PRETERM LABOR – CURRENT APPROACHES TO DIAGNOSIS AND MANAGEMENT

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PRETERM BIRTH IN THE U.S.

- U.S. preterm birth rate = 9-12 %
- U.S. ranks 20th in perinatal mortality among the industrialized nations
- incidence increasing
- mortality decreasing
- morbidity increasing...
Figure 1. Incidence of preterm birth in the United States, 1981–1999. Source of data: National Center for Health Statistics.\textsuperscript{97}

Categories of Preterm Births

- Spontaneous: 76%
- Indicated: 22%
- PPROM: 20%
Figure 2. Acute morbidity by gestational age among surviving infants. Results of a community-based evaluation of 8523 deliveries, 1997–1998, Shelby County, Tennessee. Curves smoothed by 2-point average.

Figure 3. **Chronic morbidity** by gestational age among surviving infants. Results of a community-based evaluation of 8523 deliveries, 1997–1998, Shelby County, Tennessee. Curves smoothed by 2-point average.

DEFINITION OF PRETERM LABOR

(Creasy and Gonik: AJOG 154:3, 1986)

1. GA 20-37 weeks plus
2. UC 4 in 20 min. or 8 in 60 min. plus
3 a. SROM or
   b. cx 2 cm dilate or
   c. cx 80% effaced or
   d. definite cx change

(requires 1 + 2 + a or b or c or d)
PTL: MANAGEMENT BEDREST

- No prospective RCT showing benefit
- 4 twins studies:
  - (2) no benefit
  - (2) increase in PTB
- Downside:
  - muscle weakness, osteoporosis, DVT
  - guilt, unemployment, marital, etc.
PTL: MANAGEMENT
HYDRATION/SEDATION

• Theory: Henry-Gauer reflex (ADH)
• 2 RCT for hydration (1L LR): no benefit
• 1 RCT for sedation (morphine): no benefit
• Downside: overhydration + tocolytics
  ---> pulmonary edema
TOCOLYTICS FOR PTL
META-ANALYSIS -(OG-1999)

- N=18 studies (N=1406 patients)
- decreased risk of del 48 h: OR=.47 (.29-.77)
- " " " 7 d: OR=.60 (.38-.95)
- did not reduce rate of PNM: OR=1.22
- " " " RDS: OR=.82
- " " " BWt<2500g: OR=.62
TOCOLYTICS FOR PTL
BETA-MIMETICS

• Cochrane (2004) – 11 trials (n=1332)
  OR=1.00 (.72-1.06)
• PNM
  OR=0.87 (.71-1.08)
• RDS
  OR=0.63 (.53-.75)*
• Del <48 h
  OR=0.67 (.48-1.01)
• Del <7 days
BETA-MIMETICS
SIDE EFFECTS

MATERNAL
- tachycardia, diastolic hypotension, hypokalemia, hyperglycemia, tremor, SOB, chest pain, pulmonary edema

FETAL
- fetal tachycardia, hypoglycemia
Beta-Mimetics
Clinical Use

- Terbutaline probably best used for triage:
  - terbutaline 0.25 mg subcut x1-2
- If the contractions stop with that, it’s probably not true preterm labor
- Longer use probably not justified because of side effect profile and availability of other agents
TOCOLYTICS FOR PTL
MgSO\textsubscript{4}

- Cochrane (2002) – 3 trials (n=190)
- PNM OR=1.83 (0.7-4.8)
- RDS OR=1.09 (0.98-1.22)
- BWt>2500 OR=1.06 (0.6-1.9)
- Del <48 h OR=0.57 (0.3-1.63)
**MgSO4 – Side Effects**

- **MATERNAL**
  - flushing, hypotension, vomiting, muscle weakness, desaturation, diplopia, headache

- **FETAL**
  - bradycardia, loss of variability, “floppy baby”
  - neuroprotective vs. harmful effect?

**RECOMMENDATION:**

DON’T use, “it’s s-o-o ’90’s!”
TOCOLOYTICS FOR PTL
NIFEDIPINE

Cochrane (2003) 12 trials (n=1029)

- 48-h delay in delivery 0.72 (.53-.97)*
- 7 day delay in delivery 0.76 (.60-.97)*
- Reduction in IRDS 0.63 (.46-.88)*
- superior compared to betamimetics
Nifedipine – Side Effects

- **MATERNAL**
  - flushing, headache, dizziness, hypotension, pulmonary edema
- **FETAL**
  - decels secondary to maternal hypotension
Nifedipine Clinical Use

- Nifedipine 30 mg po **loading** dose, followed by 20 mg po in 90 minutes – OR-
- Nifedipine 10 mg po q 20 min x4
- Followed by **maintenance**:
  - Nifedipine 10 mg po q6 h x 48 hours
- Reduce dose or stop if hypotension or intolerable headache
TOCOLYTICS FOR PTL
INDOMETHACIN

- Cochrane (2005) – 13 trials (n=713)
- PNM: OR=1.48 (0.2-9.2)
- RDS: OR=0.61 (0.2-2.3)
- Del <48h: OR=0.27 (.08-.96)*
- Del <7 days: OR=.88 (.52-.1.46)
Indomethacin – Side Effects

- MATERNAL
  - gastritis, reflux, nausea/vomiting

- FETAL
  - constriction of the ductus arteriosus and oligohydramnios may be seen w/ >48 h use, but long term effects (IVH, NEC, renal failure) no different than controls if <48 h use
TOCOLYTICS FOR PTL
USE OF INDOMETHACIN

- GA $\leq$ 32 weeks if $>1$ dose to be given
- no oligohydramnios
- loading dose: 100 mg rectal suppository or
  - 50 mg orally
- maintenance: 50 mg po q6h
- max dose: 400 mg in 48 hrs
- symptomatic tx if GI side effects
Cost-Effectiveness of Tocolytics

- Hayes. AJOG 2007: 19 trials (n=1073)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Side Effx</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indomethacin</td>
<td>11%</td>
<td>$15</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>27%</td>
<td>$17*</td>
</tr>
<tr>
<td>MgSO4</td>
<td>22%</td>
<td>$198</td>
</tr>
<tr>
<td>Terbutaline</td>
<td>58%</td>
<td>$399</td>
</tr>
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</table>
RISK OF IRDS

28 weeks 65%
30 weeks 50%
32 weeks 40%
34 weeks 22%
35 weeks 7%
36 weeks <1%
EFFECTS OF CORTICOSTEROIDS
OXFORD DATABASE OF PERINATAL TRIALS (N=23)

- Reduction overall of IRDS (N=1635)
  OR = 0.49 (.41-.60)
- Reduction < 31 weeks
  OR = 0.38 (.24-.60)
EFFECTS OF CORTICOSTEROIDS
OXFORD DATABASE - IRDS - TIME

• Reduction IRDS (24h → 7d)
  OR = 0.31 (.23-.42)

• Reduction IRDS ( > 7d)
  OR = 0.69 (.50-.94)
Puffs
EFFECTS OF CORTICOSTEROIDS
OXFORD DATABASE - OTHER
OUTCOMES

- neonatal death  OR = .59 (.47-.75)
- IVH  = .45 (.21-.97)
- neurologic abn  = .61 (.34-1.08)
- NEC  = .37 (.17-.69)
EFFECT OF CORTICOSTEROIDS in PPROM - OXFORD DATABASE

- IRDS after PPROM = .55 (0.40-0.75)
- MAT. INFX after PPROM = 2.10 (0.69-8.47)
- NN. INF after PPROM = 1.61 (0.87-2.98)
CORTICOSTEROIDS and INFECTION - Oxford Data Base

- maternal infection = 1.11 (.81-1.51)
- neonatal infection = .83 (.54-1.26)
How babies are REALLY delivered
Normal Pattern of Uterine Activity Night: Day Ratio

- 20 wks: 1.8:1
- 30 wks: 2.3:1
- 40 wks: 2.8:1
- 67% of all contractions occurred after dark
Normal Pattern of Uterine Activity

- Only 26% had contractions
- 85% of those had only 1-3 contractions/hour
- Day animals deliver at night
- How helpful is bedrest?
Normal Pattern of Uterine Activity

Effect of Activity, Sex, Stress

- No increase with exertion (-.1%)
- Rest decreased UC X 3 hours (-1.1%)
- Sex increased UC X 1 hours (+5.5%)
- Stress had no effect (+0.2%)
Case #1

- 25 y/o G2P1 at 29 weeks presents with uterine contractions every 3 min x last 3 hrs. On exam her cx is FT dilated, 50% effaced, vertex -3 station. The monitor shows q3’ UC that are perceived, but not painful. Is she at risk of PTB?
So..., is this woman really having PTL? Two Useful Tools

- Transvaginal Cervical Length
- Fetal Fibronectin
Figure 3. Transvaginal ultrasound image of the cervix obtained from a woman with symptoms of preterm labor. The image supports a diagnosis of preterm labor because of the length (23 mm) and the Y-shaped appearance of the cervix.

FIGURE 2. How to calculate funneling on transvaginal ultrasound

\[
\frac{B}{A+B} = \text{Funneling \%}
\]
Figure 1. Schematic to display the process of cervical effacement as it proceeds from the internal os, caudad toward the external os, as seen on transvaginal sonography. The letters T, Y, V, and U depict the relationship between the lower uterine segment and the cervical canal. Gray, cervical configuration; blue, fetal head; orange, cervix; red, cervical change. (Modified with permission from Zilianti M, Azuaga A, Calderon F, Pages G, Mendoza G. Monitoring the effacement of the uterine cervix by transperineal sonography: A new perspective. J Ultrasound Med 1995;14:719–24. Copyright © 1995 American Institute of Ultrasound in Medicine.)

How to measure the cx length with transvaginal sonography

- Empty bladder
- Probe in the anterior fornix
- Avoid excess pressure on cx
- Endocx canal visualized
- Enlarge image (cx 2/3 of screen)
- Average 3 measurements
- Appy abdominal compression and re-measure
Cervical Length (24 - 28 WKS)  
Risk of Preterm Delivery

- NL : $3.5 \pm 8$ cm
- $< 10^{th}$ % : $< 2.5$ cm
- Risk of PTD: RR - 6.2
- funnel ($> 1.5$ cm) : RR - 5.0
Cervical Length and the Risk of PTB in Asymptomatic Women

<table>
<thead>
<tr>
<th>Cervical Length</th>
<th>Probability of PTB</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;3 cm</td>
<td>7%</td>
</tr>
<tr>
<td>2 cm*</td>
<td>15%</td>
</tr>
<tr>
<td>&lt;1 cm</td>
<td>42%</td>
</tr>
</tbody>
</table>

*PPV only 18%, but NPV 96%
FETAL FIBRONECTIN
WHAT IS IT?

- extracellular matrix protein
- concentrated at the chorio-decidual juncture
- extracellular interface between mom & fetus
- proteolysis during labor ⇔ “leaks” thru cervix
**fFN in ASYMPTOMATIC WOMEN - MFMU NETWORK - 1994**

- Cx specimen 24 wks (N=2208) (4% pos.)
- GA <30 wks <32 wks <35 wks
  - PTB 0.9% 1.7% 4.7%
  - OR 42 23 11
  - SENS 52% 37% 20%
fFN in SYMPTOMATIC WOMEN
PEACEMAN - AJOG (1997)

- symptomatic patients (n=763) - 24-34 weeks
- outcomes: delivery <7 days <37 weeks
- NPV 99.5% 85%
- PPV 13% 43%
FETAL FIBRONECTIN
CLINICAL USE

- Intact membranes
- NO bleeding
- NO coitus/24 hours
- NO lubricant
- Collect from posterior fornix
- Leave swab x 10 seconds
Cervical Length + fFN in the triage of women with preterm contractions

- CL<1.5 cm $\rightarrow$ 51% PTB in next 7 days
- CL>1.5 cm $\rightarrow$ 1% PTB
- CL<1.5 cm + (+)fFN $\rightarrow$ 72% PTB
- CL>1.5 cm + (-)fFN $\rightarrow$ 0.6% PTB
- “If the cervix is long and the fFN is negative, you can say ‘So long’”!
CHORIOAMNIONITIS PATHOGENESIS

- ROM⇒ ascending infection
  - OR -
- Ascending infection ⇒ ROM
- role of microbial colonization and production of collagenase and elastase resulting in ROM
ANTIBIOTICS FOR PTL-EFFICACY

RCT (N=860)

- Erythro, Amp, clinda
- Delay in del. ? - NO - 4,
  YES - 4
- Increase BWT? - NO - 8/8
• increased PROM - del. interval
• ?decreased NN sepsis
• No reduction NN mortality
## ANTIBIOTICS FOR PPROM
### MATERNAL OUTCOMES (n=649)

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latency &gt; 1 week</td>
<td>1.97</td>
<td>(1.48 - 2.61)</td>
</tr>
<tr>
<td>Chorioamnionitis</td>
<td>0.45</td>
<td>(.33 - .60)</td>
</tr>
<tr>
<td>PP infection</td>
<td>0.63</td>
<td>(.41 - .97)</td>
</tr>
</tbody>
</table>
## ANTIBIOTICS FOR PPROM INFANT OUTCOMES (n=649)

<table>
<thead>
<tr>
<th>Condition</th>
<th>OR</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perinatal death</td>
<td>0.74</td>
<td>(.50 - 1.11)</td>
</tr>
<tr>
<td>IRDS</td>
<td>0.90</td>
<td>(.71 - 1.15)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>0.57</td>
<td>(.36 - .88)</td>
</tr>
</tbody>
</table>
ANTIBIOTICS AND PPROM

- **ORACLE I (2001) n=4826**
- erythromycin 250 mg qid x 10 d
- co-amoxiclav 250/125 mg “ “ -vs- placebo
- primary outcome composite:
  - neonatal death
  - chronic lung disease
  - major CNS abnormality
# ORACLE I: ANTIBIOTICS/PPROM

**Placebo vs. Erythro vs. Amox**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo</th>
<th>Erythro</th>
<th>Amox</th>
</tr>
</thead>
<tbody>
<tr>
<td>Del&lt;48 hrs</td>
<td>41%</td>
<td>35%</td>
<td>31%*</td>
</tr>
<tr>
<td>IRDS</td>
<td>22</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Sepsis</td>
<td>8</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>NEC</td>
<td>0.5</td>
<td>0.7</td>
<td>1.9*</td>
</tr>
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ANTIBIOTICS AND PTL with Intact Membranes

- ORACLE II (2001) N=6295
- same composite primary outcome
- erythromycin, co-amoxiclav, placebo
- 5.6% vs. 5.0% vs. 5.0%
- antibiotics of no value for PTL-IM
IS THERE AN OPTIMAL TIME TO DELIVER WOMEN WITH PPROM?

- When are the infant’s risks of IRDS outweighed by the risk of sepsis?
- What about minor morbidity and LOS?
- 6 studies (n=1,087) PPROM 32-36 wks
- less chorio/sepsis if induced immediately
- no significant benefit to expectant management after 34 weeks
BACTERIAL VAGINOSIS AS A RISK FOR PRETERM BIRTH

• Leitich (2003) – meta-analysis#1
• -18 studies (n=20,232)
• BV increased the risk of PTB:
  – OR = 2.19 (CI: 1.54-3.12)
  – (BV was not associated with PNM however)
ANTIBIOTIC TREATMENT OF BV AND PRETERM BIRTH

- Leitich (2003) – meta-analysis#2
- 10 studies (n=3,969)
- Antibx tx of BV did not reduce PTB:
  - OR=.83 (CI: 0.22-1.12)
  - (in a subset of 338 high-risk women, tx for >7d did reduce PTB: OR=.42 (CI: .27-.67)
RCT of Metro and Erythro to Prevent Preterm Birth in fFN(+) Women

MFMU/NICHD - 2003

- n=16,317 women: 715 (4.3%) were fFN(+)
  100 (14%) were BV(+)

- screened at 21-26 wks

- tx w/ metro 250 tid + erythro 250 qid x 10d

- no difference in PTB rate, even if BV(+):
  - OR=1.17 (CI: .80-1.70)
  - subset w/ BV: OR=.84 (.41-1.74)
PERIODONTAL DISEASE AND PRETERM BIRTH:
“The Perio-Premie Connection”

- theory: gingivitis → LPS → PGE → labor
- 10 studies (n=2,559)
- association between perio and PTB:
  - OR ranged from 2.7 to 7.9
- only 3 intervention trials → more needed
- it’s good to go to the dentist if you’re pg…
PREVENTING PTB: the future?

17a-OH-Progesterone

- RCT (n=463 high risk women)
- prior sPTB, enrolled <20 wks
- weekly 17P 250 mg vs. placebo to 36 wks
- PTB<37 wks: 36 vs. 55% (RR=0.66)*
- PTB<32 wks: 11 vs. 20% (RR=0.58)*
- decreased NEC, IVH, O2 need

- *p<.01 (Meis-NEJM 2003)