RESPIRATORY DISORDERS IN THE LATE-PRETERM INFANT

Pediatric Grand Rounds
July 16, 2009

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University at Buffalo
Women & Children’s Hospital of Buffalo

Disclosure

- I have no financial relationship with any manufacturer of any commercial product and/or provider of commercial services discussed in the CME activity.
- I do not intend to discuss an unapproved/investigative use of a commercial product or device in my presentation.

Late-Preterm Infants

- Increasing in occurrence
- Increased respiratory morbidity
  - Worsened by Cesarean delivery (CD)
  - Worsened by delivery without labor
- Also have
  - Increased mortality
  - Increased non-respiratory morbidities

Preterm births
US, 1996-2006

Late preterm births
US, 1996-2006
Late preterm births by maternal age

US, 2006

Percent of live births

Late preterm is between 34 and 36 completed weeks gestation.


Total cesarean deliveries

US, 1996-2006

Percent of live births


### TABLE 1
**Demographic Data for the Preterm and Term Groups**

<table>
<thead>
<tr>
<th></th>
<th>Preterm*</th>
<th>Term**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total births, n</td>
<td>6454</td>
<td>88,988</td>
</tr>
<tr>
<td>Live births, n</td>
<td>6381</td>
<td>88,867</td>
</tr>
<tr>
<td>Stillbirths, n</td>
<td>73</td>
<td>121</td>
</tr>
<tr>
<td>Total neonatal deaths, n</td>
<td>24</td>
<td>60</td>
</tr>
<tr>
<td>Preterm neonatal deaths, n</td>
<td>12</td>
<td>82</td>
</tr>
<tr>
<td>Preterm infant mortality rate*</td>
<td>13.79</td>
<td>1.72</td>
</tr>
<tr>
<td>Term infant mortality rate**</td>
<td>5.64</td>
<td>1.60</td>
</tr>
<tr>
<td>Neoregional survival rate**</td>
<td>990.58</td>
<td>990.52</td>
</tr>
</tbody>
</table>

* Preterm denotes birth from 339 / 7 to 366 / 7 weeks of gestation.
** Term denotes birth from 37/0 to 40/6 weeks of gestation.
* Rates per thousand total births.
** Rates per thousand live births.


### FIGURE 1

RR of mortality, preterm versus term. Error bars represent 95% CIs.

Kashu et al *Pediatrics* 2009;123:109-113

### FIGURE 3

RR of maternal complications, preterm versus term. Error bars represent 95% CIs.

Kashu et al *Pediatrics* 2009;123:109-113
Changes in the Gestational Age Distribution among U.S. Singleton Births: Impact on Rates of Late Preterm Birth, 1992 to 2002

Michael J. Davidoff, M.P.H.1, Todd Dias, M.S.1, Karlene Demer, R.N., Ph.D.1, Rebecca Russell, M.B.A.1, Van Bettiwenda, M.D.1,2, Stephen DeLain, M.D., M.P.H.2,3, Richard H. Schwartz, M.D.1,4, Nancy St. Green, M.D.1,4, and Joseph Petron, M.D., M.P.H.1,4

- 2006; p00-B-12
- Data from all certificates of live births submitted through the Vital Statistics Cooperative Program
- Only singletons – 3.8 million in 2002
- Excluded if the gestational age was <23 weeks, >44 weeks, or if birth weight was <500 g or unknown

Davidoff et al., Sem Perinatol 2006

- 1992 Peak: 40 weeks
  Average: 39.4 weeks
- 2002 Peak: 39 weeks
  Average: 38.9 weeks

De Luca et al., Pediatrics 2009;123:c1064-1071 • Geneva Univ, Switzerland

- All: n=50,126
  Elective CS: n = 2974
  Planned VD: n = 30,295
  Missing values: n = 719

- Emergency CS: n = 1,233
  Planned VD: n = 1,213

CS increasing (DeLaca et al, Pediatrics 2009)
Mortality

Difference in ECD vs. PVD more apparent in term infants

<table>
<thead>
<tr>
<th></th>
<th>ECD</th>
<th>PVD</th>
<th>RR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Term</td>
<td>0.41%</td>
<td>0.12%</td>
<td>3.22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Late-Preterm</td>
<td>1.34%</td>
<td>0.79%</td>
<td>1.79</td>
<td>0.323</td>
</tr>
</tbody>
</table>

But note the difference between Term and Late-Preterm

<table>
<thead>
<tr>
<th></th>
<th>ECD</th>
<th>EmCD</th>
<th>RR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Term</td>
<td>0.41%</td>
<td>0.42%</td>
<td>0.97</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Late-Preterm</td>
<td>1.34%</td>
<td>1.89%</td>
<td>0.71</td>
<td>0.605</td>
</tr>
</tbody>
</table>

Respiratory Morbidity

<table>
<thead>
<tr>
<th></th>
<th>ECD</th>
<th>PVD</th>
<th>RR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Term</td>
<td>3.5%</td>
<td>1.7%</td>
<td>2.05</td>
<td>0.001</td>
</tr>
<tr>
<td>Late-Preterm</td>
<td>18.9%</td>
<td>8.8%</td>
<td>2.15</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Respiratory morbidity is significantly higher in infants with PVD compared to ECD and EmCD.

DeLuca et al, Pediatrics 2009; 123:1064-1071
Late Preterm

- For 34 weekers 69% went to SCN after ECD, 47% after PVD

DeLuca et al, Pediatrics 2009; 123:1064-1071

Why are ECS increasing?

- Maternal risks have decreased
- Perceived risk for the neonate is small
- Convenience for mom / family
- Convenience for OB and staff

DeLuca et al, Pediatrics 2009; 123:c1064-c1071

People magazine Oct 26, 2009

Tell us your labor story.

I was asleep and all of a sudden I felt pressure and my water broke. I wasn’t in pain—I almost went back to bed because I was sleepy! David was losing his mind over which car to take. We got to the hospital at noon, when my labor pains started. I wanted to know how they felt even though I was having a CaCes. The doctor went on until 5 o’clock. By then I said, “I don’t want to feel anything else!” And David got to tell me what (sex) it was. He said “It’s Little David!” When I saw him, I mean, it was like a waterfall.

Leveno, Ob Gyn, 2008; 114(1):80-81

Rising Cesarean Delivery and Preterm Birth Rates


Complications of the Late-Preterm Infant

(Darcy, AE, J Perinat Neo Nurs 2009;23(1):78-86)


Fig. 3. Frequency of morbidity in late preterm (“near-term”) versus full-term newborns. From Wang et al, 2007.
Risk of Non-Respiratory Complications
(∼2500 late-preterm deliveries and 7400 term deliveries)

Risk of NEC

Late-preterm infants have an increased risk of apnea of prematurity

- ACOG Committee Opinion, April 2008;111(4):1029-1032
- Raju et al, Peds 2006;118:1207-1214
- Hunt, Semin Perinatol 2006;30:73-76.
- Wang et al, Pediatrics 2004;114;372-376

Table 1. Apnea of Prematurity and Related Discharge

<table>
<thead>
<tr>
<th>Gestational Age (weeks)</th>
<th>Discharge Unaffected</th>
<th>Discharge Deferred</th>
<th>Total Babies</th>
</tr>
</thead>
<tbody>
<tr>
<td>34</td>
<td>20 (7.4)</td>
<td>22 (8.0)</td>
<td>22 (8.0)</td>
</tr>
<tr>
<td>35</td>
<td>20 (7.4)</td>
<td>22 (8.0)</td>
<td>22 (8.0)</td>
</tr>
<tr>
<td>36</td>
<td>20 (7.4)</td>
<td>22 (8.0)</td>
<td>22 (8.0)</td>
</tr>
<tr>
<td>37</td>
<td>20 (7.4)</td>
<td>22 (8.0)</td>
<td>22 (8.0)</td>
</tr>
<tr>
<td>38</td>
<td>20 (7.4)</td>
<td>22 (8.0)</td>
<td>22 (8.0)</td>
</tr>
</tbody>
</table>

Dissected CHIME study data

- The relative risk for one extreme event in the late-preterm infants tested because of an ALTE or SIDS sibling was 5.6 and 7.6 respectively compared with term infants.
- The chance of having at least one extreme event remained higher in late preterm infants compared with full term infants until 43 weeks.

Darnall, Clinics in Perinatology 2006;33:883-914

Late-Preterm Birth: Does the changing obstetric paradigm alter the epidemiology of respiratory complications?

- Wilford Hall, San Antonio TX
- All deliveries ≥ 34 weeks over a 9 year period
- Tocolysis and ANS not routine for this gestation

Yoder et al, Ob Gyn, 2008

Yoder et al, Ob Gyn, March 2008
Resp diagnoses and morbidity - ≥34 weeks

- 705 infants had a resp dx → 5% of all infants
  - 75% either TTN or pneumonia
  - Any resp dx increased as you moved away from 39 0/7 – 40 6/7 range (P<0.001)
- 204 infants had clinically significant resp morbidity
  - (any mechanical ventilation or supplemental oxygen for more than 24h) → 1.4% of all infants
  - Resp morbidity also increased as you moved away from 39 0/7 – 40 6/7 range

Yoder et al, Ob Gyn, March 2008

### Clinically significant resp morbidity (O2 >24h or any MV)

<table>
<thead>
<tr>
<th>GA (wk)</th>
<th>Reference</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>34</td>
<td>28.4 (14.4–56.6)</td>
<td>28.4 (14.4–56.6)</td>
</tr>
<tr>
<td>35</td>
<td>20.3 (9.9–41.0)</td>
<td>20.3 (9.9–41.0)</td>
</tr>
<tr>
<td>36</td>
<td>4.3 (2.2–7.0)</td>
<td>4.3 (2.2–7.0)</td>
</tr>
<tr>
<td>37</td>
<td>1.5 (0.8–2.9)</td>
<td>1.5 (0.8–2.9)</td>
</tr>
<tr>
<td>38</td>
<td>1.5 (0.8–2.3)</td>
<td>1.5 (0.8–2.3)</td>
</tr>
<tr>
<td>&gt;40</td>
<td>1.8 (0.9–3.2)</td>
<td>1.8 (0.9–3.2)</td>
</tr>
</tbody>
</table>

Yoder et al, Ob Gyn, March 2008

### Respiratory Morbidity (O2 >24h or any MV)

#### Table 3. Risk Factors Associated With Development of Respiratory Morbidity Among a 9-Year Cohort of Infants Born at More Than 34 Weeks of Gestation

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio by Cesarean Delivery (95% CI)</th>
<th>Odds Ratio by Cesarean Delivery Mode (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELGA (wk)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>34</td>
<td>28.4 (14.4–56.6)</td>
<td>28.4 (14.4–56.6)</td>
</tr>
<tr>
<td>35</td>
<td>20.3 (9.9–41.0)</td>
<td>20.3 (9.9–41.0)</td>
</tr>
<tr>
<td>36</td>
<td>4.3 (2.2–7.0)</td>
<td>4.3 (2.2–7.0)</td>
</tr>
<tr>
<td>37</td>
<td>1.5 (0.8–2.9)</td>
<td>1.5 (0.8–2.9)</td>
</tr>
<tr>
<td>38</td>
<td>1.5 (0.8–2.3)</td>
<td>1.5 (0.8–2.3)</td>
</tr>
<tr>
<td>&gt;40</td>
<td>1.8 (0.9–3.2)</td>
<td>1.8 (0.9–3.2)</td>
</tr>
<tr>
<td>Delivery</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Vaginal</td>
<td>C/S</td>
<td>C/S</td>
</tr>
<tr>
<td>Cesarean</td>
<td>2.1 (1.4–3.1)</td>
<td>2.1 (1.4–3.1)</td>
</tr>
<tr>
<td>Cesarean</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Cesarean</td>
<td>Upper ceasrean</td>
<td>Upper crusarean</td>
</tr>
<tr>
<td>Weight</td>
<td>2.5 (1.8–3.4)</td>
<td>2.5 (1.8–3.4)</td>
</tr>
<tr>
<td>Blood</td>
<td>0.9 (0.4–2.1)</td>
<td>0.9 (0.4–2.1)</td>
</tr>
<tr>
<td>Venous</td>
<td>0.8 (0.4–1.3)</td>
<td>0.8 (0.4–1.3)</td>
</tr>
<tr>
<td>Male gen</td>
<td>1.5 (1.1–2.0)</td>
<td>1.5 (1.1–2.0)</td>
</tr>
<tr>
<td>Nontattering FHR</td>
<td>2.1 (1.5–3.0)</td>
<td>2.1 (1.5–3.0)</td>
</tr>
<tr>
<td>5 min Appar score</td>
<td>11.7 (8.1–16.1)</td>
<td>11.7 (8.1–16.1)</td>
</tr>
</tbody>
</table>

Yoder et al, Ob Gyn, March 2008

#### Logistic regression

- 5 factors independently related to resp morbidity:
  - GA, C/S, male, FHR, low 5 min Appar

Yoder et al, Ob Gyn, March 2008

### Compared with 39 weeks, reference group

#### Table 4. Adjusted odds ratios of perinatal outcomes using multivariable logistic regression analysis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory morbidity</td>
<td>3.2 (2.4–4.1)</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>2.0 (1.6–2.5)</td>
</tr>
<tr>
<td>Intrauterine growth</td>
<td>1.9 (1.7–2.1)</td>
</tr>
</tbody>
</table>

Indications for delivery and short-term neonatal outcomes in late-preterm as compared with term births • Lubow et al, ACOG May 2009

- Univ Cincinnati
- 2005-2006 singletons only
- 149 late-preterm infants
  - 49-34 weeks (34.07-34.67 weeks)
  - 50-35 weeks
  - 50-36 weeks
- 150 term infants
  - 50-37 weeks
  - 50-38 weeks
  - 50 = 39 weeks

Table 1

<table>
<thead>
<tr>
<th>Weeks of gestation</th>
<th>Indications (n=50)</th>
<th>32</th>
<th>33</th>
<th>34</th>
<th>35</th>
<th>36</th>
<th>37</th>
<th>38</th>
<th>39</th>
<th>≥39</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm delivery</td>
<td></td>
<td>5</td>
<td>10</td>
<td>15</td>
<td>15</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Hypertensive disorder</td>
<td></td>
<td>4</td>
<td>5</td>
<td>10</td>
<td>15</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Umbilical cord prolapse</td>
<td></td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Spontaneous rupture of membranes</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Spontaneous labor</td>
<td></td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Spontaneous rupture of membranes</td>
<td>45</td>
<td>40</td>
<td>45</td>
<td>40</td>
<td>38</td>
<td>41</td>
<td>38</td>
<td>36</td>
<td>21</td>
<td>24</td>
</tr>
<tr>
<td>Spontaneous labor</td>
<td></td>
<td>15</td>
<td>18</td>
<td>13</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

>230,000 singleton births, 1998-2005, Parkland Memorial Hospital

Risk of ventilation, TTN

Neonatal death rate (per 1000 live births)

McIntire and Leveno, Ob Gyn 2008; 111:35-42 • Parkland Memorial Hospital

Risk of Respiratory Disease (<2500 late-preterm deliveries and 7400 term deliveries)

Melamed et al, Obstet Gynecol 2009;114:353–60 • Tel Aviv Israel
Risk of Respiratory Complications

- Risk of respiratory complications as defined in the Methods section for gestational week. Presented are the rates of composite mortality, mortality (apneic/oxic-enfact), admission to neonatal intensive care unit (NICU), airflow abnormalities, respiratory mortality (defined as cyanotic and infectious mortality) during an 60-hour period at gestational weeks 24–36.

Melamed et al., Obstet Gynecol 2009;114:253–60, Tel Aviv, Israel

**Fig. 2.**

- Late-preterm babies
  - 50% of their late-preterm babies went to SCN
  - 23-34% required mechanical ventilation
  - "This causes a lot of anxiety to the parents who are expecting to room in with their baby after birth."


**Table 3.**

<table>
<thead>
<tr>
<th>Gestionate age in weeks</th>
<th>34</th>
<th>35</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of babies</td>
<td>252</td>
<td>240</td>
<td>279</td>
</tr>
<tr>
<td>Median weight gain (kg)</td>
<td>2.07 (0.90-4.00)</td>
<td>2.00 (1.18-4.10)</td>
<td>2.76 (0.52-4.52)</td>
</tr>
<tr>
<td>Median length of stay (days)</td>
<td>11 (6-20)</td>
<td>16 (11-60)</td>
<td>16 (10-100)</td>
</tr>
<tr>
<td>Median age at full-term birth (days)</td>
<td>10 (5-20)</td>
<td>10 (3-40)</td>
<td>10 (2-100)</td>
</tr>
<tr>
<td>PNN &amp; PTX</td>
<td>0.02 (0.00-0.05)</td>
<td>0.03 (0.00-0.05)</td>
<td>0.04 (0.00-0.05)</td>
</tr>
<tr>
<td>Respiratory mortality, a (%)</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
<td>0.0 (0.00)</td>
</tr>
<tr>
<td>Infectious mortality, a (%)</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
</tr>
<tr>
<td>Death at discharge, a (%)</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
</tr>
<tr>
<td>Necrotizing enterocolitis, a (%)</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>182 (73)</td>
<td>189 (79)</td>
<td>142 (50)</td>
</tr>
<tr>
<td>Death</td>
<td>7 (2)</td>
<td>12 (5)</td>
<td>23 (9)</td>
</tr>
<tr>
<td>Necrotizing enterocolitis, a (%)</td>
<td>78 (31)</td>
<td>61 (25)</td>
<td>28 (10)</td>
</tr>
<tr>
<td>Death at discharge, a (%)</td>
<td>182 (73)</td>
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</tr>
</tbody>
</table>


**Table 4.**

- "Tweeners" A little bit of RDS AND a little bit of TTN

- "This causes a lot of anxiety to the parents who are expecting to room in with their baby after birth."

Late Preterm 34 0/7 - 36 6/7

- Infant mortality rate - 3-5 fold higher than term infants
- 1 medical condition diagnosed - 4 times more likely than term
- 2 conditions - 3.5 times more likely
- Later increased risk of RSV infection in these infants.

Colin, McEvoy, Castille, Peds 2010, 126:115-128

"Newborn morbidity" in LPT (Massachusetts, 1998-2003)

- Defined as meeting any of the following during birth hospitalization:
  - Hospital stay of >5 nights and an ICD-9 code for something other than a non-life threatening condition (blinded)
  - Gestational age at birth
  - Birthmarks, Lipomas, Hemangiomas of skin
  - Hearing loss
  - Nasolacrimal stenosis, Teeth and periodontal conditions
  - Dermatitis and diaper rash non-drug related
  - Other benign skin disorders, scalp injury at birth
  - Polydactyly
  - NB hosp stay of >5 nights and transfer to a higher level medical facility
  - Death before hospital discharge

Shapiro-Mendoza et al, Pediatrics 2008;121:e223-e232

"Newborn morbidity" in LPT

- 377, 638 term and 26, 70 late-preterm
- 22.2% of the late-preterm infants versus 3.0% of the term infants had newborn morbidity during their birth hospitalization
- reference group - 40 weeks
- 36 weeks' GA Æ 5-fold increased risk
- 35 weeks' GA Æ 10-fold increased risk
- 34 weeks' GA Æ 20-fold increased risk
- Relative morbidity increased approximately twofold with every week of decreasing GA earlier than 36 weeks' GA

Shapiro-Mendoza et al, Pediatrics 2008;121:e223-e232

Prenatal Corticosteroid Prophylaxis for Women Delivering at Late Preterm Gestation

Antenatal Steroids for Term Elective Caesarean Section (ASTECS)

- Stutchfield et al. BMJ 2005;331(7518):662
- United Kingdom
- Objective: To test whether steroids reduce respiratory distress in babies born by elective caesarean section at term.
- 998 moms, ECS planned for ≥37 weeks
- Randomized to beta vs. no treatment (not blinded)
- Primary outcome was admission to SCN for respiratory distress
  - RR>60, with grunting, flaring or retracting, at <24h of age
  - NNT to prevent 1 case of RDS or even 1 NICU admission would be quite high.
  - for pregnancies <31 weeks NNT is 5 to prevent 1 case of RDS
  - 31-34 weeks, NNT approximately 15
  - at term this number would exceed 100

Bonanno and Wapner AJOG April 2009
Antenatal corticosteroid treatment: What’s happened since Drs Liggins and Howie? ANS for ECS at term?

- But term infants, even after ECS, have a very low incidence of resp morbidity → NNT to prevent 1 case of RDS or even 1 NICU admission would be quite high.
  - for pregnancies <31 weeks NNT is 5 to prevent 1 case of RDS
  - 31-34 weeks, NNT approximately 15
  - at term this number would exceed 100

Simply wait until 39 weeks ☺

Stutchfield et al BMJ 2005
Resp disorders in babies born at 34-36 weeks after ANS

- Retrospective study
- All babies born Jan 2000 – Dec 2004 at 34-36 weeks
- 1078 babies
- 94% admitted to the NICU
- No transitional nursery - all neonates born with birthweights <2500 g who developed respiratory disorders or temperature instability were admitted to the NICU

General data: Total 1078 babies, 94% admitted to NICU, no transitional nursery.

- 574 (53.2%) exposed to ANS
- 470 (43.6%) not exposed to ANS
- 34 (3.2%) unable to assess ANS exposure


Table 2 Exposure to Corticosteroids and Respiratory Disorders among Neonates Admitted to the NICU

<table>
<thead>
<tr>
<th>Total</th>
<th>Exposure to Corticosteroids</th>
<th>No Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of stay in the NICU (d)</td>
<td>7 ± 4</td>
<td>22 ± 10</td>
</tr>
<tr>
<td>All respiratory disorders</td>
<td>140</td>
<td>382</td>
</tr>
<tr>
<td>RDS</td>
<td>43</td>
<td>167</td>
</tr>
<tr>
<td>Need for ventilation</td>
<td>24</td>
<td>70</td>
</tr>
<tr>
<td>CPAP</td>
<td>43</td>
<td>82</td>
</tr>
<tr>
<td>Prolonged oxygenation</td>
<td>30</td>
<td>63</td>
</tr>
</tbody>
</table>

NICU, neonatal intensive care unit; RDS, respiratory distress syndrome; CPAP, continuous positive airway pressure.


Beneficial effect of ANS was present at 34, 35 and 36 weeks.


Respiratory Disorders

- Primary outcome - incidence of RDS
  - defined as need for intubation and ventilation, CPAP and/or surfactant administration, and confirmed by radiology
  - Also assessed the overall need for respiratory assistance
    - use of ventilation and the need for CPAP and supplemental oxygen for >24 hours


Table 3 Respiratory Disorders by Gestational Age and Exposure to Corticosteroids

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Exposure to Corticosteroids</th>
<th>No Exposure</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>34 weeks</td>
<td>98</td>
<td>25</td>
<td>0.002</td>
</tr>
<tr>
<td>RDS</td>
<td>11</td>
<td>4</td>
<td>0.050</td>
</tr>
<tr>
<td>Ventilation</td>
<td>8</td>
<td>24</td>
<td>0.004</td>
</tr>
<tr>
<td>CPAP</td>
<td>16</td>
<td>20</td>
<td>0.072</td>
</tr>
<tr>
<td>Prolonged O2</td>
<td>7</td>
<td>24</td>
<td>0.0004</td>
</tr>
<tr>
<td>35 weeks</td>
<td>106</td>
<td>46</td>
<td>0.0001</td>
</tr>
<tr>
<td>RDS</td>
<td>11</td>
<td>4</td>
<td>0.0001</td>
</tr>
<tr>
<td>Ventilation</td>
<td>8</td>
<td>24</td>
<td>0.0001</td>
</tr>
<tr>
<td>CPAP</td>
<td>16</td>
<td>20</td>
<td>0.0001</td>
</tr>
<tr>
<td>Prolonged O2</td>
<td>12</td>
<td>17</td>
<td>0.1</td>
</tr>
<tr>
<td>36 weeks</td>
<td>114</td>
<td>52</td>
<td>0.0001</td>
</tr>
<tr>
<td>RDS</td>
<td>12</td>
<td>4</td>
<td>0.0001</td>
</tr>
<tr>
<td>Ventilation</td>
<td>8</td>
<td>29</td>
<td>0.008</td>
</tr>
<tr>
<td>CPAP</td>
<td>12</td>
<td>20</td>
<td>0.01</td>
</tr>
<tr>
<td>Prolonged O2</td>
<td>11</td>
<td>22</td>
<td>0.02</td>
</tr>
</tbody>
</table>

RDS, respiratory distress syndrome; CPAP, continuous positive airway pressure; O2, oxygen.


Limitations

- Retrospective
- ANS timing not always known
- High percent of NICU admission
- Does receiving ANS correlate with something else?
  - Stress during pregnancy, eg preterm labor, better prenatal care, etc.
Why are Late-Preterm Infants at Increased Risk for Postnatal Respiratory Problems?

Facilitation of the transition to air breathing

Fetal Lung
- Lungs actively secreting lung fluid into the alveolar spaces
- Surfactant system immature
- High pulmonary vascular resistance
  - Chest wall mechanics

Neonatal Lung
- Fluid must be rapidly cleared
  - Preparation begins before birth
- Maturation of the surfactant system
- Decrease in pulmonary vascular resistance

Colin et al
- Stable Functional Residual Capacity and Effectiveness of Gas Exchange
- Maintenance of a stable and adequate functional residual capacity (FRC) is important for securing stable gas exchange. FRC is determined by the balance between the opposing forces of the chest wall and lung and, thus, is a direct function of their respective mechanical properties.

Colin et al, Peds 2010

Mechanical Properties

Fig. 30-7. Concentrations of saturated phosphatidylcholine found in lung tissue and in alveolar samples from the human and other mammalian species expressed versus percent gestational age (From Claman JH and Topper WR. In: Hodson WA, editor. Development of the lung. New York. 1977. Marcel Dekker.)

Jobe in Fanaroff and Martin, 5th ed
Lung Development

Online course in embryology for medicine students developed by the universities of Fribourg, Lausanne and Bern (Switzerland) with the support of the Swiss Virtual Campus.

http://www.embryology.ch/anglais/respiratory/phases01.html

Figure 1. Incidence of RDS decreases with increasing gestational age.

Stevens, Sinkin, Chest 2007; 131:1577-1582

Transient Respiratory of the Neonate
Lokesh Guglani, Satyan Lakshminatha and Rita M. Ryan
DOI: 10.1542/pir.29-11-e59

Figure 1. Epithelial sodium (Na) absorption in the fetal lung epithelium. Na enters the cell through the apical surface of both A1 and A3 cells via amiloride-sensitive epithelial Na channels (ENaC). Both Na channels (ENaC) and resiniferatoxin-sensitive Na channels (RSO) and adenosine nucleotide receptors (BAR) in A3 cells and A5 cells, and endo-NA and through tight junctions. The increase in cell Na stimuli leads to LC; accumulation on the basolateral aspect of the cell membrane, which drives out three linds in exchange for two linds in a process that can be blocked by the diuretic and spironolactone. The Na excretion movement from the apical surface to the interstitium, an elastic-elastic chamber would be released, which would in turn be reabsorbed in the same direction, after through spironolactone or diuretic.
During late gestation the respiratory epithelium goes from a chloride-secreting membrane to a sodium-resorbing membrane.

The Incidence of Morbidities and NICU Admissions among Early Term (37-38 Weeks) and Late Term (39-41 Weeks) Neonates at Women and Children’s Hospital of Buffalo (WCHOB)

Shaon Sengupta, MBBS MPH
Alyssa Herrmann, MD
Vivien Carrion, MD
Rita Ryan, MD
James Shelton, MS and
Satyan Lakshminrusimha, MD

Funded by the Frawley Award (SS) and Division of Neonatology, University at Buffalo

Definitions based on gestational age

Modified from:
http://www.meadjohnson.com/professional/pdf/The_Late_Premature_Infant_by_Lucky_Jain.pdf
Percent change in the distribution of births by gestational age: US 1990 and 2006

Hypothesis
Among term babies born in WCHOB, early term neonates (37-38 wks) have significantly increased morbidity compared with late term neonates (39-41 wks).

Methods
- Retrospective cohort analysis
- All inborn full term infants born at WCHOB between Jan 1st 2006 – Dec 31st 2008
- Reviewed charts for those admitted to the NICU
- Exclusion criteria:
  - Born ≥42 weeks GA
  - Congenital malformation requiring admission to NICU

Outcomes
- NICU admission
- Respiratory morbidity: Any form of respiratory support requiring NICU admission.
- Hypoglycemia: Lowest BS ≤35mg/dl requiring NICU admission for management.
- Antibiotic therapy: Presumed sepsis/culture proven sepsis/ Sepsis rule out requiring NICU admission.

Results
- 9233 Live births : 7608 full term births
- Nationally 17% early term (our data: 23%)

Results: Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Early-Term: 37-38 6/7 wks [N=2140]</th>
<th>Late-Term: 39-41 wks [N=5468]</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age Mean (SD)</td>
<td>26.5 (6.5)</td>
<td>25.6 (6.2)</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>Apgar at 1min Median</td>
<td>9</td>
<td>9</td>
<td>0.28*</td>
</tr>
<tr>
<td>Apgar at 5 mins Median</td>
<td>9</td>
<td>9</td>
<td>0.19*</td>
</tr>
</tbody>
</table>

** Mann-Whitney test  * Kruskall-Wallis test
Early term babies were more likely to be born via Cesarean section or Instrumental vaginal delivery than late term babies.

**Results**

<table>
<thead>
<tr>
<th></th>
<th>Early-Term: 37-38 6/7 wks [N=2148]</th>
<th>Late-Term: 39-41 wks [N=5477]</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NICU admission</td>
<td>187 (8.7)</td>
<td>300 (5.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Respiratory support</td>
<td>62 (2.9)</td>
<td>97 (1.8)</td>
<td>0.002</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>66 (3.1)</td>
<td>89 (1.6)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Antibiotic therapy</td>
<td>100 (4.7)</td>
<td>174 (3.2)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Data in n (percent) * p<0.05 using chi2 test

Significantly increased need for mechanical ventilation in early term neonates

<table>
<thead>
<tr>
<th></th>
<th>Early Term</th>
<th>Late Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>NICU admission</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Respiratory support</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Antibiotic therapy</td>
<td>5%</td>
<td>3%</td>
</tr>
</tbody>
</table>

* p<0.05 using chi2 test

**Limitations**

- Retrospective design
- Hospital with Regional Perinatal Center
  - Now being expanded → County based approach – all births in Erie County

**Early term vs Late term: Severe respiratory disorders & poor prognosis**

- Population based study N=180426 GA= 34-41 wks
- The rate of poor prognosis (death and/or severe neurological condition) significantly declined between 34-38 wks & remained stable thereafter

Gouyon et al, Intl J of Epidemiol March 2010
Why are US preterm births increasing?
- increasing proportion of pregnant women >35 years of age
- multiple gestation
- medically indicated deliveries secondary to better surveillance of the mother and the fetus
  - placental abruption, placenta previa, bleeding
  - infection
  - hypertension, preeclampsia,
  - idiopathic preterm labor, premature rupture of membranes
  - IUQGR
- attempts to reduce stillbirths
- stress from a variety of sources

Raju et al, Pediatrics 2006;118;1207-1214

What can we do?
- Develop evidence-based data to assess risk/benefit ratios for diagnosis-specific indications for delivery at late-preterm gestations.
- Evaluate strategies to improve specific outcomes in late-preterm infants.
  - e.g. effect of ANS in enhancing pulmonary maturity in the late-preterm fetus, especially in multiple gestations.
- Study ways to improve the precision of estimates of pregnancy duration, possibly by implementation of routine first-trimester ultrasound for dating, which has shown to improve the accuracy to within 5 days compared with other dating methods.

Raju et al, Pediatrics 2006;118;1207-1214

Summary
- Late Preterm Births are Increasing
- Late Preterm Infants have an increased risk for
  - Neonatal mortality
  - RDS, TTN
  - PPHN
- Important maturational changes in the lung have yet to be completed by 34-36 weeks
- There is a lot of attention now focused on this population

Raju et al, Pediatrics 2006;118;1207-1214