Preterm Labor Tocolysis: The Myth of Sisyphus Revisited?
Antepartum & Intrapartum Management Conference
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Complications of Prematurity
- Chronic lung disease
- Necrotizing enterocolitis
- Intracranial hemorrhage
- Retinopathy of prematurity
- Cerebral palsy
- Impact to family: emotional, financial, time
- Impact to society

U.S. Trends in Preterm Birth (PTB)
National Vital Statistics:
- 1960 7.8%
- 1981 9.4%
- 2002 12.1%
- 2006 12.8%
- 2007 12.7%
Preterm Birth

- Most of increase in moderately preterm births (32-36 weeks gestation)
- Contributing factors
  - Greater maternal age
  - Infertility treatment
- Spontaneous preterm labor – 70-80%
- Indicated preterm birth – 20-30%
  - Previa, IUGR, PET, NRFHT

Contributing factors

- Spontaneous preterm labor – 70-80%
- Greater maternal age
- Infertility treatment

Causes of Preterm Labor

- CRH
  - Placenta, fetal membranes
- Infection, inflammation
  - Prostaglandin and phospholipase A2 production
- Hemorrhage
  - Abruption, decidual bleed

Preterm Birth - cost

- 26 billion dollars annually for U.S. neonatal health costs for prematurity

December 25 1642 a widow gave premature birth to a male child “so small that he could have been put in a quart mug”

Sir Isaac Newton

Simpson AR. The Nursling. 1907

Tocolysis found its origins in prematurity and is still in search of its maturity. The history of tocolysis predominantly consists of premature actions and immature thoughts.

Marc J.N.C. Kierse 2003

Which is your first line acute tocolytic?

1. Magnesium Sulfate
2. Nifedipine
3. Indocin
4. Terbutaline
5. Nothing

Early Tocolytics

- Relaxin
  - Abramson and Reid 1955
- Ethanol
  - Fuchs 1967
- Magnesium sulfate
  - Dumont 1965

- “Tocolysis”
  - Coined by Mosler at the Symposium on Physiology and Pathology of Uterine Contractility in 1964
  - Greek words for “contraction” and “to untie or destroy”
**Tocolytic Therapy**

- Betamimetics
  - Ritodrine, Terbutaline
- Magnesium Sulfate
- Prostaglandin Synthetase Inhibitors
  - Indomethacin
- Calcium channel blocking agents
  - Nifedipine, Diltiazem
- Nitroglycerin
- Oxytocin antagonists: Atosiban

**Contraindications to Tocolysis**

<table>
<thead>
<tr>
<th>Maternal</th>
<th>Fetal</th>
<th>Maternal/Fetal</th>
</tr>
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<tbody>
<tr>
<td>Hemorrhage</td>
<td>Severe IUGR</td>
<td>Chorioamnionitis</td>
</tr>
<tr>
<td>Abruptio</td>
<td>Maturity</td>
<td></td>
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<tr>
<td>Severe</td>
<td>IUFD</td>
<td></td>
</tr>
<tr>
<td>Preclampsia</td>
<td>Lethal anomaly</td>
<td></td>
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<tr>
<td>Eclampsia</td>
<td>Pulmonary HTN</td>
<td></td>
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<tr>
<td>Cardiac disease</td>
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<td></td>
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<tr>
<td>Intolerance of tocolytics</td>
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**Ritodrine Tocolysis**

- Neonatal death
- Neonatal RDS
- Attaining ≥ 36 weeks
- Mean days gained
- Birthweight ≥ 2500g

*Merkatz et al Obstet Gynecol 1980*

**Ritodrine Tocolysis**

- 708 patients with PTL
  - randomized to D5W or ritodrine
  - delivery delayed 24-48 hours more often with ritodrine
  - no difference
    - achieving 32 or 37 weeks
    - neonatal morbidity or neonatal death
    - birthweight

*NEJM 1992*
Tocolytic Therapy

- Goal of Acute:
  - Delay delivery for 48 hours
  - Allow transport
  - Maximize steroid benefit

Tocolytic therapy

- Goal of Maintenance:
  - Following acute arrest of PTL
  - Oral therapy up to 37 weeks

Beta-adrenergic Agonists

- Mechanism
  - Activate adenylate cyclase
    - Form cyclic adenosine 3’5’ monophosphate (cAMP)
      - Decrease myosin kinase light-chain activity
        - by phosphorylation
        - Reduction of intracellular calcium
    - Smooth muscle relaxation

Betamimetics

- Side-effects
  - Cardiac arrhythmias, tachycardia, M.I.
  - Pulmonary edema
  - Hypotension
  - Hyperglycemia
Betamimetics versus placebo:  
Acute Tocolysis
- Betamimetics
- 11 studies – 1332 women
  - Fewer births within 48 hours
    - RR 0.63; 95% CI 0.53-0.75
  - No difference within 7 days (after sensitivity analysis)
    - RR 0.67; 95% CI 0.48-1.01
  - No difference in neonatal outcome
  - More side-effects

Cochrane Database 2004

Magnesium Sulfate
- Arguably most popular in U.S.
- Mechanism:
  - Decreases frequency of depolarization of smooth muscle
  - Modulating calcium uptake, binding and distribution in smooth muscle
- Calcium essential for uterine contractions

Magnesium Sulfate
- Side effects:
  - Flushing, lethargy, pulmonary edema, respiratory/cardiac depression and arrest
- Evaluate: alertness, DTR, pulmonary status, urine output
- Toxicity:
  - calcium gluconate (1 amp, 10%)
  - stop infusion

Magnesium Sulfate Trials
- Steer 1977 (vs. alcohol, dextrose water)
- Miller 1982 (vs. Terbutaline)
- Cotton 1984 (vs. Terbutaline)
- Tchilinguirian 1984 (vs. Ritodrine)
- Brall 1985 (vs. Ritodrine, Terbutaline)
- Hollander 1987 (vs. Ritodrine)
- Wilkins 1988 (vs. Ritodrine)
- Aramayo 1990 (vs. Terbutaline)
- Cox 1990 (vs. Saline)
- Armon 1992 (vs. Ritodrine)
- Chau 1992 (vs. Terbutaline)
- Floyd 1992 (vs. Nifedipine)
- Ma 1992 (vs. Barbiturate)
- Fox 1993 (vs. Hydration)
- Sciscione 1993 (vs. Ritodrine, Terbutaline)
- Glock 1993 (vs. Nifedipine)
- Morales 1993 (vs. indomethacin)
- Zhu 1996 (vs. Ritodrine)
- Mittendorf 1997 (ritodrine, terbutaline, indomethacin, nifedipine)
- Schor 1997 (vs. Ketorolac)
- El-Sayed 1999 (vs. Nitroglycerin)
- Haghighi 1999 (vs. Nifedipine)
- Larmon 1999 (vs. Nicardipine)
Magnesium sulfate compared to other tocolytics or placebo

- 23 studies – 2000 women
- No difference
  - Birth <48 hours RR 0.85 (CI 0.58-1.25)
  - PTD <34 weeks RR 0.82 (0.45 – 11.50)
  - PTD <37 weeks RR 0.91 (0.75 – 1.11)
- Neonatal outcomes – possible harm?
  
  Cochrane Database 2002

Magnesium sulfate tocolysis: time to quit

Given its lack of benefit, possible harms, and expense, magnesium sulfate should not be used for tocolysis. Any further use of magnesium sulfate for tocolysis should be restricted to formal clinical trials with approval by an institutional review board and signed informed consent for participants.

Grimes DA and Nanda K Obstet Gynecol. 2006

Magnesium Sulfate: Fetal/Pediatric Morbidity & Mortality

  - Maternal serum ionized levels and IVH
  - Umbilical cord serum ionized levels and total pediatric mortality
  - Umbilical cord serum ionized levels and adverse outcomes

Magnesium Sulfate vs. Hydration/Sedation

- Cox SM et al 1990
  - 156 women – Magnesium sulfate vs. no tocolytic
    - No difference in time gained in utero
- Cotton DB et al 1984
  - 54 patients – Magnesium sulfate vs. terb vs. placebo
    - No difference between arms
- Ma L 1992
  - 65 women – Magnesium sulfate vs. sedation/bedrest
    - 48 hr delivery delay: 76.7% vs. 8.6%
- Fox et al. 1993
  - 90 women – Magnesium sulfate vs. hydration/sedation
    - 48 hr delivery delay: 58% vs. 36%
Successful Tocolysis for 72 hrs

- 88% magnesium sulfate
- 79% ritodrine

Side effects “less alarming” with magnesium


Similar results comparing magnesium sulfate to terbutaline

Chau et al. Obstet Gynecol 1992
Miller et al J Repro Med 1982

Cochrane 2009 –MgS04 neuroprotection

- No difference in total pediatric mortality or fetal deaths between magnesium sulfate and no magnesium sulfate

Mercer 2009

- No difference in fetal or newborn death compared to no therapy or any other tocolytic

COX Inhibitors

- Indomethacin (non-selective)
  
Arachidonic acid \( \rightarrow \) Prostaglandin

prevents formation of prostaglandins from arachidonic acid

Fetal side effects

- transient ductal constriction
- oligohydramnios
- possible increase in ICH

Maternal side effects:

- G.I. Upset
- decreased urine output
- thrombocytopenia
Neonatal Outcomes

RR 0.44 (CI 0.26-0.74) – significance lost with random effects model

Birth <37 weeks

RR 0.21 (CI 0.07 – 0.62)

Neonatal Outcomes

No difference, except birthweight

Cochrane Database 2005

Any COX inhibitors vs. Placebo

Three trials – 106 women

Birth <48 hours

RR 0.19 (CI 0.07-0.51) - significance lost with random effects model

Comparison betamimetics RR 0.53 (CI 0.28-0.99)

Birth <7 days

RR 0.44 (CI 0.26-0.74) – significance lost with random effects model

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Neonatal Outcomes

No difference, except birthweight

Cochrane Database 2005

Calcium Channel Blockers

Mechanism

block calcium influx into smooth muscle via voltage mediated channels

inhibit release of calcium from organelles

Nifedipine Side-effects

Better safety profile than betamimetics and magnesium sulfate

Overall side-effects: 34%

Headache 24%

Vomiting 5%

Hypotension 5%

Shortness of breath 5%

Lethargy 3%


Calcium Channel Blockers

12 randomized trials-1029 women – ANY other tocolytic

Birth < 48 hrs RR 0.80 (CI 0.61-1.05)

Comparison betamimetics 0.72 (CI 0.52-0.97)

Fewer births < 7 days RR 0.76 (CI 0.6-0.97)

Fewer births < 34 weeks RR 0.83 (0.69-0.99)

Birth <37 weeks RR 0.95 (0.83-1.09)

Improved Neonatal Outcomes

RDS RR 0.63 (CI 0.36-0.98), NEC RR 0.21 (CI 0.05-0.96), IVH RR 0.59 (CI 0.3-0.98), Jaundice RR 0.73 (CI 0.57-0.93)

Fewer adverse drug reactions RR 0.14 (CI 0.05-0.36)

Cochrane Database 2003

Jaundice

Nifedipine Side-effects

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Cochrane Database 2003
**Nifedipine Advocated**

Should tocolysis be desired, calcium channel blockers, such as nifedipine, seem preferable.

When tocolysis is indicated for women in preterm labor, calcium channel blockers are preferable to other tocolytic agents compared, mainly betamimetics.
Cochrane Database of Systematic Reviews 2003

**Acute Tocolysis**

- Overall - effective in delaying delivery for up to 48 hours
- Possible benefit to nifedipine and indocin, in longer delay and neonatal outcomes
- Variable maternal side effect profiles

**First-line Tocolytic?**

- Magnesium sulfate (45%)
- Calcium channel blockers (32%)
- Indomethacin (20%)
- Terbutaline (3%)


**Magnesium Sulfate vs. Nifedipine?**

- Two small studies, no difference
  - Glock and Morales, 1993: 80 patients
  - Highaghi, 1999: 74 patients
Magnesium sulfate compared with nifedipine for acute tocolysis of preterm labor: a randomized controlled trial

- Oral presentation SMFM 2006
- #1 most downloaded article from *Obstetrics & Gynecology* 7/2007

To compare the *efficacy* and *side-effects* of magnesium sulfate and nifedipine for acute tocolysis of preterm labor.

### Results

<table>
<thead>
<tr>
<th></th>
<th>MgSO4</th>
<th>Nifedipine</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quiescence without delivery by 48 hours</td>
<td>87%</td>
<td>72%</td>
<td>0.01</td>
</tr>
<tr>
<td>Delivery w/in 48 hours</td>
<td>7.6%</td>
<td>8.0%</td>
<td>0.92</td>
</tr>
<tr>
<td>GA at del. (weeks)</td>
<td>35.8</td>
<td>36.0</td>
<td>0.61</td>
</tr>
<tr>
<td>Del. &lt; 37 weeks</td>
<td>57%</td>
<td>57%</td>
<td>0.97</td>
</tr>
<tr>
<td>Del. &lt; 32 weeks</td>
<td>11%</td>
<td>8%</td>
<td>0.39</td>
</tr>
<tr>
<td>Recurrent PTL</td>
<td>0.44</td>
<td>0.40</td>
<td>0.32</td>
</tr>
</tbody>
</table>

### Neonatal Outcomes

<table>
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<th>MgSO4</th>
<th>Nifedipine</th>
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<tbody>
<tr>
<td>BW (grams)</td>
<td>2660</td>
<td>2729</td>
<td>0.72</td>
</tr>
<tr>
<td>BW &lt; 2500 grams</td>
<td>44%</td>
<td>37%</td>
<td>0.35</td>
</tr>
<tr>
<td>Composite Morbidity</td>
<td>25%</td>
<td>20%</td>
<td>.32</td>
</tr>
<tr>
<td>RDS</td>
<td>23%</td>
<td>19%</td>
<td>.48</td>
</tr>
<tr>
<td>IVH</td>
<td>3%</td>
<td>2%</td>
<td>.61</td>
</tr>
<tr>
<td>NEC</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>5%</td>
<td>3%</td>
<td>.43</td>
</tr>
<tr>
<td>Death</td>
<td>2%</td>
<td>0</td>
<td>.15</td>
</tr>
<tr>
<td>Days in NICU</td>
<td>8.7</td>
<td>4.2</td>
<td>.007</td>
</tr>
</tbody>
</table>
**Maintenance Tocolysis**

- **Rationale**
  - On-going stimulus for preterm labor may remain
  - Contraction and prostaglandins may upregulate oxytocin receptors
  - Possible lower threshold for recurrence

**Maintenance Tocolysis**

- **ACOG:** Prolonged oral, subcutaneous, or intravenous tocolytic treatment is not effective.
  - Management of Preterm Labor, 2003

**Maintenance Tocolysis**

- Betamimetics – compared to placebo/no treatment
  - Birth <37 weeks RR 1.08 (CI 0.88-1.32)
  - No difference in neonatal outcomes
    - Cochrane Database of Systemic Reviews 2006

- Indocin - Compared to terbutaline
  - No difference in birth <34 weeks
  - Indocin
    - 27% constriction of ductus
    - 38% oligohydramnios

**Risks of in utero beta 2 adrenergic agonist exposure**

- Permanent shift in sympathetic-to-parasympathetic tone balance as result of B2AR overstimulation
- B2AR – expressed in mammalian brain during gestation
  - Early in fetal life B2AR stimulation
    - Basic cell processes – axonal outgrowth in neural cells, differentiation, migration
- Functional and behavioral teratogenesis
  - Autism, psychiatric disorders, poor cognitive and motor function
  - Witter et al. AJOG 2009
**FDA Safety Announcement 2/17/2011**

“The U.S. Food and Drug Administration (FDA) is warning the public that intravenous terbutaline should not be used in pregnant women for prevention or prolonged treatment (beyond 48-72 hours) of preterm labor in either the hospital or outpatient setting because of the potential for serious maternal heart problems and death.

The agency is requiring the addition of a Boxed Warning and Contraindication to the terbutaline injection label to warn against this use.

In addition, oral terbutaline should not be used for prevention or any treatment of preterm labor because it has not been shown to be effective and has similar safety concerns.

The agency is requiring the addition of a Boxed Warning and Contraindication to the terbutaline tablet label to warn against this use.”

**Maintenance Tocolysis**

- 29% MFM specialists use routinely
- 31% MFM specialists: not routine, but use if patient desires
- 79% use nifedipine first-line


**Nifedipine Maintenance Tocolysis**

- No placebo-controlled trials
- Two randomized studies
  - Nifedipine vs. no treatment
  - Not blinded
  - Conflicting results
    - No benefit: Carr DC et al., Am J Obstet Gynecol 1999 (n=74)
    - Increased latency and gestational age at delivery: Sayin NC et al, J Perinat Med 2004 (n=73)

**Maintenance nifedipine vs. placebo: a prospective, double blind trial**

*SMFM Oral Presentation 2008
*Lyell et al, *Obstet Gynecol* 12/08
*#1 most downloaded article 12/08
*2009 ACOG Roy Pitkin Award
Outcomes

- Primary
  - Achievement of 37 weeks’ gestation

- Secondary
  - Mean gestational age at delivery
  - Delivery delay: >48 hours, 1 week, 2 weeks, 3 weeks, 4 weeks
  - Birth weight
  - Neonatal morbidity

Achieved 37 weeks

![Chart showing the percentage of patients who achieved 37 weeks of gestation, with Nifedipine and Placebo groups compared.](chart)

- Nifedipine: 39%
- Placebo: 37%
- p=1.00

Gestational Age at Delivery

![Chart showing gestational age at delivery, comparing Nifedipine and Placebo groups.](chart)

- Nifedipine: 35.0 weeks
- Placebo: 35.1 weeks
- p=0.82

>1 Episode Recurrent Preterm Labor

![Chart showing the percentage of patients with >1 episode of recurrent preterm labor, comparing Nifedipine and Placebo groups.](chart)

- Nifedipine: 42.4%
- Placebo: 40.0%
- p=1.00
Neonatal Outcomes

- No differences in:
  - Birth weight, low birth weight, composite morbidity (RDS, IVH, NEC, death), or days in the NICU

Labor as a two-stage process
- Activation
  - Gap junctions, ion channels, agonist receptors
- Stimulation
  - Oxytocin and prostaglandins

Two ways tocolytics can work
- Inhibit the stimulators (oxytocin inhibitors, COX inhibitors, calcium channel antagonists)
- Stimulate the inhibitors (beta agonists, nitric oxide donors)

GN Smith 2003

Conclusion

- Maintenance nifedipine does not confer a large, significant difference in:
  - Preterm birth
  - Delay of delivery
  - Gestational age at delivery
  - Neonatal outcomes

A narrow therapeutic window and more questions than answers

- Benefit of tocolysis is delay delivery for 48 hours
  - Combined use of tocolytics and steroids widespread
  - Support in retrospective, observational trials
  - Most large placebo-controlled acute tocolysis trials performed before steroids were in standard use

- Canadian Preterm Labor Investigators Group study 1992
  - Proportion of women completing steroid Rx
    - 34.6% Ritodrine vs. 36% Placebo

6/10/2011
The Myth of Sisyphus

- Despite a mountain of studies
  - Are we really changing the outcomes with tocolysis?
  - Does the time gained with tocolysis really enhance the steroid effect?

March of Dimes – Preterm Birth Research Targets

- **Epidemiologic study**  Green et al. AJOG 2005
  - Biomarkers, Overlap with adverse outcomes
- **Genes and gene-environment interactions**
  - High-risk phenotypes, analytic techniques & bioinformation systems
- **Racial/ethnic disparities**
  - Risk factor analysis, genetic factors, behavioral factors & health care delivery
- **Role of inflammatory responses and preterm birth**
  - Microorganisms, Effect of antibiotics, role of cervix, immune modulation
- **Stress responses and preterm birth**
  - Maternal and fetal stress, stress on racial/ethnic disparities
- **Clinical trials**
  - Biomarkers, infection, abruption, Progesterone supplementation

- **One approach**
  - Nifedipine (or Indocin) for acute tocolysis
  - Corticosteroids
- **Or**
  - Nifedipine (or indocin) for acute tocolysis
  - Corticosteroids
  - Magnesium sulfate as rescue or for failed tocolysis for neuroprotection
- **Or**
  - No tocolysis
  - Corticosteroids
  - Magnesium sulfate in active labor for neuroprotection
- **Or**
  - Magnesium Sulfate for tocolysis and neuroprotection
  - Corticosteroids