The ARRIVE Study and Induction of Labor at Term: What Now?

Alan T. N. Tita, MD, PhD

Who Said This?
"Imagination is more important than knowledge. For knowledge is limited, whereas imagination embraces the entire world, stimulating progress, giving birth to evolution."

Disclosures
• No conflicts
Objectives

- To discuss the rationale for the ARRIVE trial
- To describe the design and results of the ARRIVE Trial
- To discuss the implications of the ARRIVE trial and potential impact on public health

When is the best time for delivery?

- ≥ 42 weeks: Delivery
- < 39 weeks: Expectant management
- 39 - 41 weeks: Neither

Increasing maternal and perinatal risks after 39 weeks
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

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>
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

Induction and cesarean delivery: Common wisdom

CD Risk - Elective inductions only

ACOG Recommendation

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

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 CD rate

<table>
<thead>
<tr>
<th>39 weeks N= 100</th>
<th>Spontaneous labor</th>
<th>CS rate=20% N=20</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOL</td>
<td>CS rate=35% N=35</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>39 weeks N= 100</th>
<th>50% Spontaneous labor at 39 weeks</th>
<th>CS rate=30% N=11</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOL</td>
<td>50% labor at 40 weeks</td>
<td>CS rate=40% N=14</td>
</tr>
</tbody>
</table>

35 weeks

<table>
<thead>
<tr>
<th>39 weeks N= 100</th>
<th>Medical or post dates IOL</th>
<th>CS rate=31%</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Induction vs. Spontaneous Labor

<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>
</tr>
</tbody>
</table>

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

### Induction vs. Expectant Management

<table>
<thead>
<tr>
<th>Week of Induction</th>
<th>IOL</th>
<th>Spontaneous</th>
<th>Expectant</th>
</tr>
</thead>
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<tr>
<td>38 weeks</td>
<td>11.9%</td>
<td>7.0%</td>
<td>13.3%</td>
</tr>
<tr>
<td>39 weeks</td>
<td>14.3%</td>
<td>9.1%</td>
<td>15.0%</td>
</tr>
<tr>
<td>40 weeks</td>
<td>20.4%</td>
<td>10.9%</td>
<td>19.0%</td>
</tr>
<tr>
<td>41 weeks</td>
<td>24.3%</td>
<td>14.9%</td>
<td>26.0%</td>
</tr>
</tbody>
</table>

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

### When is the best time for delivery?

- Delivery
- Expectant management

39 - 41 weeks
Conclusions

• At 41-42 weeks, IOL better than EM
• 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 (1:3 IOL)
• We actually don’t know whether EM or IOL is better

Conclusion

An adequately powered study of elective induction is needed
**Maternal Outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>EM (314)</th>
<th>IOL (304)</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cesarean Delivery</td>
<td>32%</td>
<td>33%</td>
<td>0.99 (.87 - 1.14)</td>
</tr>
<tr>
<td>Epidural use</td>
<td>35%</td>
<td>29%</td>
<td></td>
</tr>
</tbody>
</table>

*No differences in perinatal outcomes (underpowered)*

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**A Randomized Trial of Induction of labor Versus Expectant management of labor in nulliparous women (ARRIVE)**

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**Objective**

Test the hypothesis that elective IOL at 39 wks compared with expectant management among low-risk nulliparous women reduces the risk of a composite of perinatal mortality and severe neonatal morbidity.
Methods

• Randomized, controlled, un-masked trial
• Inclusion criteria
  • Nulliparous women
  • Singleton gestations
  • Reliably dated
  • No contraindication to vaginal delivery
  • Low risk (no indication for delivery at 39 wks)

Methods

• Randomized between 38 0/7 and 38 6/7 wks:
  • IOL (39 0/7 – 39 4/7)
  • EM
  • Forego elective delivery < 40 5/7
  • Be delivered ≤ 42 2/7
ARRIVE Protocol

• Do not induce expectant without indication
• Document cervical exam on admission
• Cervical ripening if modified Bishop <5
• ≥12 hours oxytocin + ROM before failed IOL diagnosis
• Avoid elective operative delivery

Primary outcome

• Composite describing perinatal mortality or severe morbidity
  • Fetal or neonatal death
  • Respiratory support within the first 72 hours of life
  • Apgar score ≤ 3 at 5 minutes
  • Hypoxic ischemic encephalopathy
  • Seizure
  • Infection
  • Meconium aspiration syndrome
  • Birth trauma
  • Intracranial or subgaleal hemorrhage
  • Hypotension requiring pressor support

Maternal outcomes

• Cesarean delivery
• Hypertensive disorder of pregnancy
• Postpartum hemorrhage
• Chorioamnionitis
• Postpartum infection
• Labor pain
• Labor Agentry Scale
Sample size = 6000

• Expected rate of the primary outcome: 3.5%
• Power: 85%
• Alpha: 5%
• RR decrease: 40%
• Compliance with group assignment: 92.5%

Results

The NEW ENGLAND JOURNAL of MEDICINE

Labor Induction versus Expectant Management in Low-Risk Nulliparous Women

Warren G. Goldstein, M.D., Melinda M. Rice, M.D., Uma M. Reddy, M.D., M.P.H., Allan T. Taffe, M.D., M.P.H.,
Robert W. Silver, M.D., Carl Whelton, M.D., D.M.Sc., D.C.C., Jin Hui, M.D., M.P.H., Elizabeth A. Thorp, M.D.,
Yasser Y. El-Sayed, M.D., Arvind P. Desai, M.D., Dwight J. Hu, M.D., George R. Saade, M.D.,
Kim A. Biggs, M.D., Carmen F. Charlie, M.D., Jerry J. Jaffe, M.D., David L. Chen, W.D., Louis M. Gotsky, M.D.,
and George A. Macleod, M.D., M.S.C. E., for the Eunice Kennedy Shriver National Institute of Child Health
and Human Development Maternal-Infant Medicine Trials Network.
Participant diagram

50,581 eligibility screening
27,600 ineligible
16,875 declined
6,106 randomized

3062 IOL
2 lost to F/U
2 withdraw
3099 analyzed

3044 EM
2 lost to F/U
5 withdraw
3037 analyzed

Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>IOL N = 3062</th>
<th>EM N = 3044</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age – yr</td>
<td>24 (21-28)</td>
<td>23 (20-28)</td>
</tr>
<tr>
<td>Race and ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>1227 (40.4)</td>
<td>1319 (43.7)</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>707 (23.1)</td>
<td>699 (23.0)</td>
</tr>
<tr>
<td>Asian</td>
<td>87 (2.8)</td>
<td>106 (3.5)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>866 (28.3)</td>
<td>808 (26.5)</td>
</tr>
<tr>
<td>Other or unknown</td>
<td>73 (2.4)</td>
<td>72 (2.4)</td>
</tr>
<tr>
<td>Private insurance for prenatal care</td>
<td>1404 (45.9)</td>
<td>135 (43.9)</td>
</tr>
<tr>
<td>Previous pregnancy loss</td>
<td>688 (22.6)</td>
<td>716 (23.8)</td>
</tr>
<tr>
<td>BMI ≥30 kg/m² at randomization</td>
<td>1633 (54.8)</td>
<td>1575 (52.0)</td>
</tr>
<tr>
<td>Modified Bishop score at randomization &gt;5</td>
<td>1919 (62.7)</td>
<td>1954 (64.2)</td>
</tr>
</tbody>
</table>

Data are presented as median (interquartile range) or N (%)

Results

• IOL vs. EM:
  • 39.3 vs. 40.0 wks, P < .001
  • 3300g vs. 3380g, P < .001
  • 94% vs. 95% protocol adherence
### Primary perinatal composite

<table>
<thead>
<tr>
<th>IOL</th>
<th>EM</th>
<th>RR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.3%</td>
<td>5.4%</td>
<td>0.80</td>
<td>0.639 - 0.999</td>
<td>0.049</td>
</tr>
</tbody>
</table>

* P<0.046 indicates statistical significance

### Perinatal outcomes

<table>
<thead>
<tr>
<th></th>
<th>IOL</th>
<th>EM</th>
<th>RR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory support</td>
<td>0.3%</td>
<td>4.2%</td>
<td>0.71</td>
<td>0.33 - 1.48</td>
<td></td>
</tr>
<tr>
<td>Perinatal death</td>
<td>0.1%</td>
<td>0.1%</td>
<td>0.66</td>
<td>0.32 - 1.33</td>
<td></td>
</tr>
<tr>
<td>Apgar ≤ 3 at 5 minutes</td>
<td>0.4%</td>
<td>0.6%</td>
<td>0.66</td>
<td>0.32 - 1.37</td>
<td></td>
</tr>
<tr>
<td>HIE</td>
<td>0.4%</td>
<td>0.6%</td>
<td>0.68</td>
<td>0.34 - 1.37</td>
<td></td>
</tr>
<tr>
<td>Seizure</td>
<td>0.4%</td>
<td>0.1%</td>
<td>2.73</td>
<td>0.91 - 8.12</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>0.3%</td>
<td>0.4%</td>
<td>0.74</td>
<td>0.31 - 1.76</td>
<td></td>
</tr>
<tr>
<td>SGA</td>
<td>0.6%</td>
<td>0.9%</td>
<td>0.65</td>
<td>0.35 - 1.19</td>
<td></td>
</tr>
<tr>
<td>Birth trauma</td>
<td>0.5%</td>
<td>0.6%</td>
<td>0.77</td>
<td>0.38 - 1.55</td>
<td></td>
</tr>
<tr>
<td>ICH or subgaleal hemorrhage</td>
<td>0.3%</td>
<td>0.2%</td>
<td>1.28</td>
<td>0.48 - 3.42</td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>0.1%</td>
<td>0.2%</td>
<td>0.40</td>
<td>0.06 - 1.79</td>
<td></td>
</tr>
</tbody>
</table>

### Cesarean delivery

<table>
<thead>
<tr>
<th>IOL</th>
<th>EM</th>
<th>RR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.6%</td>
<td>22.2%</td>
<td>0.84</td>
<td>0.76 - 0.93</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
## Maternal outcomes

<table>
<thead>
<tr>
<th>Condition</th>
<th>IOL %</th>
<th>EM %</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertensive disorder of pregnancy</td>
<td>9.1</td>
<td>14.1</td>
<td>0.64</td>
<td>0.56 -0.74</td>
</tr>
<tr>
<td>Chorioamnionitis</td>
<td>13.3</td>
<td>14.1</td>
<td>0.94</td>
<td>0.83 -1.07</td>
</tr>
<tr>
<td>Third or fourth degree perineal laceration</td>
<td>3.4</td>
<td>2.9</td>
<td>1.15</td>
<td>0.87 -1.52</td>
</tr>
<tr>
<td>Postpartum hemorrhage</td>
<td>4.6</td>
<td>4.5</td>
<td>1.03</td>
<td>0.82 -1.29</td>
</tr>
<tr>
<td>Postpartum infection</td>
<td>1.6</td>
<td>2.1</td>
<td>0.76</td>
<td>0.53 -1.10</td>
</tr>
<tr>
<td>ICU admission</td>
<td>0.1</td>
<td>0.3</td>
<td>0.50</td>
<td>0.13 -1.55</td>
</tr>
</tbody>
</table>

All data are presented as medians (interquartile range)
Summary

- Labor induction:
  - No change in perinatal composite outcome...
  - Lower frequency of
    - Neonatal respiratory support
    - Cesarean delivery
    - Hypertensive disorder of pregnancy
  - Lower perceived pain in labor
  - Greater perceived control during childbirth process
  - Longer stay on L&D by 6 hours

Interpretation – Population level

<table>
<thead>
<tr>
<th>Condition</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cesarean delivery</td>
<td>28</td>
</tr>
<tr>
<td>Neonatal respiratory support</td>
<td>83</td>
</tr>
<tr>
<td>Hypertensive disorder of pregnancy</td>
<td>20</td>
</tr>
</tbody>
</table>
ACOG and SMFM

• Reasonable to offer elective IOL to low risk nullips
• Conditional upon the values and preferences of the woman
  • Shared decision-making
• System in place to accommodate increased IOL
• Non-intervention in the latent phase unless indicated for maternal-fetal reasons (avoid unnecessary cesarean)
  • Latent phase of IOL 24 hours or longer
  • At least 12-18 hours of ROM + oxytocin
• Uncertain if applicable to multiparous
• Evaluate real-life implementation

Future Directions/Issues

• Evaluate real-life implementation
• What to do with multiparous?
• Cost effectiveness
• Outpatient ripening
So What at UAB?

• Offer eIOL to low risk patients (390-396/7)
  • Including multips (evaluate)
  • Reliable dating (US <21 weeks)
• Increased IOL slots by 1/day (n=7)
• Overflow to triage if necessary
• Evaluate outpatient cervical ripening (foley)

Albert Einstein, 1929

"Imagination is more important than knowledge. For knowledge is limited, whereas imagination embraces the entire world, stimulating progress, giving birth to evolution."
### Effect modification (subgroups)?

<table>
<thead>
<tr>
<th></th>
<th>Primary composite</th>
<th>CD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race/ethnicity</td>
<td>0.72</td>
<td>0.23</td>
</tr>
<tr>
<td>Modified Bishop &lt;5</td>
<td>0.93</td>
<td>1.00</td>
</tr>
<tr>
<td>BMI ≥ 30 kg/m²</td>
<td>0.76</td>
<td>0.10</td>
</tr>
<tr>
<td>Maternal age &gt; 35 years</td>
<td>0.70</td>
<td>0.51</td>
</tr>
</tbody>
</table>
IOL & Adverse neonatal outcome

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

Conclusion

- Strengths
  - Size
  - Strict criteria for dating
  - Generalizability?

Conclusion

- Limitations
  - Not masked
  - Low power to detect differences in infrequent outcomes