Progress in OBGYN 2015

Obstetrics on the Cutting Edge: Research Information on the Horizon

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Conflict of Interest

- PI for some these studies

Objective

- Briefly review research that will likely influence obstetric practice including:
  - Selected UAB / MFMU Network research
  - Other recently completed research
CESAREAN SECTION OPTIMAL ANTIBIOTIC PROPHYLAXIS (C/SOAP) TRIAL

Hypotheses

Extended-spectrum prophylaxis (with azithromycin) compared to cefazolin alone reduces risk of

1. Post-cesarean infection
2. Neonatal morbidity
**Antibiotic Prophylaxis**

- Infectious morbidity: 50%
- Cost-effective

*Mugford: BMJ, 1989*
*Smalil: Cochrane, 2013*
*Chelmow: AJOG, 2004*

**Unsafeled cesareans: Standard pre-incision cefazolin**

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Puerperal Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discharge</td>
<td>5%</td>
</tr>
<tr>
<td>6 weeks PP</td>
<td>7-12%</td>
</tr>
</tbody>
</table>

**Extended Prophylaxis**

- Cefazolin +
- 2nd Antibiotic
  - Azithromycin
  - Metronidazol
Why Azithromycin?

- Covers additional organisms
  - Ureaplasma sp. ++
  - Most common organisms in post-cesarean infections

Extended-spectrum Prophylaxis:

- ↓ Total infection
- ↓ Hospital stay
  - ↓ Costs

Andrews: O&G, 2003

*Extended vs. Standard*
Extended Prophylaxis: Concerns

- Generalizability (1 center)
- No data on pre-incision use
  - Benefits
  - Neonatal exposure
- Cost-effectiveness

C/SOAP (N=2000)

Non-elective cesarean

Exclusions

RCT (Routine cefazolin for all)

Azithromycin  Placebo
C/SOAP Trial

- Outcomes
  - Postpartum infection (6 weeks)
  - Neonatal/infant morbidity (3 months)

- Status
  - N=2013 enrolled (13 sites)
  - Completing follow-up
  - Results within the next year

Antenatal Late Preterm Steroids (ALPS) RCT

Primary Research Question - ALPS

- In patients with an anticipated late PTB
  - Not previously received steroids
- Does antenatal corticosteroids reduce risk of respiratory and other neonatal morbidity?
Late Preterm Healthcare Burden

Discharge Delays: 42% LP vs. 5% at term

Mean difference in the cost of care for a LP infant: $3877
US projections based on 9.1% LP rate: $1.4 billion dollars

McIntire and Leveno, Obstet Gynecol, 2008;111:35-41

US Late Preterm Singleton Births

Source: NCHS, final natality data
Prepared by March of Dimes Perinatal Data Center, April 2006.

Late preterm infants populate the NICU

Clark R et al, Pediatric Database, 2005
Neonatal Mortality Rates

* p<0.001, † p=0.02 McIntire D, Leveno K. Obstet Gynecol, 2008;111:37-41

Can we improve outcome of LP infants?

Study Design – Inclusion Criteria

- RCT of BMZ vs. matching placebo
- Singleton at 34 0/7 to 36 5/7 weeks
- One of 3 categories:
  - ROM
  - Preterm labor
  - Planned delivery for any indication
- Likely to deliver >12 hours from 1st dose
1st Outcome:
Respiratory Support or Death in 1st 72 hours
- CPAP or high-flow nasal cannula (HHFNC)
- Mechanical ventilation
- Oxygen requirement of $\text{FiO}_2 \geq 0.3$
- ECMO
- Stillbirth or neonatal death

ALPS Status
- 2792 of planned 2800 enrolled (end 2/2015)
- Completing follow-up (3 and 6 months)
- Expect results within next year

CONGENITAL CMV INFECTION PREVENTION TRIAL
(CMV Immune globulin)
Research Question

- Does antenatal administration of CMV immune globulin to pregnant women with primary CMV lower the risk of:
  1. Congenital CMV infection
  2. Infant neurologic morbidity at age 2

CMV

- 40,000 congenital infections / year
- Primary maternal infection
  - 40% fetal transmission
- CMV Immune globulin may prevent transmission and reduce sequelae.
  - Small observational study

<table>
<thead>
<tr>
<th></th>
<th>HIG</th>
<th>None</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital CMV transmission</td>
<td>16%</td>
<td>40%</td>
<td>0.04</td>
</tr>
<tr>
<td>Symptomatic CMV</td>
<td>3.2%</td>
<td>50%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

NIGRO, NEJM, 2005
### RCT of Hyperimmune globulin

<table>
<thead>
<tr>
<th></th>
<th>HIG (N=62)</th>
<th>Placebo (N=61)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital CMV</td>
<td>30%</td>
<td>44%</td>
<td>0.13</td>
</tr>
<tr>
<td>Adverse obstetric event (PTB, SGA)</td>
<td>13%</td>
<td>2%</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Revello, NEJM, 2014

### Design

- CMV serology – early (<24 weeks)
- Enroll into trial if positive for 1<sup>st</sup> CMV
  - Sero-conversion
  - IgM + low avidity IgG
- Randomization prior to 24 weeks
  - CMV Hyperimmune globulin (100m/kg)
  - Placebo (identical)

### CMV RCT Status

- 105,000 screened
- ~200 enrolled (N=800)
- Open to all patients
Thyroxine Therapy for Subclinical Hypothyroidism or Hypothyroxinemia During Pregnancy (TSH Trial)

Research Question
Is thyroxine treatment of women with a) subclinical hypothyroidism or b) hypothyroxinemia diagnosed in the first half of pregnancy associated with intellectual improvement in their offspring at age 5 years?
- Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III)

Subclinical thyroid dysfunction
- 3-4% of pregnant women
  - Subclinical hypothyroidism: ↑TSH, ↔ FT4
  - Hypothyroxinemia: ↔ TSH, ↓FT4
- Controversy regarding:
  - Association with low IQ in offspring
  - Ameliorated by treatment during pregnancy

Haddow, NEJM 1999
Design
- TFT screen – early (<21 weeks)
- Randomization prior to 21 weeks
  - Levothyroxine vs. identical placebo
- 2 strata
  - Subclinical hypothyroid (N=670)
  - Hypothyroxinemia (N=500)
- 1st outcome: Neurodevelopment at 5 years

TSH RCT Status
- 5-year follow-up complete this spring
- Results within 6-12 months
  - Universal TFTs during pregnancy?

STAN Trial
Automated Fetal ECG STANalysis (STAN) as adjunct for FHR Monitoring (N=11000)
Intrapartum monitoring

Continuous Intrapartum FHR Monitoring

Cesarean delivery rate

% US women cEFM in labor

Trends in CS and CP Rates


The 2008 National Institute of Child Health and Human Development Workshop Report on Electronic Fetal Monitoring

Update on Definitions, Interpretation, and Research Guidelines

Sponsored by:

NICHD
ACOG
SMFM
Category II: Indeterminate

- All tracings not categorized as Category I or III
- Appreciable fraction - 33%

Examples

- Moderate variability with bradycardia
- Minimal FHR variability
- Absent variability with no recurrent decels
- Recurrent variable decels with moderate variability
- Recurrent late decels with moderate variability

A Cat II tracing needs a back up test!

- Fetal scalp pH: < 3% of institutions in the U.S. (ACOG Survey of U.S. Hospitals)
- Others have never been proven or accepted: Continuous scalp pH, fetal pulse oximetry
- ST Analysis
  - developed for this purpose in mind
  - tested in these labor situations
  - the only currently FDA approved backup
Device Description (NEOVENTA)

- Std EFM capabilities:
  - External ultrasound or fetal spiral electrode (FSE)
  - TOCO or IUPC

- Fetal ECG (ST) Analysis

Basis for STAN Technology

"Labor puts the fetus on a treadmill"

What is being recorded?

- 30 ECG complexes
- T-wave amplitude is divided by the QRS amplitude which gives T/QRS ratio
**STAN clinical management**

**FHR Classification System for ST Analysis**

The intended use of this FHR classification system is to suggest clinical conditions in which adjunctive use of ST waveform changes may aid the interpretation of specific FHR patterns.

<table>
<thead>
<tr>
<th>FHR Classification</th>
<th>Baseline Heart Rate</th>
<th>Variability</th>
<th>Decelerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Green Zone</td>
<td>110-160 bpm</td>
<td>Moderate variability (5-30 bpm)</td>
<td>Early decelerations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate variability (5-30 bpm)</td>
<td>Marked variability (50% bpm) for &gt;40 minutes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Accelerations present</td>
<td>Variability decreases with a duration of &lt;40 sec or depth &gt;40 beats</td>
</tr>
<tr>
<td>Yellow Zone</td>
<td>Bradycardia &lt;100 bpm</td>
<td>Marked variability (50% bpm) for &gt;40 minutes</td>
<td>Recurrent late decelerations</td>
</tr>
<tr>
<td></td>
<td>Tachycardia &gt;160 bpm</td>
<td>Marked variability (50% bpm) for &gt;40 minutes</td>
<td>Prolonged deceleration for &gt;5% SL regardless of variability or reactivity</td>
</tr>
<tr>
<td>Red Zone</td>
<td>Abrasion variability regardless of other FHR patterns</td>
<td>Accelerated patterns</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Marked variability (50% bpm) for &gt;40 minutes</td>
<td></td>
</tr>
</tbody>
</table>

Note: The classification of FHR development for the STAN I-110 has been updated to conform with terminology and consistent with the NICHD FHR classification. Differences between the STAN classification and the NICHD classification relate to variable definitions in the Green Zone and absent variability in other FHR patterns in the Red Zone that are in Category II of the NICHD classification.

**ST Analysis**

These guidelines indicate situations in which obstetric intervention is required. An intervention may include delivery or maternal-fetal resuscitation by alleviation of contributing problems such as tachycardia, maternal hyperventilation, and hypotension.

<table>
<thead>
<tr>
<th>ST Event</th>
<th>No ST Event</th>
<th>Episodic, Baseline or Biphasic decay messages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Green Zone</td>
<td>Expectant management, continued observation</td>
<td>Expectant management, continued observation</td>
</tr>
<tr>
<td>Yellow Zone</td>
<td>Expectant management, closer observation</td>
<td>Direct physician assessment, Intravenous resuscitation as appropriate, Expedited delivery, In second stage with active pulling, expedited delivery</td>
</tr>
<tr>
<td>Red Zone</td>
<td>Expedient delivery regardless of any ST changes</td>
<td>Expedient delivery regardless of any ST changes</td>
</tr>
</tbody>
</table>

*The time span between the Biphasic messages should be related to the FHR pattern and the clinical situation.*
Examples of STAN Tracings: Category II
FHR

Second stage recording. NVD, Apgar 9-10 CA pH 7.18, C/S pH 7.27.

CS/ID, Apgar 8-9 CA pH 7.14, Bdecf 8.7 mmol/L, CV pH 7.34, Bdecf 6.3 mmol/L.

STAN clinical experience

Cochrane Review
Neonatal Encephalopathy
# Cochrane Review

**Cord pH \(< 7.05 +\) Base Deficit > 12 mmol/L**


## Table 1

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>ECG (OR)</th>
<th>No. ECG</th>
<th>Risk Ratio</th>
<th>95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cable 2004</td>
<td>127/194</td>
<td>5/72</td>
<td>1.51 (0.74 to 3.09)</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>Neovas 2007</td>
<td>12/81</td>
<td>4/40</td>
<td>1.57 (0.64 to 3.79)</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Neovas 1993</td>
<td>1/12</td>
<td>3/12</td>
<td>2.59 (0.36 to 19.66)</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td>1.87 (1.01 to 3.46)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Operative Vaginal Delivery**


## Table 2

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>ECG (OR)</th>
<th>No. ECG</th>
<th>Risk Ratio</th>
<th>95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciba 2004</td>
<td>220/147</td>
<td>12/75</td>
<td>2.13 (1.00 to 4.55)</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Valiosh 1999</td>
<td>11/89</td>
<td>6/53</td>
<td>1.41 (0.87 to 2.26)</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Neovas 1993</td>
<td>64/121</td>
<td>20/12</td>
<td>2.63 (1.35 to 5.11)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td>2.07 (1.14 to 3.75)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Cesarean Delivery**


## Table 3

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>ECG (OR)</th>
<th>No. ECG</th>
<th>Risk Ratio</th>
<th>95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cable 2004</td>
<td>315/205</td>
<td>22/13</td>
<td>1.58 (1.00 to 2.49)</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>Neovas 2007</td>
<td>150/109</td>
<td>10/15</td>
<td>1.04 (0.56 to 1.95)</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>Neovas 1993</td>
<td>39/24</td>
<td>16/20</td>
<td>1.58 (0.70 to 3.59)</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td>1.37 (0.84 to 2.24)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
A study in US?

- No RCT in North America
- Differences in practice patterns
  - Fetal pH sampling
  - Operative deliveries
  - Intermittent EFM
- Differences in population

Study Design - STAN

RCT: 2 groups

1. Fetal STAN electrode inserted and data available to caregivers (open group)
2. Fetal STAN electrode inserted, but data masked to the caregivers (masked group)

Primary Outcome

- Any of the following:
  - intrapartum fetal death
  - neonatal death
  - Apgar score ≤ 3 at 5 minutes
  - seizure(s)
  - cord artery pH ≤ 7.05 and BD ≥ 12
  - neonatal encephalopathy
  - Intubation for ventilation at delivery
Results

- N=11,108

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Open STAN</th>
<th>Masked STAN</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st outcome</td>
<td>1.4%</td>
<td>1.3%</td>
<td>0.43</td>
</tr>
<tr>
<td>Cesarean</td>
<td>17%</td>
<td>16%</td>
<td>0.29</td>
</tr>
<tr>
<td>Operative VD</td>
<td>6.0%</td>
<td>6.0%</td>
<td>0.79</td>
</tr>
</tbody>
</table>

Effect of Expanded Midwifery and Hospitalist Services on Primary Cesarean Rates

Rosenstein, SMFM 2015

Objective

- Impact of changing L&D care from:
  - a private practice model (individual Obs)
  - to 24-hr Obstetrician-midwife hospitalist model
Design

- Prospective (2005-2014)
- Before and after design
- Singletons
- Single community hospital

Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Before</th>
<th>After</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cesarean</td>
<td>32%</td>
<td>25%</td>
<td>0.007</td>
</tr>
<tr>
<td>VBAC</td>
<td>11%</td>
<td>23%</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Rates unchanged in publicly insured service with prior hospitalist model

PRESERVE-1 RCT
Goal
- Test antithrombin (recombinant) replacement for the treatment of early onset preeclampsia

PRESERVE-1 Rationale
Antithrombin
- Anticoagulant and anti-inflammatory
- Deficient in preeclampsia
- Promising preliminary studies
  - Pregnancy prolongation (1 week)
  - Higher birth weight
  - Lower SGA risk

PRESERVE-1 Design
- RCT
  - Antithrombin infusion
  - Placebo
- Inclusion criteria
  - Early onset preeclampsia
  - 23 0/7 to 29 6/7 weeks
  - Expectant management planned
- Outcomes: GA and Neonatal morbidity