MFMU Research Network
What’s New That Will Help You

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Salt Lake City, Utah

NICHD Maternal-Fetal Medicine Units Network

• Started in 1986.
• Competitively renewed every 5 years.
• Priorities include:
  – Reduce the rates of preterm birth, fetal growth abnormalities, neurologic sequelae of the newborn, and maternal complications of pregnancy, and,
  – Evaluate maternal and fetal interventions for efficacy, safety, and cost-effectiveness.
• Has become the premiere obstetric clinical trials network on the planet.
• Has accumulated 30 years of data and biologic samples.
Antenatal Corticosteroid Therapy for Fetal Maturation

**ABSTRACT:** Corticosteroid administration before anticipated preterm birth is one of the most important antenatal therapies available to improve neonatal outcomes. A single course of corticosteroids is recommended for pregnant women between 24 0/7 weeks and 35 6/7 weeks of gestation, including those with ruptured membranes and multiple gestations. It may also be considered for pregnant women starting at 24 0/7 weeks of gestation or who are at risk of preterm delivery within 7 days, based on a family's decision regarding resuscitation, irrespective of membranes rupture status and regardless of fetal number. Administration of betamethasone may be considered in pregnant women between 24 0/7 weeks and 35 6/7 weeks of gestation at imminent risk of preterm birth within 7 days, and who have not received a previous course of antenatal corticosteroids. A single repeat course of antenatal corticosteroids should be considered in women who are less than 34 0/7 weeks of gestation who have an imminent risk of preterm delivery within the next 7 days, and whose prior course of antenatal corticosteroids was administered more than 14 days previously. Possible course corticosteroids could be provided as early as 7 days from the prior dosages, if indicated by the clinical scenario. Continued surveillance of long-term outcomes after antenatal corticosteroid exposure should be supported. Quality improvement strategies to optimize appropriate and timely antenatal corticosteroid administration are encouraged.
Maternal Complications

- Pregnancies that continue beyond 39 weeks are associated with increased risks of:
  - Cesarean delivery
  - Operative vaginal delivery
  - 3rd and 4th degree lacerations
  - Febrile morbidity
  - Hemorrhage

**MFMU FOX: Cesarean**

- Statistical significance as compared to rate of cesarean delivery in the previous week gestation: *p<.05"
**Perinatal Complications**

- Pregnancies that continue beyond 39 weeks are associated with increased risks of:
  - Stillbirth
  - Meconium aspiration syndrome
  - Mechanical ventilation
  - Birth trauma
  - Neonatal seizures/ICH/encephalopathy
  - Neonatal sepsis
  - UA pH ≤7/BE < -12

**Perinatal Death**

- Perinatal death nadirs between 37-38 weeks and increases steadily thereafter

<table>
<thead>
<tr>
<th>Gestational Age</th>
<th>Loss Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>37</td>
<td>0.7/1000</td>
</tr>
<tr>
<td>38</td>
<td>1.3/1000</td>
</tr>
<tr>
<td>39</td>
<td>1.4/1000</td>
</tr>
<tr>
<td>40</td>
<td>2.4/1000</td>
</tr>
<tr>
<td>41</td>
<td>2.8/1000</td>
</tr>
</tbody>
</table>
Cord Gas Abnormalities
39 vs. 41 weeks

<table>
<thead>
<tr>
<th>Caughey et al, 2005 UA pH&lt;7.0</th>
<th>Caughey et al, 2005 BE&lt; -12</th>
<th>Hemistad et al, 2006 UA pH&lt;7.10</th>
</tr>
</thead>
<tbody>
<tr>
<td>39 weeks</td>
<td>0.78%</td>
<td>3.40%</td>
</tr>
<tr>
<td>41 weeks</td>
<td>1.09%</td>
<td>5.30%</td>
</tr>
</tbody>
</table>

Adjusted OR
- 39 weeks (1.65 (1.01, 2.77))
- 41 weeks (1.59 (1.17, 2.16))
- Hemistad et al, 2006 (1.6 (1.4, 1.9))

Severe Neonatal Complications

| 40 vs. 39 weeks: adjusted OR 1.47 (1.1, 2.0) |
| 41 vs. 39 weeks: adjusted OR 2.04 (1.5, 2.78) |

MFMU FOX: Neonatal adverse composite

<table>
<thead>
<tr>
<th>39w</th>
<th>40w</th>
<th>41w</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>3%</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>6%</td>
<td>7%</td>
<td></td>
</tr>
</tbody>
</table>

P = 0.047

When is the best time for delivery?

- Delivery
- Expectant management

39 - 41 weeks
**Induction and cesarean delivery: Common wisdom**

- Retrospective cohort studies
  - Induction of labor prior to 41 weeks of gestation is associated with an approximately 2-fold higher risk of cesarean delivery in nulliparous women

![Graph showing induction and cesarean delivery rates](image)

**Elective inductions only**

- [Yeast et al. AJOG 1999](#)

**When is the best time for delivery?**

- [Delivery](#)
- [Expectant management](#)

- 39 - 41 weeks

**Standard of Care**

- Patients undergoing induction of labor should be counseled about a 2-fold increased risk of cesarean

[ACOG #107 Obstet Gynecol 2009; 114:386-97](#)
The problem

• Spontaneously laboring women are not the right comparison group
  – Cannot choose between EIOL (strategy) and spontaneous labor (event)
  – Choice is between EIOL and expectant management
    • The latter may lead to spontaneous labor
    • Also conveys downstream possibilities that may increase the CS rate

<table>
<thead>
<tr>
<th>Stage</th>
<th>CS Rate</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous Labor 39 weeks</td>
<td>20%</td>
<td>100</td>
</tr>
<tr>
<td>IOL</td>
<td>35%</td>
<td>35</td>
</tr>
</tbody>
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<tbody>
<tr>
<td>39 weeks</td>
<td>Spontaneous Labor</td>
<td>30%</td>
</tr>
<tr>
<td>IOL</td>
<td>50%</td>
<td>100</td>
</tr>
<tr>
<td>Medical or Post dates</td>
<td>30%</td>
<td>35</td>
</tr>
</tbody>
</table>

Induction vs. Expectant Management

– RCT of women at 41 weeks of gestation (N = 3407)

Hannah et al., NEJM, 1992
IOL prior to 41 weeks: HYPITAT

- IOL vs. expectant management for mild hypertensive disease after 36 weeks (N = 756)
  - IOL
    - Adverse maternal composite: RR 0.71 (0.59-0.86)

Koopmans et al. Lancet 2009; 374:979-88

Induction vs. Expectant Management (CS%)

<table>
<thead>
<tr>
<th>Week of Induction</th>
<th>IOL</th>
<th>Spontaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>38 weeks</td>
<td>11.9%</td>
<td>7.0%</td>
</tr>
<tr>
<td>39 weeks</td>
<td>14.3%</td>
<td>9.1%</td>
</tr>
<tr>
<td>40 weeks</td>
<td>20.4%</td>
<td>10.9%</td>
</tr>
<tr>
<td>41 weeks</td>
<td>24.3%</td>
<td>14.9%</td>
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Caughey et al, AJOG 2006;195:700-5

Induction vs. Expectant Management (CS%)

<table>
<thead>
<tr>
<th>Week of Induction</th>
<th>IOL</th>
<th>Spontaneous</th>
<th>Expectant</th>
<th>aOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>38 weeks</td>
<td>11.9%</td>
<td>7.0%</td>
<td>13.3%</td>
<td>1.80 (1.29-2.53)</td>
</tr>
<tr>
<td>39 weeks</td>
<td>14.3%</td>
<td>9.1%</td>
<td>15.0%</td>
<td>1.39 (1.08-1.80)</td>
</tr>
<tr>
<td>40 weeks</td>
<td>20.4%</td>
<td>10.9%</td>
<td>19.0%</td>
<td>1.24 (1.27-1.62)</td>
</tr>
<tr>
<td>41 weeks</td>
<td>24.3%</td>
<td>14.9%</td>
<td>26.0%</td>
<td>1.26 (0.99-1.61)</td>
</tr>
</tbody>
</table>

Caughey et al, AJOG 2006;195:700-5

EIOIL vs. expectant management

- Retrospective Cohorts: Northwestern
  - 588 women at 39 weeks with favorable cervix
    - Power: 1/3 reduction in CS from 30% at EIOIL
  - 204 women at 39 weeks with unfavorable cervix
    - Power: 1/2 reduction in CS from 40% at EIOIL

Osmundson et al. Obstet Gynecol 2011; 117:583-7
Cesarean Delivery

Osmundson et al. Obstet Gynecol 2011; 117:583-7

EIOL vs. expectant management at 39 weeks

10% decreased odds of cesarean in EIOL group
Cheng et al AJOG 2012; Stock et al BMJ 2012

RCT of EIOL prior to 41 weeks

• Six small RCT’s
• None have found an increase in cesarean delivery
  – Poor quality
  – Underpowered

EIOL vs. expectant management at 39 weeks

70% decreased odds of mec aspiration and mortality, respectively, in EIOL group
Cheng et al AJOG 2012; Stock et al BMJ 2012
IOL & adverse neonatal outcome

- IOL/augmentation associated with ASD (OR 1.13)
  - Not supported consistently by other studies (e.g., Gale et al.)
  - Incorrect control group for clinical relevance
  - Inadequate adjustment for confounding
  - Use of incorrect coding for ASD

Elective Induction vs Expectant Management

- Retrospective cohort study
- California deliveries in 2006
- No prior cesareans
- 37 – 40 weeks gestation
- Elective induction compared to expectant management at each gestational age
- Vertex, non-anomalous, singleton deliveries (N = 362, 154)

- Overall CS rate: 16%
- Perinatal mortality: 0.2%
- NICU admission: 6.2%
- OR for CS was LOWER at all gestational ages and parity for EIOL!!
- EIOL NOT associated with severe lacerations, operative vaginal delivery, shoulder dystocia, etc.

Elective Induction vs Expectant Management

- OR for CS with EIOL
  - 37 weeks: 0.44 (0.34 – 0.57)
  - 38 weeks: 0.43 (0.38 – 0.50)
  - 39 weeks: 0.46 (0.41 – 0.52)
  - 40 weeks: 0.57 (0.50 – 0.65)
- EIOL increased hyperbilirubinemia at 37 and 38 weeks gestation

Darney et al. Obstet Gynecol 2013; 122:761-9
When is the best time for delivery?

39 - 41 weeks ??

Conclusions

- We know that at 41-42 weeks, IOL better than EM
- We know that before 39 weeks, EM better than IOL
- Between 39 and 41 weeks:
  - Common wisdom that EM is better than IOL
    - Maternal and neonatal outcomes worsen with delivery after 39 weeks
    - The concern that IOL increases CD is founded on methodologically flawed study design
  - Common practice is moving away from EM
  - We actually don’t know whether EM or IOL is better

Trends in IOL


Conclusions

An adequately powered study of elective induction of nulliparous women is needed
Induction in Nulliparous Women at 39 Weeks to Prevent Adverse Outcomes: A Randomized Controlled Trial

A Randomized Trial of Induction Versus Expectant Management (ARRIVE)

Design Summary

• N = 6000
  ➢ target 167 per month for 3 years
• Nulliparous women with a singleton pregnancy
• Randomized to one of two arms:
  ➢ Elective IOL
  ➢ Expectant management

Outcomes

• Composite perinatal morbidity
• Cesarean delivery
• Maternal and fetal outcomes
• Cost (including hospital)
• Patient satisfaction

Inclusion Criteria

1. Nulliparous - no previous pregnancy beyond 20 weeks

2. Singleton gestation - twin gestation reduced to singleton is not eligible unless reduced before 14 weeks project gestational age

3. Project gestational age at randomization is between 38,0 and 38,6
Exclusion Criteria

1. Project gestational age at date of first ultrasound is > 20 weeks 6 days
2. Plan for induction of labor prior to 40 weeks 5 days
3. Plan for cesarean delivery or contraindication to labor
   - such as prior uterine surgery, active HSV infection, breech or transverse presentation
4. Signs of labor
   - regular painful contractions with cervical change
5. Fetal demise or known major fetal anomaly
6. Heparin or low-molecular weight heparin during the current pregnancy
7. Placenta previa, accreta, vasa previa
8. Active vaginal bleeding greater than bloody show
9. Ruptured membranes
10. Cerclage in current pregnancy
11. Known oligohydramnios
   - AFI < 5 or MVP < 2
12. Fetal growth restriction
   - EFW < 10th percentile
13. Major maternal medical illness associated with increased risk for adverse pregnancy outcome
   - such as any diabetes mellitus, lupus, any hypertensive disorder, cardiac disease, renal insufficiency
14. Refusal of blood products
15. Participation in another interventional study that influences management of labor at delivery or perinatal morbidity or mortality
16. Delivery planned elsewhere at a non-Network site

Timing of Procedures

- Screen and Consent 34.0 to 38.6
- Randomize 38.0 to 38.6
  - Elective IOL Arm
    - Induce between 39.0 and 39.4 weeks
  - Expectant Management Arm
    - Weekly follow-up visits with their providers
    - Expectantly manage until at least 40.5 weeks, unless valid medical indication warrants delivery before 40.5 weeks
    - Initiate antepartum fetal testing no later than 41.6 weeks according to policies at each center
    - Induce between 40.5 and 42.2 weeks

The Intervention – Both Arms

Clinical Management of Induction

- Patients should be allowed adequate time to labor before considering the induction “failed” and proceeding to cesarean section
  - “failed” if at least 12 hours have elapsed since both rupture of membranes and use of a uterine stimulant and the patient remains in latent labor
- Otherwise, no attempt will be made to alter or mandate clinical management of the patients
ARRIVE

• Over 5,400 enrolled!

Induce everyone?

Not Yet!!!!!!

Paradigm Shift?

Stay Tuned!

What do you see? By shifting perspective you might see an old woman or a young woman.