CLINICAL CASE
- You are called stat to the operating room in the labor ward for emergency cesarean section for a 38-year-old primi gravida at 23+5 week gestation with severe bleeding following placental abruption.
- As you enter the operating room the baby is delivered pulseless, apneic and pale.
- You start bag and mask ventilation while the team is scrambling getting the intubation stuff together.

CLINICAL CASE
- You intubate the baby in a flash and continue ventilation with good chest rise for 30 seconds, heart rate still remains undetectable.
- What do you do now?
  - you abandon further attempts at resuscitation.
    - The baby is too premature (1)
    - There is a very high likelihood that the baby will not survive and even if the baby survives the baby will be severely handicapped (2)
  - You continue resuscitation with epinephrine (3)

What determines viability?

Lung Development

http://www.embrology.ch/anglais/respiratory/phases27.html

Pseudograndular & Canalicular

1 Lung mesenchyma  1 Type I pneumocytes
2 Type II pneumocytes  2 Type II pneumocytes
3 Capillaries  3 Capillaries
1. Type I pneumocyte
2. Type II pneumocyte
3. Capillaries

1. Type I pneumocyte
2. Saccular space
3. Type II pneumocyte
4. Basal membrane of the air passage
5. Basal membrane of the capillaries
6. Endothelium of the capillaries

Brain – on sonogram
22 weeks
35 weeks

Signs of a Pre-viable Fetus
Fused eyelids
Severe bruising
Gelatinous skin

Evaluation of gestational age (dates)
Response to Resuscitation
Shared management decision between the health care team and parents
Birth weight usually < 400g

Creasy and Resnik’s Maternal fetal medicine 2008

Mortality for infants 501 to 1500 g, 1991 to 1999, by birth weight category at all 362 network hospitals

**IVH FOR INFANTS 501 TO 1500 G, 1991 TO 1999**


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**THE TINIEST BABIES**

- [http://www.medicine.uiowa.edu/tiniestbabies/bdorde.r.asp](http://www.medicine.uiowa.edu/tiniestbabies/bdorde.r.asp)

---

**SURVIVAL FOR INFANTS BORN <26 WEEKS**

<table>
<thead>
<tr>
<th>Week</th>
<th>22</th>
<th>23</th>
<th>24</th>
<th>25</th>
<th>26</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPICure (U.K &amp; IRE) 1995 (95% of admitted infants)</td>
<td>9</td>
<td>19.9</td>
<td>33.6</td>
<td>52.1</td>
<td>38.7</td>
<td></td>
</tr>
<tr>
<td>EPIPAGE (France) 1997 (Live births/All births)</td>
<td>0</td>
<td>0</td>
<td>31/20</td>
<td>56/20</td>
<td>36/37</td>
<td></td>
</tr>
</tbody>
</table>

Larroque et al: Arch Dis child Fetal Neonatal Ed 2004; 89: F139 – F144

---

**SURVIVAL FOR INFANTS BORN <26 WEEKS**

<table>
<thead>
<tr>
<th>Week</th>
<th>22</th>
<th>23</th>
<th>24</th>
<th>25</th>
<th>26</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPSBEL (Belgium) 1999-2000 Live Births/All Births</td>
<td>0</td>
<td>5/2/19</td>
<td>95/4/3</td>
<td>74/6/3</td>
<td>54/3/3</td>
<td></td>
</tr>
<tr>
<td>Trent (U.K) 1994-1995 Live Births</td>
<td>0/0</td>
<td>10/7</td>
<td>38/26</td>
<td>48/44</td>
<td>36/34</td>
<td></td>
</tr>
<tr>
<td>Trent (U.K) 2000-2005 Live Births/All Births</td>
<td>0/0</td>
<td>10/7</td>
<td>38/26</td>
<td>48/44</td>
<td>36/34</td>
<td></td>
</tr>
</tbody>
</table>

Vanhaesebroeck et al Pediatrics 2004; 114:663-673
Field et al: BMJ Online First doi:10.1136/bmj.39555.67018BE
OUTCOMES BASED ON VARIATION IN PRACTICE

Proactive Strategy
Increased Survival
Increased cost

Increased morbidity

Statistic Prognostic Strategy
Decreased survival
Decreased cost

In the 23 – 26 week gestational age group with a proactive strategy for every hundred live births there is an excess of 24 survivors and seven cases of disabling cerebral palsy.


TO WIN YOU WILL FIRST HAVE TO TRY !!!

THE SELF FULFILLING PROPHECY

I NEED THE INSTRUCTIONS OF THE TERRORISTS.

BUT THERE WERE NO TERRORISTS IN 1996.

THERE NOW.

Sweden

25 week Guideline not followed
Model of Care – Proactive

Outcomes
Increased incidence of live births
Higher degree of centralized management
Higher frequency of Caesarian Sections
Fewer infants with low APAR scores
Fewer infant deaths in < 24 hrs
Increased survival at 1 yr of age
No increase in morbidity among survivors

25 week guideline followed
Model of Care – Selective and Active
Restrictive attitude towards CS for fetal indications
Individualized approach to resuscitation of ELBW infants
Estimated additional 237 survivors in 23–25 weeks in the South if the incidence and survival rates of the North had prevailed in the South during 1990 to 1999.

SURVIVAL FOR INFANTS BORN <26 WEEKS

<table>
<thead>
<tr>
<th>GA</th>
<th>22–23 weeks</th>
<th>24 weeks</th>
<th>25 weeks</th>
<th>Overall</th>
</tr>
</thead>
</table>

Costello et al EPICURE 2 data

MORTALITY RATES FOR EXTREMELY LOW BIRTH WEIGHT INFANTS BORN IN JAPAN IN 2005

Total of 2030 live births

<table>
<thead>
<tr>
<th>GA</th>
<th>22–23 weeks</th>
<th>24 weeks</th>
<th>25 weeks</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admissions 1995</td>
<td>190</td>
<td>244</td>
<td>290</td>
<td></td>
</tr>
<tr>
<td>Survivors n %</td>
<td>25 (13%)</td>
<td>85 (38%)</td>
<td>156 (54%)</td>
<td></td>
</tr>
<tr>
<td>Admissions 2006</td>
<td>196</td>
<td>230</td>
<td>416</td>
<td></td>
</tr>
<tr>
<td>Survivors n %</td>
<td>51 (20%)</td>
<td>155 (47%)</td>
<td>285 (67%)</td>
<td></td>
</tr>
<tr>
<td>% change (CT)</td>
<td>-7(-1.9)</td>
<td>+12 (4.4 to 20)</td>
<td>+33 (6.0 to 53)</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.1</td>
<td>0.002</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Costello et al - EPICURE 2 data

OUTCOMES FOR 22 WEEKS

- Total pregnancies at 22 weeks – 273
- Live births at 22 weeks – 151
- Died in delivery room – 132
- Admitted to NICU at 22 weeks – 19 (12%)
- Survived to discharge – 3 (1%)
- Antenatal steroids at 22 weeks – 10%
- Cesarean section at 22 weeks – 1%

Costello et al - EPICURE 2 data

OUTCOMES FOR 23 WEEKS

- Total deliveries at 23 weeks– 377
- Died in delivery room – 122
- Admitted for intensive care – 215
- Survived to discharge – 48 (14.2%)
- Antenatal steroids at 23 weeks 52%
- Cesarean section at 23 weeks – 3% 
- Antenatal steroids at 24 weeks – 83%
- Cesarean section at 24 weeks – 13%

Costello et al - EPICURE 2 data
**MOBIDITY**

<table>
<thead>
<tr>
<th>All survivors</th>
<th>Head ultrasound scan abnormalities</th>
<th>Oxygen at 36 weeks PMA</th>
<th>Treated ROP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>41 (15%)</td>
<td>99 (75%)</td>
<td>35 (15%)</td>
</tr>
<tr>
<td>2006</td>
<td>65 (15%)</td>
<td>365 (74%)</td>
<td>104 (28%)</td>
</tr>
<tr>
<td>Change %</td>
<td>-2 (-7 to 3)</td>
<td>-0.5 (-7.06)</td>
<td>8 (-13)</td>
</tr>
<tr>
<td>p</td>
<td>0.4</td>
<td>0.8</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Costello et al - EPICURE 2 data

**MOVING BEYOND GESTATIONAL AGE**

- [http://www.nichd.nih.gov/about/org/cdbpm/pp/prog_epbo/epbo_case.cfm](http://www.nichd.nih.gov/about/org/cdbpm/pp/prog_epbo/epbo_case.cfm)

**BACKGROUND**

- Variation in practice exists in the resuscitation of infants born at the threshold of viability.
- The use of Epinephrine in the delivery room resuscitation of extremely preterm infants is controversial.
- Studies in the past have conflicting results.
- The British association for perinatal medicine discourages the use of “medications” in the DR resuscitation of extremely preterm babies <26 weeks gestation.
- The AAP or NRP does not address this issue separately in the extremely preterm babies <26 weeks gestation.

**BACKGROUND**

- 4 previous studies have looked at CPR in the DR for extremely preterm infants.
- In a study by Davis from Ottawa 1989 – 92 there were no survivors in the <750 grams birthweight group who received CPR with or without Epinephrine. (Davis Pediatrics 1993;92:447-450)
- Sims et al in their 5 year retrospective study between 1987 – 91 of infants receiving resuscitation meds (Epinephrine / Atropine or both) in the DR/ NICU.
- 3 of the 5 infants treated in the DR died and 2 survived with severe handicap.
- They concluded that the use of meds in the DR in extremely preterm infants in the first week of life may be inappropriate.

**BACKGROUND**

<table>
<thead>
<tr>
<th>Vermont Oxford Network Data 1994 – 96</th>
<th>46 infants &lt;500g and 658 infants &lt;750g received DR CPR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight</td>
<td>401 – 500 grams</td>
</tr>
<tr>
<td>CPR</td>
<td>No CPR</td>
</tr>
<tr>
<td>n (%)</td>
<td>46 (10%)</td>
</tr>
<tr>
<td>% Survival</td>
<td>23.9</td>
</tr>
<tr>
<td>% IVH</td>
<td>50</td>
</tr>
<tr>
<td>% IVH Grade 3 or 4</td>
<td>20</td>
</tr>
<tr>
<td>Survival without severe IVH</td>
<td>17.7</td>
</tr>
</tbody>
</table>

Sims et al ADC 1994;70:F3-F5
HYPOTHESES

- Extremely preterm < 26 weeks gestation infants who receive Cardiopulmonary resuscitation and epinephrine in the delivery room will have greater mortality compared to matched controls.
- The incidence of morbidities such as IVH, PVL, ROP and NEC will be higher in infants who receive CPR and epinephrine in the delivery room.

METHODS

- 17 cases identified since July 2000
- 3 cases not analyzed as airway compromise may have led to need for CPR
- 14 Cases were matched to 28 controls
- Matched for gestational age ± 1 week, sex, race and birth date within 1 year.
  - One Asian infant was matched to a Caucasian and an African American infant.

DEMOGRAPHICS

- Mean GA – 24±3 weeks
- Mean Birth weight – 707 grams ±
- 46.5% infants in Epi and 50% Controls received a complete course of Antenatal Steroids
- Placental abruption was the indication for delivery in 4 infants and cord prolapse in 1 infant who received Epinephrine in the DR

<table>
<thead>
<tr>
<th>Year</th>
<th>GA</th>
<th>Weight</th>
<th>Sex</th>
<th>Race</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>24</td>
<td>0.64</td>
<td>Male</td>
<td>African American</td>
</tr>
<tr>
<td>2000</td>
<td>25</td>
<td>0.889</td>
<td>Male</td>
<td>Caucasian</td>
</tr>
<tr>
<td>2001</td>
<td>24</td>
<td>0.767</td>
<td>Female</td>
<td>Caucasian</td>
</tr>
<tr>
<td>2001</td>
<td>25</td>
<td>0.68</td>
<td>Female</td>
<td>Caucasian</td>
</tr>
<tr>
<td>2001</td>
<td>24</td>
<td>0.703</td>
<td>Male</td>
<td>Caucasian</td>
</tr>
<tr>
<td>2002</td>
<td>25</td>
<td>0.766</td>
<td>Female</td>
<td>Asian</td>
</tr>
<tr>
<td>2002</td>
<td>24</td>
<td>0.796</td>
<td>Male</td>
<td>Caucasian</td>
</tr>
<tr>
<td>2002</td>
<td>24</td>
<td>0.454</td>
<td>Male</td>
<td>Caucasian</td>
</tr>
<tr>
<td>2003</td>
<td>24</td>
<td>0.605</td>
<td>Female</td>
<td>African American</td>
</tr>
<tr>
<td>2003</td>
<td>24</td>
<td>0.74</td>
<td>Male</td>
<td>African American</td>
</tr>
<tr>
<td>2004</td>
<td>24</td>
<td>0.74</td>
<td>Male</td>
<td>Caucasian</td>
</tr>
<tr>
<td>0606</td>
<td>24</td>
<td>0.651</td>
<td>Female</td>
<td>Caucasian</td>
</tr>
<tr>
<td>2008</td>
<td>24</td>
<td>0.714</td>
<td>Male</td>
<td>Other</td>
</tr>
<tr>
<td>2008</td>
<td>25</td>
<td>0.754</td>
<td>Male</td>
<td>African American</td>
</tr>
</tbody>
</table>

DEMOGRAPHICS

ANTENATAL STEROIDS

<table>
<thead>
<tr>
<th></th>
<th>EPI</th>
<th>CONTROL</th>
</tr>
</thead>
<tbody>
<tr>
<td>46.5</td>
<td></td>
<td>50</td>
</tr>
</tbody>
</table>

APGAR SCORE AT 1 MINUTE

![Graph showing APGAR scores at 1 minute]
**APGAR Score at 5 Minutes**

- **P** = 0.001

**Worst pH in First 24 Hours**

- **P** = 0.068

**Worst Base Deficit in First 24 Hours**

- **P** = 0.0002

**Surfactant**

- **P** = 0.07

**Hypotension %**

- EPI: 44
- Control: 35

**Cord PH**

- **P** = 0.036
INTRA VENTRICULAR HEMORRHAGE %

PERIVENTRICULAR LEUCOMALACIA %

VENTILATOR DAYS

BPD %

LENGTH OF STAY (DAYS)

SURVIVAL TO DISCHARGE %

P = 0.15
POWER ANALYSIS

- Vanderbilt Power and Sample size calculator
- Back calculation of power
- With 14 patients matched 1:2 we would have 80% power to be able to exclude a 50% difference in survival i.e. a reduction of survival from 70% to 35% with an alpha of 0.05.

CONCLUSIONS

- Survival was no worse in babies who received epinehrine in the DR.
- There were no differences in any of the morbidities i.e. IVH, NEC & ROP.
- Although not statistically significant the rate of PVL is very high in the group that received epinephrine in the DR.
- There was no difference in length of time to all PO feeds or the requirement for G -Tube feeds.
- There were no differences in the length of stay in the NICU.

CONCLUSIONS

- This study, although limited by small number of patients, suggests the use of epinephrine in the delivery room resuscitation appears to be safe for all of the short term morbidities that were studied.
- Since approximately 40% of these events are triggered by placental abruption, long-term follow up outcomes of these infants would be very important before any recommendations regarding the safety of use of epinephrine in delivery room in extremely preterm infants can be made.

THANK YOU FOR YOUR ATTENTION

I would like to thank:
Dr. Ryan & Dr. Lakshmin for their help with the design and presentation of this study
Tara Cronin for help with the database

There will always be appropriate arguments for instigating intensive care for some very immature infants, but perhaps it should be viewed as an experimental therapy with properly informed consent rather than the automatic process that it often becomes. It is too easy to start the carousel of intensive care for baby and family rather than reserve this for the minority who truly understand what this treatment entails.
M Levene Acta Paediatrica 2004; 93: 149-152

Currently, we all are engaged in a large uncontrolled experiment. The effectiveness of the neonatal intensive care technology at the extreme limits of birth weight or gestational age is essentially unknown. There are no randomized, clinical trials of any of the interventions (surfactant, mechanical ventilation) currently in use for infants at this birth weight. The debate regarding who is too small and too immature to live will probably never end.
J Lucey Pediatrics 2004; 103: 539-66