Late preterm and early term deliveries

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“So he’s a little premature... what’s the big deal?”

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Disclosures

I have no financial disclosures or conflicts of interest
Objectives

• Define late preterm and early term birth
• Understand the potential consequences of infants born at this age
• Grasp the economic burden of caring for these infants
• Understand current indications for delivery at <39 weeks gestation
INTRODUCTION
Making headlines…

U.S. preterm birth rate hits lowest mark in a decade

1 in 8 preterm
World View: Low Birth Weight Related Deaths (<2500gms)

12.9 million births preterm
10.9 million preterm births in Africa & Asia

BUT.. Equal Preterm Birth RATES between North America and Africa & Asia
Infant mortality: 2008

Percent of total deaths

- Placenta/cord complications
- Accidents
- Maternal complications
- SIDS
- Preterm birth
- Birth defects

N=4,754

Adapted from: http://www.cdc.gov/nchs/data/nvsr/nvsr60/nvsr60_06.pdf
Ranking by infant mortality: US ranks 51st

<table>
<thead>
<tr>
<th>Country</th>
<th>Rate per 1000 live births</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kuwait</td>
<td>7.68</td>
</tr>
<tr>
<td>Russia</td>
<td>7.19</td>
</tr>
<tr>
<td>United States</td>
<td>5.9</td>
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<tr>
<td>Hungary</td>
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<tr>
<td>Greece</td>
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<td>Canada</td>
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<td>Cuba</td>
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<td>Portugal</td>
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<td>United Kingdom</td>
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<td>Israel</td>
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<td>Norway</td>
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<td>Spain</td>
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<td>France</td>
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<td>Italy</td>
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<td>Iceland</td>
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<td>Sweden</td>
<td>2.73</td>
</tr>
<tr>
<td>Japan</td>
<td>2.17</td>
</tr>
</tbody>
</table>

Rate per 1000 live births

Racial disparity in preterm birth, 2009

Precent preterm birth

- Hispanic: 12%
- Black: 17.5%
- White: 10.9%

Adapted from: http://www.cdc.gov/nchs/data/nvsr/nvsr60/nvsr60_01_tables.pdf
Cost of preterm birth

- **Medical care services:**
  - 16.9 billion ( $33,200 per preterm infant) - 2/3 total cost

- **Maternal delivery cost:**
  - 1.9 billion ( $3,800 per preterm infant)

- **Special education services:**
  - 1.1 billion ( $2,200 per preterm infant)

- **Lost household and labor market productivity:**
  - 5.7 billion ( $11,200 per preterm infant)

Source: Institute of Medicine of the National Academies 2006, page 47
Economic Burden

• Direct costs for late preterm infants
  – $2,630 greater than a term gestation per infant\(^1\)
• California (1996) discharge criterion study\(^2\)
  – Average total cost per gestation age group:
    • 25 weeks = $38 million
    • 35 weeks = $41 million
• Given that 72% of all preterm births are late preterm – cost is staggering\(^2\)

Average Expenditures for Newborn Care

- Uncomplicated: $4,551
- Premature/LBW: $49,033
- Other Complications: $10,327
- All Births

Total: $26.2 BILLION
The short and long term PROGNOSIS for a neonate born preterm or early term is a function of GESTATIONAL AGE AT BIRTH.
Survival by gestational age among live-born resuscitated infants

Results of a community-based evaluation of 8523 deliveries, 1997–1998, Shelby County, Tennessee

Acute morbidity by gestational age among surviving infants

Results of a community-based evaluation of 8523 deliveries, 1997–1998, Shelby County, Tennessee

Changing definitions...

Definition of 'term' pregnancy changing
By Ashley Hayes, CNN
updated 10:34 AM EDT, Fri October 25, 2013

'Full-term' pregnancy gets a new, narrower definition

Full-term pregnancy definition changes
Definitions

“Late preterm” delivery...no longer “near term”

– Coined by Raju in 2006
– Endorsed by AAP, ACOG, NICHD
– Infants born between 34 0/7 to 36 6/7 weeks
– Increasing group:
  • 1990: 7.3%
  • 2006: 9.1%
  • 2008: 8.8%
Why the change in terminology?

• Higher risk for neurodevelopmental problems
• Higher % infant death
• More NICU admissions
• Larger % health care expenditures

Behrman, National Academies Press, 2005
Matthews, National Center for Health Statistics, 2010
Definitions

Early term birth

– Infants born between 37 0/7 to 38 6/7 weeks
– Endorsed by March of Dimes, NICHD, SMDM, ACOG

Why?
Why?

• Prospective cohort of 24,077 repeat cesareans at term (>37 weeks)
• Composite outcome of neonatal death and adverse events (RDS, hypoglycemia, sepsis, NICU admission)
• 13,258 performed ELECTIVELY
  – 6% at 37 weeks- O.R. 2.1 for composite outcome
  – 30 % at 38 weeks- OR 1.5 for composite outcome
  – 49 % at 39 weeks

Tita, NEJM, 2009
Timing of Indicated Late-Preterm and Early-Term Birth.
Obstetrics & Gynecology. 2011.
Respiratory complications

Immature respiratory tree, delayed ability to clear pulmonary fluid and suboptimal surfactant

- Transient tachypnea of the newborn
- Respiratory distress syndrome
- Apnea
- Persistent pulmonary hypertension
- Sudden infant death syndrome

Incidence increases with decreasing EGA and cesarean delivery\(^1,2\)

Hypothermia

• Decreased brown adipose tissue stores and hormones available to utilize such energy$^1$
• Decreased white adipose and increased body-surface area to body-weight ratio$^1$
  • Increased heat loss
• Increased likelihood for temperature instability$^2$

Hypoglycemia

• Immature hepatic enzymes for gluconeogenesis and glycogenolysis
• Decreased hepatic glucose stores which normally accumulate in third trimester
• Upregulated insulin release from immature pancreatic cells
  • Hypoglycemia (<40mg/dl) 3X more common than term infants¹
  • Neuronal cell death and adverse neurodevelopmental outcomes²

Hyperbilirubinemia

• Immature hepatic bilirubin conjugation pathways
• Increased enterohepatic circulation caused by poor gastrointestinal function and motility\(^1\)
• Severe jaundice predicted by gestational age\(^2\)
• Feeding difficulties can contribute to elevated serum bilirubin levels
  • Higher risk of bilirubin induced brain injury and kernicterus

1. Bhutani VK et al. Semin Perinatol 2006
Other potential morbidities

• Infection
  – 4X more likely to be screened for sepsis
  – More likely to develop pneumonia and sepsis
  – Prolong hospital admission

• Feeding difficulties
  – Immature oral-buccal coordination/swallowing
  – More gastroesophageal reflux

Readmission

• Jaundice
• Feeding difficulties
• Poor weight gain
• Dehydration
• Apnea
• Respiratory illness
Neurodevelopmental Outcomes
Long Term Outcomes

• Increased developmental delay\(^1\)
• Mental retardation\(^1\)
• Decline in vision and hearing\(^1\)
• More likely to be diagnosed with cerebral palsy\(^2\)
• Lower reading and math skills\(^3\)
• Higher special education\(^3\)
  – May be related to brain maturation
  – Neuronal vulnerability to insult\(^4\)

1. Morse SB et al. Pedicatrics 2009
Morality

- British Columbia Population study 1999-2002
  - 33-36 weeks compared with term infants\(^1\)
    - 8X greater perinatal mortality
    - 5X greater neonatal mortality
    - 3X greater infant mortality
- Utah Population study\(^2\)
  - Neonatal mortality increased as EGA decreased
    - 34 weeks: 8 per 1000 live births
    - 40 weeks: 0.5 per 1000 live births

## Neonatal & Infant Mortality

<table>
<thead>
<tr>
<th>Gestational age</th>
<th>Neonatal Mortality rate (per 1,000 live births)</th>
<th>Relative Risk</th>
<th>Infant Mortality rate (per 1,000 live births)</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>34</td>
<td>7.1</td>
<td>9.5</td>
<td>11.8</td>
<td>5.4</td>
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<td>35</td>
<td>4.8</td>
<td>6.4</td>
<td>8.6</td>
<td>3.9</td>
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<td>36</td>
<td>2.8</td>
<td>3.7</td>
<td>5.7</td>
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<td>1.2</td>
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<td>1.00</td>
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<td>0.8</td>
<td>1.0</td>
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Reddy, Pediatrics, 2009
However... sometimes (many times!) we need to deliver prior to 39 weeks

- Placental and uterine
- Fetal
- Maternal
Placenta & Uterus

Goal: avoidance of catastrophic complications for mom and fetus

Obstetrical hemorrhage, Uterine rupture, fetal anemia from vasa previa, emergent surgery

Consequences of prematurity
Abnormal placentation: Previa

- 0.3-0.5% pregnancies

Risk Emergent Bleed with Hemorrhage in Previa

Oyelese, Obstet Gynecol, 2006
Spong, Obstet Gynecol, 2011
Abnormal placentation: Accreta

- 0.2% pregnancies in women with prior CD
- 3.3% of women with prior CD and previa

In cohort of 99 women with accreta:
- 44% required emergent delivery with hemorrhage after 36 weeks
- O’Brien: after 35 weeks, 93% experience hemorrhage

Delivery at 34-35 weeks after course of ACS

Warshak, Obstet Gynecol, 2010
O’Brien, AJOG, 1996
Spong, Obstet Gynecol, 2011
Abnormal placentation: Vasa previa

• Definition: FETAL vessels within the membranes which overlie the cervix
• Incidence: 1 in 2500 pregnancies
• Risk: catastrophic fetal hemorrhage
• Data on delivery:
  – Consider hospitalization at 30-32 weeks with ACS
  – \(^1\)Decision analysis model: 34-35 weeks
  – \(^2\)Others recommend 35-36 weeks
  – \(^3\)Canadian guidelines: 34-36 weeks

1 Robinson, Obstet Gynecol, 2011
2 Oyelese, Obstet Gynecol, 2006
3 Gagnon, JOGC, 2009
Prior uterine surgery

<table>
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<tr>
<th>Type of surgery</th>
<th>Risk for uterine rupture</th>
<th>Delivery recommendations</th>
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Haplerin, BJOG, 1988
Rosen, Obstet Gynecol, 1991
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Chauhan, Obstet Gynecol, 2002
Stotland, AJOG, 2002
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Uterine rupture can occur PRIOR to the onset of labor—this is why we deliver early.
Fetal

Goal: avoidance of stillbirth, optimization of neonatal management

Consequences of prematurity, risk for failed induction and cesarean
Abnormal fetal growth

Singleton
- Growth at <10%, <5%, <3%

Twin
- Discordance of >20%

Genetics vs. pathology

Concurrent conditions (dopplers, maternal, fluid) and trends over time
FGR: Timing of delivery

<table>
<thead>
<tr>
<th></th>
<th>Singleton</th>
<th>Dichorionic twins</th>
<th>Monochorionic twins</th>
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</thead>
<tbody>
<tr>
<td>Isolated FGR</td>
<td>38-39</td>
<td>36-37</td>
<td>32-34</td>
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<tr>
<td>FGR with concurrent conditions</td>
<td>34-37</td>
<td></td>
<td>32-34</td>
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<td>Persistent abnormal fetal surveillance</td>
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Spong, Obstet Gynecol, 2011
### FGR: Timing of delivery

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</table>

*** oligohydramnios, abnormal Dopplers, maternal risk factors, any co-morbidity

*Spong, Obstet Gynecol, 2011*
Fetal anomalies

• Complicate 2% of all pregnancies
• Complex topic
  – Maternal complications
    • Contractions, discomfort from polyhydramnios
  – Fetal complications
    • Worsening hydrocephalus
  – Delivery planning
    • EXIT procedure
  – Majority require planning with perinatology, neonatology and various other subspecialties
Multiple gestation
Fetal vs. Neonatal Deaths in Twins

Kahn et al, Obstet Gynecol 2003;102
“Postdates” Pregnancy in Twins

- Prospective risk of fetal & neonatal death intersects ~ 38 -39 weeks in twins (Kahn et al, ObGyn 2003;102)

- Study of multiple gestations (99.8% twins) risk of fetal & neonatal death were equivalent at 37 – 38 weeks  (Sairam S et al, ObGyn 2002;100)

- Take home point: deliver at 38 weeks
The problem: these data do not address chorionicity!
Studies arguing for early delivery

Trial 1
- 1000 twins (20% MC, 80% DC)
- MC twins: higher stillbirth rates than the DC twins (3.6% vs. 1.1%; $P = .004$)

Trial 2
- A retrospective analysis from the United Kingdom
- 151 uncomplicated monochorionic pregnancies
- Risk for unexpected stillbirth after 32 weeks was 4.3% (1 in 23)

Lee et al, Obstet Gynecol, 2008
Study arguing for later delivery

Breathnach, Obstet Gynecol, 2012:
• Prospective ESPIRiT study, Twins, Ireland
• N = 1001 pregnancies (20 % MC, 80% DC)
• Prospective risk fetal death:
  – 1.5% after 34 weeks for MC,
• Compositive morbidity: 41% at 34 weeks vs 5% at 37 weeks.
• Consider delivery at 37 weeks for MC.

Robinson, AJOG 2012
• Decision analysis of 9 strategies to deliver 32-38 weeks
• Optimal GA for delivery always >36 weeks
• Preferred 38 weeks
## SUMMARY OF RECOMMENDATIONS

### TWINS

<table>
<thead>
<tr>
<th>Type of twin</th>
<th>Timing of delivery (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dichorionic-Diamniotic</td>
<td>38</td>
</tr>
<tr>
<td>Monochorionic-Diamniotic</td>
<td>34-37</td>
</tr>
<tr>
<td>Monochorionic-Monoamniotic</td>
<td>32-34</td>
</tr>
<tr>
<td>Death of 1 twin</td>
<td>Consider delivery</td>
</tr>
</tbody>
</table>
Abnormal fluid: oligohydramnios

Defined:

- AFI <5 cm
  - Complicates 4.8% of pregnancies 34-36 weeks
  - Complicates 10% of pregnancies at 37 weeks

- Maximal vertical pocket <2 cm
  - Complicates 2.3% of pregnancies 34-36 weeks
  - Complicates 3% of pregnancies at 37 weeks
Consequences of oligohydramnios

**Risks**
- NRNST: 1.5x higher
- FHR decelerations: 1.8x higher
- Fetal intolerance in labor
- Stillbirth: 4.5x higher
- APGAR ≤ 3 at 5 minutes: 11x higher
- Meconium aspiration: 12x higher

**Recommendation**
Delivery at 36-37 weeks in absence of other findings
MATERNAL
Maternal

Goal: avoidance of worsening of a maternal medical condition and its effects on the fetus
Acute conditions

- PTL
- PPROM
- ICP
Chronic conditions: Diabetes

- GDM: 15% of pregnancies
- 3-4% pregestational DM
- Why deliver early?
  - Less risk macrosomia and associated birth trauma
  - Less risk stillbirth
- Higher risk uncontrolled hyperglycemia and CD
- Timing of delivery complex: dz severity, co-morbidities, meds, superimposed OB conditions
<table>
<thead>
<tr>
<th>CONDITION</th>
<th>DELIVERY</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1 GDM</td>
<td>39+ weeks</td>
</tr>
<tr>
<td>A2 GDM- Optimal control</td>
<td>39+ weeks</td>
</tr>
<tr>
<td>A2 GDM- poor control</td>
<td>34-39 weeks</td>
</tr>
<tr>
<td>Pre-gestational DM, well-controlled</td>
<td>39+ weeks</td>
</tr>
<tr>
<td>Pre-gestational DM, vascular disease</td>
<td>37-39 weeks</td>
</tr>
<tr>
<td>Pre-gestational DM, poor control</td>
<td>34-39 weeks</td>
</tr>
</tbody>
</table>
Chronic conditions: HTN

- 30% nulliparous pregnancies develop PIH or preeclampsia
- 80% preeclampsia occurs after 38 weeks
- Maternal risk: severe disease, hypertensive crisis, HELLP, abruption, renal failure, DIC, eclampsia, death;
- Fetal risk: FGR, asphyxiation, death

Roberts, NEJM, 2010
## HYPIYAT trial

- **IOL** versus expectant management for mild gestational HTN/preeclampsia at ≥ 36 0/7 weeks

<table>
<thead>
<tr>
<th></th>
<th>Induction, n=377</th>
<th>Expectant, n=379</th>
<th>RR (95% CI)</th>
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</thead>
<tbody>
<tr>
<td><strong>Composite adverse outcome</strong></td>
<td>117</td>
<td>166</td>
<td>0.71 (0.59-0.86)</td>
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<tr>
<td><strong>HELLP</strong></td>
<td>4</td>
<td>11</td>
<td></td>
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<tr>
<td><strong>Pulmonary edema</strong></td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>Abruption</strong></td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Eclampsia</strong></td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>MICU</strong></td>
<td>6</td>
<td>14</td>
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<tr>
<td><strong>Cesarean</strong></td>
<td>54</td>
<td>72</td>
<td>0.75 (0.55-1.04)</td>
</tr>
<tr>
<td>CONDITION</td>
<td>DELIVERY</td>
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<tr>
<td>---------------------------------</td>
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<tr>
<td>Gestational hypertension</td>
<td>37-38 weeks</td>
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</tr>
<tr>
<td>Chronic HTN- no meds</td>
<td>38-39 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic HTN- well controlled with meds</td>
<td>37-39 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic HTN- poor control</td>
<td>36-37 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preeclampsia- mild</td>
<td>37 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preeclampsia- severe</td>
<td>At diagnosis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Antihypertensive therapy

• “Maintenance antihypertensive therapy should NOT be used to treat gestational hypertension.”

Spong, Obstet Gynecol, 2011
Prior stillbirth

• Risk for recurrent stillbirth = 8%
• More likely with earlier loss, recurrent losses, FGR, black race [Reddy, Obstet Gynecol, 2010]
• Risk for continued pregnancy: FGR, preterm birth, PEC, maternal anxiety, stillbirth
• NOT indication for early birth in the ABSENCE of FGR and co-morbidities.
• Consider amnio for FLM if delivery prior to 39 weeks due to maternal anxiety. Mature amnio does NOT assure absence of neonatal complications
What can we do to mitigate consequences of PTB?

- Amniocentesis for FLM
  - Controversial
- Antenatal corticosteroids
  - No clear indication after 34 weeks
  - Trials are ongoing to assess outcomes in late preterm period

http://clinicaltrials.gov/ct2/show/study/NCT012247?term=ALPS
“It is critical that the totality of the clinical picture be taken into account when deciding on the optimal timing of delivery.”
Thank you!