotection?*

MgSO₄ for Seizure Prophylaxis
Pre-eclampsia and Eclampsia

- **1995**
  - Lucas et al, NEJM:
    - MgSO4 superior to phenytoin in pre-eclampsia
  - Eclampsia Trial Collaborative Group, Lancet:
    - MgSO4 superior to phenytoin or diazepam

- **2002**
  - Magpie, Lancet:
    - MgSO4 better than placebo (eclampsia 58% lower)

MgSO4 as a Tocolytic

Recent Editorial Attention

Current Commentary

**Magnesium Sulfate Tocolysis**

*Time to Quit*

David A. Grimes, MD, and Kavita Nanda, MD, MS

*Obstet Gynecol* 2006;108:986-9
<table>
<thead>
<tr>
<th>Magnesium Sulfate Tocolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time to Quit</strong></td>
</tr>
<tr>
<td>- &quot;Magnesium sulfate is ineffective as a tocolytic, potentially harmful to infants, and unpleasant for women&quot;</td>
</tr>
<tr>
<td>- &quot;Further use of this agent is inappropriate unless in the context of a formal clinical trial&quot;</td>
</tr>
<tr>
<td>- &quot;7% of infant mortality may be caused by this agent&quot;</td>
</tr>
<tr>
<td>- &quot;Worthless as a tocolytic&quot;</td>
</tr>
<tr>
<td>- &quot;Tocolysis with magnesium sulfate is ineffective, and the practice should stop&quot;</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>History of Magnesium as a Tocolytic</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Late 1960s: Magnesium found in vitro to impair myometrial contractility via calcium antagonism</td>
</tr>
<tr>
<td>- First 3 US trials drew unsupportable conclusions, poor control groups, and had no neonatal data</td>
</tr>
<tr>
<td>- &quot;a shaky start: poor science and worse ethics&quot;</td>
</tr>
<tr>
<td>- First RCT that included pediatric mortality published 10 years later (1980s)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tocolytics Reviews</th>
</tr>
</thead>
<tbody>
<tr>
<td>- <strong>One Cochrane Review</strong></td>
</tr>
<tr>
<td>- <strong>6 Meta-analyses</strong></td>
</tr>
</tbody>
</table>


### Tocolytics

**Cochrane Reviews**

- "Cochrane Collaboration" – international non-profit and independent organization
- Evidenced-based approach to healthcare using a systematic review of current best evidence with predefined, explicit methodology.
  - Typically randomized or quasi-randomized studies
  - NOT a meta-analysis

### 1 Cochrane Review 2002

- Included trials comparing Mg as sole agent with placebo, no placebo, or alternate tocolytic
- 29 trials identified, 23 met inclusion criteria (>n=2000), 9 randomized, only 2 used placebo
- No trials rated of high quality
- "Magnesium sulphate is ineffective at delaying birth or preventing preterm birth, and its use is associated with an increased mortality for the infant"


#### Analysis 0.1. Comparison of magnesium sulphate with control group - all included trials. Outcome 0.2 (Rec 60 hours after trial entry)

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
<th>Relative Risk (RR)</th>
<th>Weight</th>
<th>Natural Risk (Standard)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avaroa 2005</td>
<td>5/5</td>
<td>5/4</td>
<td>4.4</td>
<td>0.97 (0.81, 1.17)</td>
<td></td>
</tr>
<tr>
<td>Cheng 2005</td>
<td>3/4</td>
<td>4/3</td>
<td>4.5</td>
<td>0.87 (0.71, 1.08)</td>
<td></td>
</tr>
<tr>
<td>de Almeida 2001</td>
<td>5/3</td>
<td>5/3</td>
<td>0.5</td>
<td>0.9 (0.57, 1.42)</td>
<td></td>
</tr>
<tr>
<td>Ewens 2002</td>
<td>1/2</td>
<td>2/2</td>
<td>0.1</td>
<td>0.75 (0.49, 1.17)</td>
<td></td>
</tr>
<tr>
<td>Nagraj 2002</td>
<td>3/3</td>
<td>3/3</td>
<td>1.0</td>
<td>0.75 (0.49, 1.17)</td>
<td></td>
</tr>
<tr>
<td>O'Suilleabhain 2004</td>
<td>3/3</td>
<td>3/3</td>
<td>1.0</td>
<td>0.75 (0.49, 1.17)</td>
<td></td>
</tr>
<tr>
<td>O'Brien 2003</td>
<td>1/1</td>
<td>1/1</td>
<td>0.9</td>
<td>0.75 (0.49, 1.17)</td>
<td></td>
</tr>
<tr>
<td>Tong 2003</td>
<td>2/2</td>
<td>2/2</td>
<td>1.0</td>
<td>0.75 (0.49, 1.17)</td>
<td></td>
</tr>
<tr>
<td>Treasure 2004</td>
<td>2/2</td>
<td>2/2</td>
<td>1.0</td>
<td>0.75 (0.49, 1.17)</td>
<td></td>
</tr>
<tr>
<td>Total N (CI)</td>
<td>42 (42)</td>
<td>42 (42)</td>
<td>1.0</td>
<td>0.75 (0.49, 1.17)</td>
<td></td>
</tr>
</tbody>
</table>

11 trials
### Benefit from magnesium? Ma 1992

- 65 cases of PTL at 28-36 weeks randomized:
  - 30 to high-dose Mag
  - 35 to barbiturates and bedrest
  - Excluded “complicated PTL”
  - Allocation concealment unclear
- Delivery delayed 48 hrs in 23/30 cases (77%) and 3/35 (9%) controls
- Delayed 7 days in 17/30 (57%) cases and 2/35 (6%) of controls (p<0.01)
- "Side effects to the mothers, fetus, and the neonates were mild and not prominent"


### Benefit from magnesium? Fox 1993

- 90 women at 34-37 weeks randomized
  - 45 magnesium
  - 45 hydration/sedation
  - No steroid use
- In each group, 3 women had transient tachypnea and 1 had RDS
- No serious neonatal complications
- Neonatal morbidity after delivery between 34 and 37 weeks’ gestation is unchanged whether or not attempts to arrest labor are unsuccessful.


### Meta-analysis #1 Macones’ review

- Efficacy and side effects of magnesium sulfate for acute tocolysis (from RCTs) compared with placebo and beta-agonists
- 8/12 studies included in analysis
- MgSO4 vs placebo: No difference in any measured outcomes for delay in delivery
- Magnesium sulfate vs beta-agonists: No difference in achieving clinically significant tocolysis
- “Available data are not sufficient for a rational choice between these agents”

Meta-analysis #2
Tocolytics vs Placebo

- Meta-analysis of all RCTs comparing any tocolytic with placebo or no treatment
- Decreases in odds of delivery within
  - 24 hrs (OR 0.54, 95%CI 0.32-0.91)
  - 48 hrs (OR 0.47, 95%CI 0.30-0.75)
- seen for beta-agonists, atosiban, and indomethacin, but not magnesium
- These benefits did not translate into improved neonatal outcomes
- "time gained in utero must be optimised"
- "there is no clear first-line tocolytic agent"


Meta-analysis #3
Canadian Preterm Birth Council

- Included all RCTs that compared effect of a tocolytic with placebo or no tocolytic in women in PTL, and reported perinatal, neonatal, or maternal outcomes
- 18/76 articles met inclusion criteria
- Betamimetics, indomethacin, atosiban, and ethanol, but not MgSO4, associated with significant prolongations in pregnancy
- Tocolytics not associated with improved perinatal outcomes
- ACS use? Not stated in 13 studies, some patients in 3, none in 2 studies


Meta-analysis #4
Higby et al, 1993

- Comprehensive review of tocolytic agents in the treatment of premature labor.
- 328 studies (1933-1992)
- Analysis of randomized, placebo-controlled, clinical trials showed that magnesium sulfate is not better than placebo in the treatment of premature labor
- "Magnesium sulfate should not be used to treat premature labor."

Meta-analysis #5
Haas et al., 2009
• Comprehensive review: To determine the optimal first line tocolytic agent for treatment of premature labor.
• 58 studies; all RCT; Delivery delay 48H, 7 days and until 37 weeks.
  – All tocolytics superior to placebo: delivery delay 48H & 7 days;
  – PG inhibitors superior to other agents (used < 32 weeks)
  – Ca²⁺ channel blockers best at delaying deliver until 37 weeks.


MgSO₄ for Neuroprotection

Neuroprotection → Prevention of CP

Cerebral Palsy
Background
• Most prevalent chronic childhood motor disability
• Overall prevalence: 1.5-3.6/1000 LB
  – And increasing
• ½ of cases occur at term
  – Incidence of 1/1500
• United Cerebral Palsy Foundation
  – 800,000 affected children and adults
• Life-time cost (2003): $1 million/person
Cerebral Palsy (CP)

**Background**

- Major risk factors:
  - PTB
  - Multiple gestation
  - PTB
  - TTTS
  - Death of one twin
- CP rate inversely proportional to GA
  - <34 weeks: 25% of all new cases
  - In VLBW infants: 4-8%

Cerebral Palsy (CP)

**Rates**

- Rates of CP (%)
  - 22-27: 14.6%
  - 28-31: 6.2%
  - 32-36: 0.7%
  - Term: 0.1%

(Systematic review and meta-analysis)
Hints of MgSO4 Neuroprotection
1980s & 90s

- ↓ CP rate with MgSO4 tx
  - Hauth et al. AJOG 1995;172:419
  - Schendel et al. JAMA 1998;279:1805

- No association b/w MgSO4 and ↓ CP rate
  - Panneth et al. Ped 1997;99:E1
  - Grether et al. AJOG 2000;183:717
  - Costantine et al. AJOG 2007;196:e6-8

History of Antenatal MgSO4 and Neonatal Effects

Nelson and Grether from NIH published “magnesium hypothesis”

- Data from California Birth Defects Surveillance Program used for retrospective case-control study of 150,000 children followed from birth to 3 years of age.
- 7% (3 of 42) of VLBW infants exposed to antenatal MgSO4 diagnosed with cerebral palsy, compared with 36% (27 of 75) of gestational-age matched children selected at random who subsequently developed cerebral palsy (OR 0.14; 95% CI 0.05-0.51).
- Data led to hypothesis that MgSO4 could possibly be used as a neuroprotectant for high risk fetuses/infants.

MgSO4 for Prevention of CP

5 RCTs
- MagNET 2002
- ACTOMgSO4 2003
- MAGPIE 2007
- PREMAG 2008
- BEAM 2008

1 Cochrane Review
- Doyle et al. 2009

2 Systematic Reviews and Metanalyses
- Conde-Agudelo et al. 2009
- Costantine et al. 2009
5 RCTs

- **MagNET**: Magnesium and Neurologic Endpoints Trial
  Mittendorf et al. AJOG 2002;186:1111-8
- **ACTOMgSO4**: Australasian Collaborative Trial of MgSO4
  Crowther et al. JAMA 2003;290:2669-76
- **MAGPIE**: Magnesium Sulfate for the Prevention of Eclampsia
  Magpie Trial Group. BJOG 2007;114:289-99
- **PREMAG**: MgSO4 given b/f very preterm birth to protect infant brain: the PREMAG Trial
  Marret et al. BJOG 2007;114:310-8
- **BEAM**: Beneficial Effects of Antenatal Magnesium Sulfate Trial
  Rouse et al. NEJM 2008;359:895-905

Outcomes

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Mg Exp v. No Exp</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MagNET</td>
<td>97</td>
<td>Toco Combo events</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>52</td>
<td>NP 32% vs 19%</td>
<td></td>
</tr>
<tr>
<td>ACTOMgSO4</td>
<td>1062</td>
<td>D &amp; NP 19.8% v 24%</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NP only 3.4% v 6.6%</td>
<td>0.02</td>
</tr>
<tr>
<td>MAGPIE</td>
<td>2895</td>
<td>D 13.8% v 24%</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NS only 1.3% v 1.9%</td>
<td>NS</td>
</tr>
<tr>
<td>PREMAG</td>
<td>564</td>
<td>PM rate 9.4% v 10.4%</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CP rate 16.1% v 20.2%</td>
<td>0.07</td>
</tr>
<tr>
<td>BEAM</td>
<td>2241</td>
<td>D &amp; CP 11.3% v 11.7%</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CP only 1.9% v 3.5%</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Cochrane Reviews & Metanalyses

<table>
<thead>
<tr>
<th>Analysis</th>
<th>n</th>
<th>Mg Exp v. No Exp</th>
<th>RR: 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doyle (Cochrane Rvw)</td>
<td>6145</td>
<td>Mort CP only</td>
<td>1.04; 0.92 - 1.17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CP only</td>
<td>0.09; 0.02 - 1.17</td>
</tr>
<tr>
<td>Conde-Agudelo (Meta-analysis)</td>
<td>5357</td>
<td>D &amp; CP CP only</td>
<td>1.01; 0.89 - 1.14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CP only</td>
<td>0.09; 0.02 - 1.17</td>
</tr>
<tr>
<td>Costantine (Meta-analysis)</td>
<td>5235</td>
<td>D &amp; CP CP only</td>
<td>0.92; 0.83 - 1.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CP only</td>
<td>0.09; 0.02 - 1.17</td>
</tr>
</tbody>
</table>
Pros & Cons For MgSO4 Neuroprotection

CON
- BEAM: only 2 of the 99 deaths in the MgSO4 group would need to survive and have CP to make the CP finding NS.

PRO
- Maybe true if you only have one RCT, but there are 5 RCTs and the meta-analyses/Cochrane review collectively show a benefit of MgSO4 to reduce CP

Cahill A, Caughey A. AJOG 2009:200:590-94

Pros & Cons For MgSO4 Neuroprotection

CON
- Intent of meta-analysis to combine small studies with limited power and similar trends in results to detect an answer that may have been missed. These 2 larger studies were powered correctly for the primary endpoint.
- The studies are very different making the meta-analyses somewhat questionable:
  PPROM: BEAM=87% v ACTOMgSO4 = 8%

PRO
- The fact that MgSO4 had the similar beneficial effects to reduce CP across different clinical scenarios and patient populations speaks to the effectiveness of MgSO4

Pros & Cons For MgSO4 Neuroprotection

CON
- Similar to the first point that was brought up about the BEAM trial, when looking at the meta-analysis, only 1 additional case of CP or death in the MgSO4 group is enough to make the meta-analysis finding NS.

PRO
- There are no “do-overs” in clinical trials – a RCT study looking at MgSO4 will very likely never be repeated; 2 meta-analyses and 1 Cochrane review found benefit.
### Pros & Cons For MgSO4 Neuroprotection

**PRO**
- Number-to-treat (NNT) analysis:
  - Overall 5% CP rate (RR 0.68): treat 63 moms to prevent one case of CP
  - <28w (6.2% CP rate; RR 0.45): treat 29 moms to prevent one case of CP
  - >28w (1.3% CP rate; RR 0.71): treat 265 moms to prevent one case of CP
- MAGPIE: treat approximately 500 patients to prevent one eclamptic seizure.

**CON**
- Need to consider maternal risk:
  - MAGPIE study: 2 maternal cardiac events
  - Also consider that these were done in excellent centers
  - overall a safe drug, but still with risk

### MgSO4 for Neuroprotection

**Remaining Questions**
- Patient selection
- Route
- Dose
- Urine output / magnesium levels
- Duration of exposure
- Timing of exposure relative to delivery

### Dosing Magnesium
- For preterm labor
  - 4-6 gram loading dose
  - 2-4 grams/hour infusion
  - 52-102 grams/24 hours
- For pre-eclampsia
  - 4 gram bolus
  - 1-2 grams/hour
  - 27-50 grams/24 hours
- For Neuroprotection
  - 4 gram bolus + 1 g/h infusion
  - 6 gram bolus + 2 g/h infusion
OB/GYN Organization Positions

- ACOG/RCOG - Neither endorses the use of magnesium sulfate tocolysis.
- ACOG: “…all (tocolytic agents) have demonstrated only limited benefit. Hence, there is no clear first-line tocolytic drug”
- SMFM statement on neuroprotection???

UCDHSC Div of MFM Guidelines

Tocolysis

- Magnesium Sulfate no longer used
- First choice: Nifedipine
- Second choice: Indomethacin (<32 wks)

Re-evaluation of Tocolytics & MgSO4 for Neuroprotection

UCDHSC Div of MFM Guidelines

Changes?

- <32 weeks: Tocolysis with PG inhibitors
  - Neuroprotection with MgSO4
  - BEAM protocol
  - 4g load, 1g/h
  - if undelivered w/in 12H, d/c
  - if PTL resumes and >6 hours since MgSO4 d/c'd, re-bolus with 4g
- >32 weeks: Nifedipine (no MgSO4)
What is your tocolytic or tocolytic classification of choice?

A. Sedation & Hydration  
B. β-agonists (Ritodrine; terbutaline)  
C. NSAIDS (Indomethacin; COX-2 inhibitors; Sulindac)  
D. Oxytocin receptor antagonists  
E. Calcium channel blockers  
F. Magnesium Sulfate

Do you currently use MgSO4 for tocolysis?

A. Yes  
B. No

Do you currently use MgSO4 for neuroprotection?

A. Yes  
B. No
If you did not use MgSO4 for neuroprotection previously, will you start using it now?

A. Yes
B. No

If you use MgSO4 for neuroprotection or plan to start using it, below what gestational age will you use it?

A. 28 weeks
B. 32 weeks
C. 37 weeks

**MgSO4 Tocolysis & Neuroprotection**

*Key Points*

1. PTL major cause of neonatal morb & mortality.
2. Tocolytic agents are more effective than placebo at delaying delivery.
3. Indomethacin is the most effective tocolytic at delaying delivery for up to 7 days.
4. Limit use of anti-prostaglandin drugs to <32w.
5. Nifedipine is the most effect tocolytic agent at delaying delivery until 37 weeks.
6. MgSO4 appears to have neuroprotective effects for the preterm neonate.
– 70% of CP occurs b/f onset of labor
– Only 4% of CP solely attributable to IP events
ACOG Practice Bulletin, No 70; December, 2005; Hankins et al, 2003, NEJM

Why do American obstetricians still use magnesium for preterm labor?

So what, if anything, do we use?
Tocolytics

- Betamimetics
  - Shown to prolong pregnancy to 7 days
  - No beneficial impact on perinatal mortality
  - Associated with maternal morbidity
- Atosiban (oxytocin receptor antagonist)
  - First line agent in many European countries
  - Cochrane review (2005): No Benefit over betamimetics or placebo
  - FDA Advisory Report (1998) voted against its use
    - Report of 9 NN deaths in Atosiban gp vs 1 death in placebo gp

Tocolytics

NSAIDS

- Indomethacin
  - Most frequently used;
  - MOA: non-specific inhibition of COX 1 & 2 → inhibits conversion of AA into PG precursors → suppressed formation of PG E₂ and F₂α.
  - Trials showing efficacy few in number; small patient #s
    - superior in tocolytic activity as compared to betamimetics, magnesium sulfate, atosiban, and ethanol, especially in delaying delivery by 48 hours and 7 days.
    - There has been no documented neonatal benefit

Tocolytics

NSAIDS

- Adverse Effects:
  - Platelet dysfunction may occur
  - >72 hours = oligohydramnios; ductus arteriosus constriction
    - Gestational age-dependent
    - Reversible prior to 32 weeks
    - Monitor after 48 hours
  - Prolonged use after 32 wks associated with neonatal IVH, NEC, oliguria, PPHN
**Tocolytics**

*NSAIDS*

- COX-2 Inhibitors:
  - Promise for tocolytic effect
  - Less effect on ductus arteriosus and AF
  - Many withdrawn due to increased risk of adverse CV events such as MI and CVA
- Currently little evidence with small patient numbers to recommend as a tocolytic

---

**Tocolytics**

*Calcium Channel Blockers (CCB)*

- Dihydropyridine agents
- MOA: Act peripherally on SM contractility by blocking influx of extracellular Ca++ ions
- Nifedipine most commonly used
- Trials:
  - No comparisons to placebo – only other tocolytics
  - Maternal tolerance significantly less over other common tocolytics

---

**Tocolytics**

*Calcium Channel Blockers (CCB)*

- Significantly reduce risk of:
  - Delivery within 7 days (RR 0.76, 95% CI 0.60-0.97)
  - PTB prior to 34 weeks (RR 0.83, 95% CI 0.69-0.99)
- Significantly reduces rates of:
  - RDS (RR 0.63, 95% CI 0.46-0.88)
  - NEC (RR 0.21, 95% CI 0.05-0.96)
  - IVH (RR 0.59, 95% CI 0.36-0.98)
  - NN Jaun (RR 0.73, 95% CI 0.57-0.93)
• **Nifedipine**
  - Initial dose: 10mg short-acting tablet po
  - Repeat 10mg dose q 15min if ctx’s greater than 1 / 15min; max dose 1 hour = 40mg
  - Depending upon total dose needed in first hour, maintenance dose of 10-20 mg every 4 – 6 hours of short-acting nifedipine can be given per day, with a maximum nifedipine dose of 160 mg/24 hours

• **Nifedipine**
  - Can convert to maintenance regimen consisting of an equivalent dose of extended-release nifedipine after 24 to 48 hours of acute short-acting therapy
  - Can be tapered after 48 hours or maintained at the patient-specific therapeutic dose until 34 weeks gestation (e.g. especially if the initial episode of PTL is considerably remote from term or advanced cx dilation)

• **Nifedipine**
  - Transport on IV MgSO₄ tocolysis, d/c MgSO₄ and transition, based upon physical exam, within 1 to 4 hours to a maintenance regimen of short-acting nifedipine for 24 to 48 hours or until completion of the corticosteroid course (a nifedipine load is not necessary)
**Tocolysis Guidelines**

- **Nifedipine - Additional notes:**
  - Contraindications:
    - known coronary artery disease or congestive heart failure
    - use with caution in patients with advanced class diabetics, chronic hypertensives or patients with dyslipidemia - a normal 12-lead ECG should be documented prior to use of nifedipine.

- **Nifedipine - Contraindications:**
  - Hypotension (hold for SBP < 90 mm Hg or DBP < 45 mm Hg or HR > 110 bpm)
  - drug allergy, hepatic dysfunction,
  - concurrent use of magnesium sulfate or IV betamimetics

- **Nifedipine – Additional Notes:**
  - Monitor BP and fetal CTG recorded during acute administration
  - Maternal side effects: Headache, Hypotension (not as pronounced in normotensive patients as in hypertensive patients), Tachycardia, Palpitations, Flushing, Dizziness, Nausea, Dyspnea, Rare: myocardial ischemia/infarction and pulmonary edema
Tocolysis Guidelines

• Indomethacin
  – Initial Dose: 50-100mg PO load
  – Maintenance: 25mg PO q 4-6
• Additional Notes:
  – Given anti-inflammatory properties, may consider as first line agent with inflammatory conditions such as degenerating fibroids.
• Limit to 48-72H unless DA and AF followed

Tocolysis Guidelines

• Indomethacin - contraindications
  – IUGR, Oligo, PPROM, TTT syndrome
  – Complex fetal CHD
  – GA >32 weeks
  – Vaginal bleeding
  – Bleeding disorders or anticoagulated pts
  – Moderate to severe asthma

Tocolysis Guidelines

• Indomethacin - contraindications
  – Hypersensitivity to ASA
  – Hepatic dysfunction
  – GI ulcerative disease
  – Renal dysfunction
  – Impending surgery
Clinical Characteristics of PTL

- Regular or irregular contractions
- Nonspecific symptoms
  - Backache
  - Pelvic pressure
  - Increased vaginal discharge
  - Bleeding
- Cervical exam not always informative

Preterm Labor and Delivery (<37 Weeks)

- Preterm Labor
  - 800,000 (1 in 5) pregnant women exhibit signs and symptoms of preterm labor
  - 70% of women identified as "high risk" deliver at term
- Preterm Delivery
  - >452,000 (11%) of all pregnancies result in preterm birth
  - Single largest cause of perinatal mortality and morbidity
  - $4 to $6 billion annual acute care costs


Prediction Strategies

- Clinical history
  - Clinical scoring systems / Risk classification
  - High Risk
    - Prior PTB
    - Multiple Gestation
    - Medical Complications
- Patient presentation
- Nulliparity—Risks not established
- Cervical Length
- Fetal Fibronectin

MagNET

<table>
<thead>
<tr>
<th>Case</th>
<th>Gestational age (wks)</th>
<th>SGA (y/n)</th>
<th>Clinical diagnosis</th>
<th>Other findings</th>
</tr>
</thead>
<tbody>
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<td>1</td>
<td>28½ x 360.6</td>
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<td>Rh incompatibility</td>
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<td>31 x 350.5</td>
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<td>Severe growth restriction</td>
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<td>3</td>
<td>34 x 370.2</td>
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<td>Preterm birth due to PE</td>
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<tr>
<td>4</td>
<td>26 x 340.6</td>
<td>0</td>
<td>Other complications</td>
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<tr>
<td>8</td>
<td>28 x 370.2</td>
<td>0</td>
<td>Other complications</td>
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</tr>
</tbody>
</table>

*Other studies: High MgSO4 doses > 50gm/24 hours

Primary hypothesis: in the setting of preterm labor, determine if antenatal exposure to MgSO4 reduces neonatal markers for brain injury:

- IVH
- PVL
- Decreased prevalence of CP among survivors
- Decreased overall perinatal mortality
- 9 deaths in Mag group; 1 in placebo group

MagNET
# Deaths Associated with MgSO₄ Exposure

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (w/d/o)</th>
<th>Weight (g)</th>
<th>Age at death (days)</th>
<th>Attainable causes, place of death</th>
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<tbody>
<tr>
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<td>56 w 1 d/o</td>
<td>15000</td>
<td>128</td>
<td>Sudden Infant death, DOA at other ER</td>
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<tr>
<td>2</td>
<td>33 w 0 d/o</td>
<td>15000</td>
<td>96</td>
<td>Sudden Infant death, In other ER</td>
</tr>
<tr>
<td>3*</td>
<td>30 w 2 d/o</td>
<td>1000</td>
<td>61</td>
<td>Sudden Infant death, In other ER</td>
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<tr>
<td>4*</td>
<td>30 w 5 d/o</td>
<td>15000</td>
<td>24</td>
<td>Congenital anomaly, NICU</td>
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<tr>
<td>5*</td>
<td>26 w 0 d/o</td>
<td>19000</td>
<td>2</td>
<td>Intra-uterine cyanosis, NICU, NICU</td>
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<td>6T</td>
<td>35 w 6 d/o</td>
<td>6000</td>
<td>115D</td>
<td>Tracheoesophageal fistula, labour and delivery</td>
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<td>9</td>
<td>36 w 1 d/o</td>
<td>865</td>
<td>1</td>
<td>Cardiopulmonary arrest, labour and delivery</td>
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</tbody>
</table>

* Other studies: High MgSO₄ doses > 50gm/24 hours