Can Cesarean Sections Reduce Professional Liability Costs?

Andrew W. Beckwith, M.D.*, Katherine E. Economy, M.D., M.P.H., and James A. Greenberg, M.D.

Brigham and Womens’ Hospital, Boston, MA

OBJECTIVE: To model the effect of universal cesarean delivery on professional liability costs.

METHODS: We examined professional liability claims for all pregnancies covered by the Controlled Risk Insurance Company (CRICO) from January 1, 1990 to December 31, 2000. We reviewed each case to establish whether a cesarean section could reasonably have prevented the malpractice allegation (e.g. ruptured VBAC in labor) or whether vaginal delivery could reasonably have prevented the liability action (e.g. claims of unnecessary cesarean sections with bowel injuries). Malpractice costs were calculated by adding the cost of processing the claim, the legal defense, the settlement payments and/or the actuarially derived adjustments. We assumed a 20% cesarean rate for the study population at baseline and compared this to a model in which cesarean rates approached 100%.

RESULTS: There were 205,241 pregnancies covered by CRICO during the study period and 91 professional liability lawsuits were initiated. During the study period, the true cost of the liability actions was $53,731,903. We estimated potential savings of $39,070,661 from a hypothetical policy requiring cesarean sections for all patients. We estimated $804,489 in claims-costs might have been saved if patients had delivered vaginally rather than by cesarean. Finally, we identified costs of $10,638,797 in which the route of delivery would not have affected the outcome. Using such figures we calculated that malpractice costs for a model of universal cesarean delivery would be $14,661,242 or a potential savings of $39,070,661 (73%).

CONCLUSIONS: In the current malpractice environment, a policy of 100% cesarean sections could hypothetically reduce professional liability costs by 73%. Such savings need to be balanced against other costs and potential morbidities associated with such a policy. Perhaps, more importantly, we need to consider whether a policy which subjects a majority of patients to medically unindicated surgery is ever appropriate, whatever the costs or savings.
How useful is first trimester increased nuchal translucency as a screening tool for the
detection of congenital heart disease? Richard Benoit, MD, MPH, Women and Infants’ Hospital.
Providence RI.

Objective:
The goal of this review and meta-analysis is to describe the diagnostic accuracy and utility of increased nuchal
translucency (NT) thickness in the detection of congenital heart disease.

Study Design:
The selection criteria included population based cohort studies, either retrospective or prospective, describing the
use of fetal nuchal translucency thickness between 10-14 weeks gestation for first-trimester screening. Antenatal
and postnatal outcomes must have been assessed, particularly karyotype and prevalence of congenital heart
anomalies. Studies included reported the outcome of a chromosomal normal cohort with respect to nuchal
translucency thickness between 10-14 weeks gestation, allowing for determination of the relative risk, sensitivity,
specificity, likelihood ratio, and risk difference for an abnormal test and congenital heart malformation (with 95%
CI). The prevalence of congenital heart defects in the population screened was assessed as high or low.

Results:
Five cohort studies met inclusion criteria (4 prospective, 1 retrospective). All five assessed a low risk population, as
confirmed by the prevalence range of 1.7 to 3.3 per 1000. Among three of the studies reporting a NT ≥ 2.5 mm as a
cut-off for abnormal screen, sensitivity for the detection of congenital heart anomaly among chromosomal normal
live births ranged from 15-27%; specificity 97-99%, and likelihood positive from 4.4 to 18.5. Among the two
reporting NT ≥ 95th percentile with respect to crown-rump length norms, sensitivity ranged from 36-56%,
specificity 94-97%, and likelihood ratio positive 9 to 10.8. For the three studies reporting NT ≥ 99th percentile or
≥3.5mm, sensitivity ranged from 12-40%, specificity 99%, and likelihood ratio positive 14.8 to 39. The risk
difference for a NT ≥ 99% was 4-6%. The one case-control study reported an odds ratio of 6.8 for CHD in
chromosomal normal live births with an increased nuchal measurement of ≥ 2.5 mm at 10-14 weeks gestation.

Conclusions:
Nuchal translucency (NT) measurement between 10-14 weeks gestation is a useful screening tool in the low-risk
population for the detection of congenital heart disease, warranting referral for fetal echocardiography, although it is
not sensitive enough to serve as a single test.
Title Neonatal outcomes associated with placentation in gestational age matched twins
Alan Bolnick, M.D.*, Naveed Hussain, M.D., Jim Egan, M.D., Adam Borgida, M.D., Carolyn Zelop, M.D., Melinda Sanders, M.D., Erika Walz, P.A.
University of Connecticut

OBJECTIVE We sought to evaluate whether there are differences in neonatal outcomes of gestational age matched twins with regard to placentation.

STUDY DESIGN We reviewed our obstetrical, neonatal and pathology databases from Jan 1994 to June 2001 to obtain placentation and newborn outcomes of twin gestations that delivered at our institution. Chorionicity was established by histologic examination and the cohort was divided into three groups: monochorionic monoamniotic (M/M), monochorionic diamniotic (M/D), and dichorionic diamniotic (D/D). We analyzed placentation by gestational age, birth weight at delivery, one and five minute APGARs, NICU admission days, NEC, PDA IVH, days on the ventilator and RDS. We used chi square for categorical and student “t” test for continuous variables with Fisher exact as appropriate.

RESULTS There were 600 twin gestations delivered during the study period. Two hundred and sixty nine twin pairs were excluded because of missing placentation. Of the remaining 331 pregnancies, 218 (65%) were D/D, 91 (21%) were M/D, and 22 (14%) were M/M. There were no statistically significant differences in the gestational age and birth weight in the three groups by placentation.

Outcome measures are seen in the table below.

<table>
<thead>
<tr>
<th>Outcome measures for twins by placentation.</th>
<th>D/D</th>
<th>M/D</th>
<th>M/M</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational Age (wks. +/- SD)</td>
<td>31.8</td>
<td>3.3</td>
<td>31.9</td>
<td>2.8</td>
</tr>
<tr>
<td>Birth weight (gms. +/- SD)</td>
<td>1741</td>
<td>573</td>
<td>1721</td>
<td>532</td>
</tr>
<tr>
<td>1 min APGAR &lt;7 (%)</td>
<td>29.9%</td>
<td>27.3%</td>
<td>57.1%</td>
<td></td>
</tr>
<tr>
<td>5 min APGAR &lt;7 (%)</td>
<td>3.9%</td>
<td>4.6%</td>
<td>23.8%</td>
<td></td>
</tr>
<tr>
<td>NICU days</td>
<td>34.6</td>
<td>37.5</td>
<td>46.4</td>
<td></td>
</tr>
<tr>
<td>RDS (%)</td>
<td>36.5%</td>
<td>33.0%</td>
<td>52.4%</td>
<td></td>
</tr>
<tr>
<td>Days on vent</td>
<td>4.3</td>
<td>2.9</td>
<td>9.7</td>
<td></td>
</tr>
<tr>
<td>ROP &gt;=2 (%)</td>
<td>3.4%</td>
<td>2.3%</td>
<td>14.3%</td>
<td></td>
</tr>
<tr>
<td>IVH &gt;2 (%)</td>
<td>2.9%</td>
<td>2.3%</td>
<td>4.8%</td>
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</tbody>
</table>

CONCLUSION There were significant differences in 1 and 5 minute APGARs, days on ventilator and ROP >= 2 for gestational age matched twin gestations when analyzed by placentation.
INHIBITION OF SEROTONERGIC NEURONS IN THE PARAGIGANTOCELLULARIS LATERALIS (PGCL) DISRUPTS SLEEP IN PIGLETS: IMPLICATIONS FOR SIDS.

R.A. Darnall, M.B. Harris, W.G. Gill, M.M. Niblock, Departments of Pediatrics and Physiology, Dartmouth Medical School, Lebanon, NH, USA

A substantial subset of SIDS victims have abnormal serotonergic receptor binding in several neuron groups in the caudal medulla including the arcuate nucleus, the midline raphé nuclei (Obscurus and Pallidus), and the more lateral n. Gigantocellularis, and n. Paragigantocellularis Lateralis (PGCL). In animals, this region of the brainstem is important for many autonomic functions, including central chemoreception, thermoregulation, sensory modulation, motor facilitation at the level of the spinal cord, and upper airway control. We have previously shown in piglets that unilateral dialysis of 8OH-DPAT, a 5-HT₁A agonist, into the PGCL near the ventral surface and medial to the facial nucleus (VII) disrupts sleep, producing alternating periods of NREM and WAKE and a dramatic decrease in the amount of REM. We hypothesized that these effects were due to inhibition of serotonergic activity secondary to 5-HT₁A auto-receptor activation. To test this hypothesis further, we unilaterally dialyzed 5,7-DHT (DHT) into the same region in 4 piglets to specifically destroy serotonergic neurons. Sleep was evaluated before and after unilateral dialysis of 8OH-DPAT into the PGCL one week after DHT dialysis and compared to control experiments before DHT dialysis. Using immunohistochemical techniques to identify neurons containing tryptophan hydroxylase, the rate limiting enzyme in serotonin synthesis (TPOH⁺), we determined the location of the dialysis probe tips, and the extent of serotonergic neuron destruction. All of the probe tips were located medial to VII, > 3 mm from the midline, and within 2 mm of the ventral surface. By counting the TPOH⁺ cells on both sides, we were able to determine that DHT destroyed, on average, 66% of serotonergic neurons in the PGCL on the side of dialysis. One week after DHT, sleep architecture was not as dramatically affected as with 8OH-DPAT in our previous experiments. Nevertheless, compared to control studies more periods of NREM were interrupted by wakefulness disrupting normal NREM-REM-WAKE cycling in some animals. An unanticipated finding was that minute ventilation and respiratory frequency were greatly increased one wk after DHT dialysis. In addition, further sleep disruption by 8OH-DPAT was markedly reduced after DHT. These data support the hypothesis that the sleep disruption caused by 8OH-DPAT is secondary to 5-HT₁A auto-receptors located on serotonergic neurons rather than post-synaptic 5-HT₁A receptors on non-serotonergic neurons. Our results further support the hypothesis that serotonergic neurons in these lateral, non-raphé, groups of serotonergic modulate sleep and/or participate in state dependent functions, perhaps mediated through alterations in the integration of sensory inputs to the region. These data also support the hypothesis that abnormalities in the caudal medullary serotonergic neuron groups may result in abnormal sleep homeostasis, increasing risk for sudden death. Support Contributed By: NIH PO1-HD36379; First Candle/SIDS alliance.
Completion of Anatomical Surveys Using AIUM Criteria by Gestational Age

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Objective: To determine how often an anatomical survey is completed using American Institute of Ultrasound in Medicine (AIUM) criteria based on gestational age.

Study Design: We reviewed our obstetrical ultrasound database from Jan 1996 to June 2003 for women presenting for an initial scan between 14-23 completed weeks gestation to see how often a complete anatomic survey was accomplished. AIUM criteria includes the following: spine, four chamber heart, stomach, cord insertion, abdominal wall, kidneys, bladder, lateral ventricles and posterior fossa. In those anatomic surveys that were incomplete, we determined the views which could not be obtained. Data was compared at two week intervals using Chi-square.

Results: There were 15,670 initial scans of singleton gestations during the study period. Gestational age followed a Gaussian distribution with a median of 18.6 weeks. The percent of complete anatomic surveys by two week intervals is illustrated. More exams were completed by at 16-17.9 weeks vs 14-15.9 weeks (p<.0001) and 18-19.9 weeks vs 16-17.9 weeks (p<.0001). Beyond 18 weeks gestation, there was no significant improvement in the ability to complete the anatomic survey. The primary reason for an incomplete exam was the inability to document a four chamber heart. Visualization of the four chamber heart reached a plateau at 94% of exams by 18 weeks gestation.

Conclusion: This large, population based study addresses the ability to successfully complete an anatomical survey using established AIUM criteria. This information suggests the optimal time for performing an adequate anatomic survey is 18 weeks gestation.
Neonatal Cumulative Illness Severity Is Associated With But Does Not Improve Prediction of Progression from Prethreshold to Threshold Retinopathy of Prematurity

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Background: Severe sustained or labile clinical illness may increase risk for development of severe ROP in premature infants.

Objective: To compare neonatal cumulative illness severity (cIS) and lability of illness severity in infants with prethreshold retinopathy of prematurity (Pre) not progressing to threshold (Thr) to infants developing Thr, and assess whether a measure of neonatal cIS enhances a risk model for progression to Thr.

Design/Methods: Data were collected retrospectively for all infants admitted to 4 level III NICUs 1995-2001 who developed Pre. cIS was measured by summing daily SNAP scores for the first 28 days of life (cSNAP28). Logistic regression was used to determine clinical factors associated with progression to Thr with and without adjustment for cSNAP28.

Results: Compared to infants with Pre not progressing to Thr (n=130), those with Pre progressing to Thr (n= 79) had significantly (p<0.05) lower gestational ages (25.2 ± 1.1 vs 25.8 ± 1.4 wk) and higher cSNAP28 (255 ± 77 vs 224 ± 63). In the 1st 28 days of life, infants with Thr received more days of mechanical ventilation, larger volumes transfused blood and smaller volumes of enteral feedings. In regression analysis (Table) GA as well as chronological age and presence of Plus Disease at 1st diagnosis of Pre were associated with development of Thr. cSNAP28 was significantly associated with Thr after adjusting for these factors, but addition of cSNAP28 to the model only increased ROC curve area from 0.77 to 0.78 (NS).

<table>
<thead>
<tr>
<th>Risk Model for Progression from Prethreshold to Threshold ROP</th>
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<tbody>
<tr>
<td><strong>OR</strong></td>
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<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Gestational age, wks</td>
</tr>
<tr>
<td>Chronological age at 1st diagnosis Pre, days</td>
</tr>
<tr>
<td>Plus Disease present at 1st diagnosis Pre</td>
</tr>
<tr>
<td>Cumulative Illness Severity, 1st 28 days (cSNAP28)</td>
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</tbody>
</table>

Other clinical and ophthalmological factors, including lability of SNAP scores, were NS after adjusting for this model.

Conclusions: Neonatal cIS as measured with daily SNAP scores is an independent risk factor for progression from Pre to Thr. However, after adjusting for simpler clinical factors, measurement of neonatal cIS with daily SNAP scores does not significantly enhance assessment of risk for progression to Thr.

Disclosure: Funded by NEI K23EY00420 and the SPR Student Research Program
Inhibition of serotonergic (5-HT) neurons in the paragigantocellularis lateralis (PGCL) of piglets decreases shivering thermogenesis in response to a cold stress. Jill M. Hoffman, M.B. Harris, W.H. Gill, M.M. Niblock, R.A. Darnall, Departments of Pediatrics and Physiology, Dartmouth Medical School, Lebanon, NH

A substantial subset of Sudden Infant Death Syndrome victims have decreased 5-HT receptor binding in medullary 5-HT neuron groups, including the PGCL. Neurons in this region project to the spinal cord and are involved in many autonomic functions, including thermoregulation. We hypothesized that 5-HT neurons in the PGCL may play a role in thermoregulatory effector systems, including shivering. To test this hypothesis, we cooled piglets before and after unilateral dialysis of a 5-HT1A auto-receptor agonist, 8-OH-DPAT (DPAT), into the PGCL. Cooling resulted in shivering, increases in integrated neck EMG amplitude (nEMG), an increase in wakefulness, and a decrease in REM sleep. Prior to DPAT dialysis, during periods of cooling, shivering occupied 99% of the total NREM time, with an increase in nEMG (416 ± 136% of control). Similarly, during wakefulness, shivering occurred 87% of the time with an increase in nEMG to 239 ± 64% of control. After DPAT dialysis, during NREM, there was a delay in the onset of shivering, and significant reductions in the amount of shivering (49% vs 99%) and increase in nEMG (312 ± 126% vs 416 ± 136%). In summary, inhibition of 5-HT neurons in the PGCL with 8-OH-DPAT dialysis decreased shivering in response to a cold stress, particularly during sleep. These data suggest that these neurons play a role in motor related thermoregulatory effector mechanisms. This may be secondary to a general effect on motor facilitation, or a specific thermoregulatory mechanism.
Influence of Feeding Practice on Neonatal Outcome
Laurie A. Hogden, MD* and William H. Edwards, MD  Dartmouth Hitchcock Medical Center

Objective: Providing optimal nutrition to the VLBW neonate is challenging and feeding practices may affect short and long-term outcomes. This study was designed to determine differences in providing enteral nutrition to VLBW infants among 9 NICUs and whether a unit’s time to first feed and to full enteral nutrition was associated with length of stay (LOS), nosocomial sepsis (NOS), chronic lung disease (CLD) and necrotizing enterocolitis (NEC).

Design/Methods: Enteral feeding data collected in a quality improvement project (Vermont Oxford NICQ 2000) on VLBW infants discharged home were matched with VON database outcomes for each infant (N=730). Time to first enteral feed and to full enteral nutrition was compared at the center level using multivariate regression analysis adjusting for case mix and a number of co-variates. Centers were split into groups based on time to first enteral feed (early, late) and time to full enteral nutrition (shortest, average, longest). The relationships between group and outcome were analyzed by stepwise linear regression.

Results: The median time to 1st enteral feed ranged from 2 to 5 days among centers, and time to full enteral feeds ranged from 14 to 26 days (P<0.00001). There was no significant correlation between time to 1st enteral feed and time to full enteral feeds. The group with a later time to first enteral feeding had a higher incidence of NEC (adj. OR 3.19, p=0.018). The early or late center grouping for 1st enteral feed was unrelated to LOS, NOS or CLD. For time to full enteral nutrition, the group of centers with the longest time had the highest incidence of NEC (p=0.011) as well as the shortest LOS (p=0.016). There was no significant correlation between time to full feed and NOS or CLD.

Conclusions: Feeding practices were highly variable among centers, with significant differences in times to 1st and full enteral feeds. Time of initiation of first feed did not correlate with time to full enteral nutrition. Centers with later initiation of feeding had a high incidence of NEC. The correlation between time to full feeds and NEC is likely due to withholding feeds as part of treatment. When analyzed by multivariate analysis, centers’ time to achievement of full enteral feeds was remarkably unrelated to rates of NOS or CLD, and had minimal effect on LOS.
A Quantitative Model of Uterine Growth and Cervical Funneling

Michael House, M.D., Kristin Myers, M.S., Anastassia Paskaleva, M.S., and Simona Socrate, Ph.D. From the Division of Maternal Fetal Medicine, Tufts-New England Medical Center (M.H.); and the Department of Mechanical Engineering, MIT (K.M., A.P., S.C.).

Objective: Our objective was to develop a quantitative, constitutive model of cervical mechanical function in order to investigate the factors that govern cervical funneling.

Methods: MODEL DEVELOPMENT: Cervical stroma is composed primarily of a network of collagen fibers, intertwined proteoglycans and interstitial fluid. We hypothesized that the mechanical behavior of cervical stroma is governed by the interplay of these constituent parts. Mathematical expressions for the mechanical behavior of the collagen and proteoglycan networks were derived using known structure – function relationships. A constitutive model of the tissue was developed by integrating both the collagen and proteoglycan network response into a macroscopic tissue response. MODEL FITTING: Cervical specimens were taken from premenopausal women undergoing hysterectomy for benign disease. Small discs of stroma were created using a slicing fixture. Cervical specimens were tested in unconfined and confined compression. The parameters of the constitutive model were fit to the observed mechanical response of the tissue. The final model was implemented in a mechanical design software program to simulate the effects of uterine growth and gravity.

Results: The mechanical response of the cervical stroma was captured by the constitutive model. An axisymmetric model of the uterus and cervix demonstrated how funneling and membrane prolapse can occur under physiologic conditions of uterine growth and gravity.

Conclusion: The constitutive model of cervical stroma captures the essential features of cervical funneling and membrane prolapse.
Have the New NRP Guidelines Changed the Delivery Room Management or Outcome of Meconium Stained Infants?
Prakash M Kabbur and Victor C Herson. Neonatology, Connecticut Children's Medical Center, Hartford, CT and Neonatology, University of Connecticut Health Center, Farmington, CT.

Background: Infants born through meconium stained amniotic fluid (MSAF) are at risk for meconium aspiration (MA). New NRP guidelines published in 2000 recommend a selective approach, avoiding intubation (INT) for vigorous babies. We sought to determine the effect of these guidelines on the delivery room (DR) management and outcome of these infants.

Objective: To compare the incidence of DR-INT and subsequent respiratory problems for infants born through MSAF before and after the new NRP recommendations.

Design/Methods: Computerized DR records for infants born at Hartford Hospital (~4000 births/yr) were analyzed. Meconium consistency, APGAR scores and INT for suctioning were recorded. Infants with 1 minute AGPAR of 8-10 were considered "vigorous." A detailed chart review was done for meconium stained (MS) newborns subsequently admitted to the NICU with respiratory distress (RD). Those with RD >24 hrs and a CXR typical of aspiration were coded as MA; those with RD <24 hrs or CXR consistent with alternative diagnoses were coded as RD-other. Patients were divided into Period 1: 1997-1999 (pre-new NRP) and Period 2: 2000-2002 (post new NRP). Groups were analyzed using chi-squared tests.

Results: The incidence of MSAF remained constant between Periods 1 and 2 while the proportion of infants intubated fell from 67% to 41% (p<.001).

<table>
<thead>
<tr>
<th></th>
<th>Period 1(N=12927)</th>
<th>Period 2 (N=11718)</th>
<th>p</th>
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<tbody>
<tr>
<td>Meconium stained (MS)(%)</td>
<td>1762(13.6)</td>
<td>1539(13.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thin (% INT)</td>
<td>845(54)</td>
<td>752(25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Moderate (%INT)</td>
<td>437(74)</td>
<td>337(42)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thick (%INT)</td>
<td>460(85)</td>
<td>450(66)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>APGAR 8-10(%INT)</td>
<td>1328(62)</td>
<td>1107(30)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>APGAR 0-7(%INT)</td>
<td>425(81)</td>
<td>431(68)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MA (% of MS)</td>
<td>15(0.85)</td>
<td>20(1.3)</td>
<td>0.21</td>
</tr>
<tr>
<td>RD-other (% of MS)</td>
<td>33(1.9)</td>
<td>22(1.4)</td>
<td>0.32</td>
</tr>
<tr>
<td>MA+RD-other (% of MS)</td>
<td>48(2.7)</td>
<td>42(2.7)</td>
<td>0.99</td>
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</tbody>
</table>

INT rates fell significantly in all subgroups. There was no significant difference between groups in the incidence of MA, RD-other or MA+ RD-other. The proportion of infants with severe disease (needing mechanical ventilation) was also unchanged [10 of 48 vs 10 of 42; NS].

Conclusions: Since the implementation of the new NRP guidelines, the rate of DR-INT for tracheal suctioning has fallen significantly without a change in overall newborn respiratory complications. These results support the efficacy of the new recommendations for DR management of infants born through MSAF.
DETECTION OF FETAL GENDER AND TRISOMY 21 USING DNA MICROARRAY ANALYSIS OF CELL-FREE FETAL DNA (CFFDNA) IN AMNIOTIC FLUID: A PRENATAL MOLECULAR KARYOTYPE.

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Background: Metaphase karyotype analysis of cells obtained by amniocentesis or CVS is the gold standard for prenatal cytogenetic diagnosis, particularly for the detection of trisomy 21. We previously demonstrated that large quantities of cffDNA are easily extracted and amplified from amniotic fluid (Clin Chem 2001;47:1867-9). In this study, we explored clinical applications of cffDNA by testing its hybridization to DNA microarrays.

Methods: With IRB approval, frozen amniotic fluid supernatant samples were obtained from 14 mid-trimester pregnant women carrying euploid fetuses (4 were 46,XX; 10 were 46,XY) and from one carrying an aneuploid fetus (47,XY,+21). CffDNA was extracted, labeled, and hybridized to the GenoSensor(TM) Array 300 (Vysis, Inc.) This microarray allows for the quantitative analysis of DNA sequences from all human chromosomes, including subtelomeres. All analyses were performed blindly without knowledge of fetal karyotype.

Results: Samples from 10 of 11 male fetuses showed increased hybridization signals on SRY and decreased signals on X chromosome markers compared to female reference DNA. Samples from all four female fetuses showed the reverse. For all 14 euploid fetal samples, markers on chromosome 21 were not significantly different from reference DNA (euploid karyotype). As expected, the aneuploid fetal sample had increased hybridization signals on 5 of 6 chromosome 21 markers.

Conclusions: These preliminary results suggest that microarrays can be used to analyze cffDNA extracted from amniotic fluid and to correctly identify gender and trisomy 21. Molecular analysis of cffDNA from amniotic fluid allows for rapid screening of samples for aneuploidy and may augment standard karyotyping techniques.

*In training

Corresponding author:
The Probability of Neonatal Respiratory Distress Syndrome as a Function of Gestational Age and FLM S/A II Value

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OBJECTIVE: Neonatal respiratory distress syndrome (RDS) affects approximately 1% of live births, and the probability of RDS continues to be a major determinant in the timing of delivery. This study was designed to investigate the optimal gestational age-specific cutoff value for the FLM S/A assay (Abbott Laboratories) for predicting RDS.

STUDY DESIGN: Amniotic fluid FLM S/A data were collected prospectively over a 2-year period. Women were included in the study if they delivered within 72 h of FLM S/A estimation. RDS was defined as a persistent oxygen requirement for >24 hours in the presence of radiographic evidence of neonatal pulmonary hyaline membrane disease.

RESULTS: A total of 415 mother-neonate pairs (28 RDS, 387 non-RDS) met criteria for analysis. Both gestational age and FLM S/A values were independent predictors of RDS. By modeling the odds of RDS using a logistic regression with gestational age and FLM S/A values as continuous variables, a probability of RDS of ≤15 can be achieved with a FLM S/A cutoff of ≥60 mg surfactant/g albumin at 28 weeks’ gestation, ≥50 at 30 weeks, ≥40 at 33 weeks, ≥30 at 35 weeks, and ≥20 at 37 weeks.

CONCLUSIONS: These data describe a means of stratifying the probability of neonatal RDS using both gestational age and FLM S/A value, and may be a useful model for clinical decision making. We are currently prospectively verifying these findings.
Placental Pathology and Neonatal Outcome Among Growth Restricted Fetuses in Pregnancies Complicated by Preeclampsia, Idiopathic Growth Restriction, and Intrauterine Inflammation

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*B Brigham & Women's Hospital, Division of Maternal-Fetal Medicine, Harvard Medical School
+Children’s Hospital of Boston, Department of Neuroepidemiology, Harvard Medical School

OBJECTIVE: We hypothesize that IUGR reflects heterogeneous pathologic processes, some of which can be distinguished by shared forms of placenta morphology.

STUDY DESIGN: We conducted a retrospective cohort analysis of 134 singleton gestations born 26-36 weeks in 5 hospitals, 1/91-12/93. Each pregnancy was complicated by growth restriction defined as a birth weight Z-score of <-2. Pregnancies complicated by TORCH infections, or congenital abnormality were excluded. A research committee of pathologists examined each placenta.

RESULTS: Among the 134 pregnancies, 69 were complicated by severe preeclampsia (PE), 34 because of non-hypertensive growth arrest (GA), and 29 because of concurrent preterm labor or membrane rupture (PL/MR). The groups had similar demographic characteristics, gestational age, and steroid exposure. The GA placentas were smallest (mean 184 vs. 213g;p=0.05) and most likely to have chronic villitis (p=0.02). Histologic inflammation was most common among the PL/MR (30%;p<0.01) and was rare among the PE and GA placentas (1%). Maternal vascular disease (decidual arteriolar pathology, abruption and infarction) (p<0.01) and syncytial knots (P=0.04) were most common among the PE placentas. Villous capillary proliferation was common to the PE and GA but not the PL/MR placentas (p=0.01). Rates of neonatal death, hypothermia, polycythemia, hypoglycemia, nucleated RBCs and RDS were similar in all groups.

CONCLUSIONS: Placenta morphology distinguishes three groups among IUGR preterm newborns. These morphologies correlate with maternal presentation. PE: Maternal vascular disease (decidual arteriolar pathology, abruption and infarction), syncytial knots and villous capillary proliferation. GA: Chronic villitis, villous capillary proliferation. PL/MR: Inflammation. The neonatal outcomes were similar among the different presentations. We hypothesize that the placenta integrates multiple pathologies into the common expression of IUGR.


OBJECTIVE: We evaluate if infants delivered prior to 28 weeks gestation after prolonged latency in pregnancies complicated by pPROM are at increased risk of neonatal white matter damage.

STUDY DESIGN: We conducted a retrospective cohort analysis of 312 singleton gestations born before 28 weeks in five hospitals, 1/91-12/93. Eligible births had at least one of three protocol cranial scans read by a blinded consensus committee and had available placental pathology. Outcome variables were Placental (histologic chorioamnionitis, fetal vasculitis) and Fetal (intraventricular hemorrhage, echolucencies, ventriculomegaly). Latency was divided into 5 intervals and outcomes in 4 were compared to those in infants delivered <1 hour after membrane rupture. Each outcome-latency relationship was evaluated in a logistic model with confounders specific to the pair.

RESULTS: Odds ratios (OR) and confidence intervals (CI) for each latency interval controlling for confounders including gestational age, maternal race, antenatal steroid and antibiotic administration, and delivery mode are shown.

<table>
<thead>
<tr>
<th>Latency Interval (hrs)</th>
<th>Chorioamnionitis</th>
<th>Fetal Vasculitis</th>
<th>IVH</th>
<th>Echolucencies</th>
<th>Ventriculomegaly</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (CI)</td>
<td>P</td>
<td>OR (CI)</td>
<td>P</td>
<td>OR (CI)</td>
</tr>
<tr>
<td>&lt;1.0</td>
<td>reference</td>
<td>-</td>
<td>reference</td>
<td>-</td>
<td>reference</td>
</tr>
<tr>
<td>1.0 –23.9</td>
<td>2.6(1.2-5.3)</td>
<td>0.01</td>
<td>1.9(1.0-3.5)</td>
<td>0.04</td>
<td>1.0(0.6-1.9)</td>
</tr>
<tr>
<td>24.0-47.9</td>
<td>3.6(0.8-15.9)</td>
<td>0.09</td>
<td>5.3(1.8-16.2)</td>
<td>&lt;0.01</td>
<td>1.3(0.5-3.3)</td>
</tr>
<tr>
<td>48.0-119.9</td>
<td>34.5(4.5-266)</td>
<td>&lt;0.01</td>
<td>15.7(6.0-41)</td>
<td>&lt;0.01</td>
<td>0.6(0.3-1.2)</td>
</tr>
<tr>
<td>120+</td>
<td>5.3(1.8-16.0)</td>
<td>&lt;0.01</td>
<td>7.8(3.1-19.7)</td>
<td>&lt;0.01</td>
<td>0.8(0.3-0.9)</td>
</tr>
</tbody>
</table>

CONCLUSIONS: Ascending trans-cervical infection after pPROM is documented by the increasing odds ratios of placental inflammation. The risk of neonatal brain damage, however, did not increase with increasing latency.
Inhibition of erbB Receptor Function in Murine and Human Pulmonary Epithelial Cells
Sandy Murray, Lucia Pham, Christiane E.L. Dammann, and Heber C Nielsen. Newborn Medicine, Floating Hospital at Tufts-NEMC, Boston, MA, United States and Pediatrics, Hannover Medical School, Hannover, Germany.

**Background:** The EGFR family of tyrosine kinases (erbB1, erbB2, erbB3, erbB4) are involved in fetal lung growth and maturation. ErbB receptors form homo- and heterodimers to produce their effects. The dimers formed in lung growth and maturation are unknown.

**Objective:** We hypothesized that antibodies directed against erbB receptors during growth and ligand binding would prevent dimers necessary for tyrosine phosphorylation leading to proliferation and surfactant synthesis.

**Design/Methods:** We used MLE-12 cells, an SV40-transformed mouse lung epithelial cell line and A549 cells, isolated from human lung epithelial carcinoma. Preconfluent MLE-12 cells were incubated with blocking antibodies directed against extracellular epitopes of erbB1, erbB2, erbB3 and erbB4 then incubated in serum-free media with EGF (10ng/ml), NRG(10nM) or fibroblast-conditioned medium (FCM). $^3$H-thymidine was added for 6 hrs as an index of proliferation. Preconfluent A549 cells were treated with antibodies (directed against C-terminal epitopes) plus EGF (50ng/ml) or FCM plus either $^3$H-thymidine to measure proliferation or $^3$H-choline to measure surfactant synthesis.

**Results:** In MLE-12 cells EGF or NRG stimulated baseline proliferation 39 and 54%; FCM had no effect. Pretreatment with anti-erbB1 or erbB2 blocked EGF and NRG stimulation completely. Anti-erbB3 and erbB4 receptor antibodies reduced baseline proliferation by 25 and 50%. Neither EGF nor NRG could restore or stimulate proliferation. In A549 cells EGF stimulated baseline proliferation by 63%. Co-incubation with anti-erbB1, 2 or 4 antibody blocked both EGF and FCM stimulation. Anti-erbB3 was ineffective. EGF increased choline incorporation by 50%. This stimulation was blocked by anti-erbB1, 2 and 3. Anti-erbB4 had no effect.

**Conclusions:** In MLE-12 cells, antibodies directed against extracellular epitopes on the 4 erbB receptors all inhibited proliferation. Inhibition was greatest with anti-erbB4 then erbB3 suggesting that dimerization with these partners is highly significant in pulmonary cell proliferation. In A549 cells, antibodies against C-terminal epitopes of erbB1 and B2 blocked proliferation and surfactant synthesis. However anti-erbB3 did not block proliferation and erbB4 was ineffective with surfactant synthesis. These data suggest that heterodimers involving erbB3 and/or erbB4 are important in proliferation and phospholipid synthesis.
Title: Predictors of Knowledge and Use of Contraception among Postpartum Adolescents in El Salvador

Authors: S. Newmann\textsuperscript{1*}, A. Goldberg\textsuperscript{1}, R. Aviles\textsuperscript{2}, O. Molina\textsuperscript{2}, T. McElrath\textsuperscript{1}, A. Foster-Rosales\textsuperscript{3}

\textsuperscript{1} Brigham and Women’s Hospital, Boston, MA, \textsuperscript{2} Hospital de San Juan de Dios, San Miguel, El Salvador, \textsuperscript{3} University of California, San Francisco, CA

Objective: To describe demographics, contraceptive familiarity and use patterns among postpartum adolescents in El Salvador.

Methods: Interviews in Spanish with 50 postpartum adolescents.

Results: Ages ranged from 13 to 18. 84% were nulliparous, 80% had partners, 6% were married. 84% reported contraception knowledge; 18% reported contraception use. Educational experience and literacy predicted birth control knowledge. Of those with contraceptive knowledge, 83% had more than 6 years of education (p=0.008). 70% of illiterate adolescents had no knowledge of contraception vs. 12% of literate adolescents (p=0.000).

After receiving postpartum contraception education, 58% stated they intended to use birth control. Having a partner and living with that partner were predictors of intent to use (97% vs. 3%, p=0.001 and 86% vs. 14%, p=0.001, respectively). Being single was a negative predictor of future use (90% vs. 10%, p=0.001).

Planned pregnancy rate was 4% and desired pregnancy rate was 82%. Having a partner was a significant predictor of desired pregnancies (90 vs. 10%, p=0.003). Living with parents significantly predicted undesired pregnancies (67 vs. 33%, p=0.05) and contraceptive use (67 vs. 33% p=0.05). Of adolescents with prior contraceptive use, 78% were older than 15, and 77% were more likely to have family support.

Discussion: Although education and literacy were predictors of contraceptive knowledge, they were not predictors of use or intent to use. Contraceptive use patterns were related to family support and partnership status, implying that utilization of contraception does not only depend on knowledge but is a decision that most adolescents make in the context of their support systems.
Control of ErbB Receptor Expression and Function In Fetal Lung Development
Heber C. Nielsen, Zackary M. Lesko, Seth H. Nielsen, Lucia Pham, Sandy Murray, Christiane E.L. Dammann. Newborn Medicine, Floating Hospital at Tufts-NEMC, Boston, MA, United States and Pediatrics, Hannover Medical School, Hannover, Germany.

Background: Fetal lung maturation involves fibroblast-type II (T2) cell communication. Glucocorticoids mediate this process; so do ErbB receptors (ErbB1, ErbB2, ErbB3, ErbB4) and their ligands EGF (E), TGFα (T), and Neuregulin (N). ErbB receptors are differentially activated by E, T, and N in fetal lung fibroblasts, with different cell responses. Control of ErbB receptor expression and activation in development is unknown.

Objective: We hypothesized that E and dexamethasone (Dex) differentially regulate ErbB receptor expression and response to ligand stimulation in fetal lung development.

Design/Methods: Sex-specific fetal mouse lung fibroblast cultures (d16 and d18 of gestation) were grown in media with 10% stripped fetal calf serum (control) ± E (10ng/ml) or Dex (10^-8 M). At confluence cells were stimulated 3min with E (100ng/ml), T (100ng/ml), or N (33nM). Western blots were probed for ErbB1, 2, and 4, tyrosine phosphorylation, and actin as an internal standard. Densitometry results were normalized to unstimulated controls.

Results: Differences by sex, gestation, and treatment were seen. In d16 males both E and Dex treatments reduced total ErbB1 and 2 but increased ErbB4. ErbB1, 2, and 4 phosphorylation was stimulated by E and T; N stimulated only ErbB1 and 2. Both E and Dex treatment increased baseline ErbB2 phosphorylation but had no effect on ligand stimulation. In d16 females, total ErbB1 and 2 were not affected by E or Dex, but E increased ErbB4. E stimulation of E-treated cells increased ErbB4 phosphorylation and reduced ErbB2 phosphorylation. Dex did not affect stimulation. In d18 males E treatment but not Dex increased total ErbB1 and 4. E stimulated phosphorylation of ErbB1, 2, and 4 in untreated and E-treated but not Dex-treated cells. In d18 females E treatment increased total ErbB1 and 4; Dex treatment had no effect. E stimulated phosphorylation of all 3 receptors in untreated and E-treated cells. In Dex-treated cells baseline phosphorylation was reduced. E stimulated phosphorylation of ErbB1, 2, and 4; N stimulated ErbB4 phosphorylation.

Conclusions: E and Dex treatments differentially affect ErbB expression and activation. Major effects were seen on ErbB1 and 4. E and Dex may prime cell responsiveness to ErbB ligands to regulate fetal lung fibroblast-T2 cell communication in lung maturation. Funded by HL37930, HL04436, Peabody Foundation, Charles Hood Foundation.
Time of Birth and Its Relationship to Poor Obstetrical Outcomes
Adam C. Urato, MD Tufts-New England Medical Center; Sabrina D. Craigo, MD Tufts-New England Medical Center; William F. O’Brien, MD University of South Florida-Tampa General Hospital

Objective: To determine if there exists an association between the time of birth and severe fetal neurologic injury resulting in death.

Background: In 1988, the Florida legislature established the Florida Birth-Related Neurologic Injury Compensation Association Act (NICA.) NICA provides for compensation regardless of fault after “injury to the brain or spinal cord of a live infant weighing at least 2,500 grams at birth caused by oxygen deprivation or mechanical injury occurring in the course of labor, delivery, or resuscitation in the immediate post-delivery period in a hospital which renders the infant permanently and substantially mentally and physically impaired.” From November 1989 to August 2002, 447 NICA cases were identified. Of these 447 cases, 81 resulted in the immediate death of the neonate or the eventual death of the child.

Study Design: All 81 cases that resulted in death were reviewed by a single author who collected information on date and time of birth, maternal age, race, gravidity, parity, gestational age, prenatal care, past medical and surgical history, past obstetrical history, medication use during the pregnancy, fetal monitoring in labor, complications of labor, mode of delivery, complications of delivery, and neonatal resuscitation. Birth times of cases were compared with birth times from a sample of all deliveries in the state of Florida for the year 1996.

Results: Of the 81 NICA cases of severe neurologic injury resulting in the death of the child, 36/81 (44.4%) had birth times from 11 PM to 8 AM (Sunday through Saturday.) Assuming a random distribution of birth times 30/81 (37.0%) would be expected. 14/81 (17.3%) had birth times from 9 AM to 5 PM, Monday through Friday. Assuming a random distribution of birth times 19/81 (23.5%) would be expected. Moreover, a preliminary sampling from the state records appears to show that delivery during the day is more common than a random distribution would demonstrate, suggesting an even stronger association between nighttime delivery and neurologic injury.

Conclusion: Time of birth appears to be associated with neurologic injury, with nighttime and early morning delivery (11 PM to 8 AM) placing a fetus at risk and daytime delivery during the week (9 AM to 5 PM) being protective. Factors that lead to neurologic injury and how these factors can be modified should be further investigated.
Title: Serum Alkaline Phosphatase Values for Infants Born ≤ 32 weeks Gestation.

Authors: Vidavalur, R *, Hussain N, McLean CE, Pappagallo M
University of Connecticut Health Center, Farmington, CT

Text: Current literature states normal serum alkaline phosphatase (ALKP) values for preterm infants as less than 5 times the adult normal limit. ALKP values within this range have been observed in preterm infants with rickets. Data obtained from one neonatal intensive care unit (NICU) is difficult to extrapolate to another NICU population due the variability of acuity, patient population and medical practice.

The objective of this retrospective data analysis was to determine the mean and median serum ALKP values for infants born ≤ 32 weeks gestation. Data were reviewed from information entered into a Neonatal Information Database at John Dempsey Hospital Level III NICU between Jan 1, 1998 and Dec 31, 2002.

Based on 769 ALKP data points, the mean and median ALKP values are 346 IU/L and 308 IU/L respectively. In two univariate analyses, ALKP values demonstrated a negative linear relationship to weight at birth (P<0.0001) and gestational age at birth (P<0.0001). Multivariate analysis was utilized to determine the statistical significance of gender, race, chronological gestational age, week of life ALKP value measured, and average weight gain on ALKP values. African American infants were found to have a statistically significant higher mean ALKP value compared to both Caucasian and other racial groups (P<0.0001). ALKP values had a positive linear relationship to the week of life ALKP value measured (P<0.0001). Gender, chronological gestational age, and weight gain showed no significance.

In conclusion, infants born of lower birth weights and gestational ages had higher ALKP values than those born closer to 32 weeks gestation at higher birth weights. ALKP values decreased with increasing post conceptual age. Further research is required to determine if this elevation in ALKP reflects increased bone turnover for growth or demineralization.
Does the frequency of soft sonographic aneuploidy markers vary by fetal gender? Joseph R. Wax, M.D., Angelina Cartin, Michael G. Pinette, M.D., Jacquelyn Blackstone, D.O. Division of Maternal-Fetal Medicine, Department of Ob/Gyn, Maine Medical Center, Portland, Maine

Objective: To determine if the frequency of soft sonographic aneuploidy markers varies by fetal gender.

Methods: We identified all singleton fetuses with known gender undergoing genetic sonography at 17-0/7-21-6/7 weeks’ gestation in a single perinatal center from 1/1/00-12/31/02. Markers studied were biparietal diameter/femur length, transcerebellar diameter, ear length, echogenic bowel, femur length, humerus length, absent middle 5th phalanx, nuchal fold, renal pelvis dilation, echogenic cardiac focus, and choroid plexus cysts. Additional information extracted from the prospectively ascertained database included maternal age, referral indications, and chromosomal analyses. Multiple gestations, and fetuses with structural or chromosomal abnormalities were excluded. The study received exempt review status by the Institutional Review Board. Dichotomous variables were compared by the Chi Square or Fisher exact tests; continuous variables were compared by the unpaired t-test.

Results: 2485 eligible fetuses, 1289 (51.8%) male and 1196 (48.2%) female, were examined at 18.9 ± 0.9 weeks. Referral indications included maternal age ≥ 35 (n = 1822), abnormal second trimester serum screen (n = 421), ultrasound abnormality (n = 313), prior aneuploid offspring (n = 15), or other (n = 80). More than one referral indication was possible for a given fetus. Overall, male fetuses exhibited echogenic cardiac focus [odds ratio 1.24 (95% CI = 1.0-1.54); p = .05] and renal pelvis dilation [odds ratio 2.03 (95% CI = 1.17-3.53); p = .009] significantly more often than females. However, when fetuses were evaluated with respect to single isolated markers, only the male predominance of echogenic cardiac focus persisted [odds ratio 1.23 (95% CI = 1.0-1.59); p = .05]. No markers were seen with increased frequency in female offspring.

Conclusions: Male fetuses exhibit a statistically, but not clinically significant increased frequency of echogenic cardiac foci as compared to females. Gender-specific adjustment of sonographically-derived aneuploidy risks are not indicated.
Are intracardiac echogenic foci markers of congenital heart disease in the chromosomally abnormal fetus? Joseph R. Wax, M.D., Angelina Cartin, Michael G. Pinette, M.D., Jacquelyn Blackstone, D.O. Division of Maternal-Fetal Medicine, Department of Ob/Gyn, Maine Medical Center, Portland, Maine.

Objective: To determine whether intracardiac echogenic foci (ICEF) are markers of congenital heart disease (CHD) in chromosomally abnormal fetuses. Methods: We identified all chromosomally abnormal fetuses undergoing targeted sonography at 17 0/7 – 21 6/7 weeks’ gestation in a single perinatal center from 1/1/94 – 6/30/03. Information extracted from the prospectively ascertained database included maternal age, referral indication, ultrasound findings, and chromosomal analyses. Routinely recorded aneuploidy markers included femur, humerus, and ear lengths, transcerebellar diameter, echogenic bowel, ICEF, CHD, duodenal atresia, absent middle fifth phalanx, pyelectasis ≥ 4 mm, and choroid plexus cyst. The study received exempt review by the Institutional Review Board. Statistical comparisons of dichotomous variables were performed by the Fisher exact test. Descriptive statistics including odds ratios (OR) with 95% confidence intervals (CI) were also used. Results: 139 chromosomally abnormal fetuses met inclusion criteria. Women aged 32 ± 7 years were examined at 18.9 ± 1.2 weeks’ gestation. Referral indications, of which more than one was possible, included maternal age ≥ 35 (n = 41), abnormal second trimester serum screen (n = 22), or other (n = 38). Chromosomal abnormalities and accompanying ICEF and CHD are summarized in the table. Two of 25 (8%) fetuses with ICEF had CHD as compared to 38/114 (33.3%) fetuses without ICEF (P = .006; OR [95% CI] = 0.17 [0.05 – 0.87]). ICEF sensitivity, specificity, positive, and negative predictive values for detecting CHD were 5%, 77%, 8%, and 66.7%, respectively. Similarly, 1/18 (5.6%) fetuses with trisomy 21 and ICEF had CHD as compared to 16/43 (37.2%) fetuses with trisomy 21 not demonstrating ICEF (P = .009; OR [95% CI] = 0.09 [0.01 – 0.82]). In this subset, ICEF sensitivity, specificity, and positive and negative predictive values for CHD were 5.9%, 61.4%, 5.6%, and 62.8%, respectively. Conclusion: An ICEF in a chromosomally abnormal fetus, including those with trisomy 21, is not a useful marker for CHD, and appears to be associated with a decreased frequency of CHD.

Table 1. Frequency of ICEF and CHD by chromosomal abnormality.

<table>
<thead>
<tr>
<th>Chromosome Abnormality</th>
<th>n (%)</th>
<th>ICEF n (%)</th>
<th>CHD n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy 21</td>
<td>61 (43.8)</td>
<td>18 (29.5)</td>
<td>17 (27.8)</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>14 (10.0)</td>
<td>0 (0)</td>
<td>8 (57.1)</td>
</tr>
<tr>
<td>Trisomy 13</td>
<td>13 (9.3)</td>
<td>2 (15.4)</td>
<td>5 (38.5)</td>
</tr>
<tr>
<td>Triploidy</td>
<td>10 (7.1)</td>
<td>1 (10)</td>
<td>3 (30)</td>
</tr>
<tr>
<td>Numerical sex chromosome</td>
<td>13 (9.3)</td>
<td>1 (7.7)</td>
<td>1 (7.7)</td>
</tr>
<tr>
<td>Other *</td>
<td>28 (20.1)</td>
<td>3 (10.7)</td>
<td>6 (21.4)</td>
</tr>
<tr>
<td>------------------------------</td>
<td>139 (100)</td>
<td>25 (17.9)</td>
<td>40 (28.8)</td>
</tr>
</tbody>
</table>

*structural rearrangements (25); other trisomies (3)
Changes in Morbidity and Mortality in Very Low Birth Weight Neonates with Prophylactic Surfactant Administration.  AI Whitsel+, N Hussain, HN DeSilva, and BA Bernstein.

* University of Connecticut Health Center, Farmington, CT and + Saint Francis Hospital and Medical Center, Hartford, CT.

**Background:** For over a decade, intra-tracheal surfactant therapy has been used for treatment of neonatal respiratory distress (RDS). Infants at highest risk of respiratory complications are those < 1000 grams (extremely low birth weight, ELBW) and / or < 28 weeks estimated gestational age (EGA). Prophylactic treatment (PT) was found to be more beneficial than rescue treatment (RT) for high risk neonates by a metanalysis published in the Cochrane Collaboration (Soll and Morley, “Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants,” 2000). Between November 1999 and January 2000 our hospitals changed their surfactant administration regimen from selective, delayed use after clinical evidence of RDS to prophylactic delivery room administration in high-risk neonates before symptoms of RDS.

**Objectives:** (1) Determine if there are mortality differences in the high-risk neonates before and after starting the prophylactic regimen. (2) Determine if there is a significant difference in the frequency of bronchopulmonary dysplasia (BPD) defined as the use of supplemental oxygen at day 28 of life and / or the corrected 36 weeks EGA. (3) Evaluate the differences in secondary morbidities: pneumothorax, presence and grade of retinopathy of prematurity (ROP), periventricular and intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), patent ductus arteriosis (PDA), early and late bacterial sepsis and fungal infections.

**Methods:** The outcomes of 490 viable, non-anomalous infants ≥ 22 weeks EGA weighing < 1000 gms born within the University and community hospitals and either resuscitated in the delivery room and / or admitted to the neonatal intensive care units between January 1997 and December 2002 were evaluated. The neonates were divided into two groups: those born before the use of prophylactic surfactant administration [RT group, N=228] and those born after the use of prophylactic surfactant [PT group, R=262]. T-tests were used to compare the groups’ average birth weights and mean EGAs at birth. Chi square analyses were used to assess differences in gender ratios, surfactant use and mortality rates for all neonates. Differences in morbidities among the survivors were evaluated by chi square analyses. A Wilcoxon Rank Sums analysis was performed comparing the ROP grades.

**Results:** There were no differences in mean birth weights, gender ratios or average gestational age between treatment groups. The mortality rate (RT =18.0% and PT = 17.6%) and the incidence of BPD were unchanged. The frequency of pneumothorax, PDA, IVH, early bacterial sepsis, fungal infection and NEC were similar. There was a significant increase in the number of infants receiving surfactant (91% vs. 79%). PVL was decreased in the PT group (RR = 0.40, 95% CI=0.18, 0.89). The diagnosis (RR=1.38, 95% CI=1.14, 1.66) and grade of ROP (p < 0.001) and late bacterial sepsis (RR = 2.52, 95% CI=1.26, 5.04) increased in the PT group.

**Conclusion:** The University and community hospitals survival rates and the incidence of BPD for high-risk neonates remained stable during the change in our surfactant regimen from rescue to prophylactic treatment. Of the secondary morbidities, there was an increased risk for ROP (presence and higher grade) and late bacterial sepsis; however, the relative risk of PVL was decreased in the PT group. In our hospitals, it remains unclear if exposure of a greater percentage of high-risk neonates to surfactant treatment in the delivery room has an overall benefit.
ErbB Receptor Cross-talk and Co-localization in Mouse Lung Epithelial Cells
Katja Zscheppang*, Elenar Korenbaum, Sujatha M. Ramadurai, Heber C. Nielsen, Christiane E.L. Dammann. Department of Pediatrics, Hannover Medical School, Hannover, Germany, University of Applied Sciences Lausitz, Senftenberg, Germany, Department of Biophysical Chemistry, Hannover Medical School, Hannover, Germany, and Department of Pediatrics, Tufts New England Medical Center, Boston, MA.

Background: ErbB receptors, critically important for embryonic neuronal, cardiac, and lung development, are expressed in late gestation lung where they play a major role regulating the onset of surfactant synthesis (AJRCCM 167:1711-16, 2003). ErbB receptor ligands neuregulin (NRG) and epidermal growth factor (EGF) initiate this process. We previously showed that all four erbB receptors are expressed in both fetal lung type II cells and fibroblasts, and differ in phosphorylation and cellular response after ligand stimulation. Different erbB receptor ligands can cause diverse biologic results by stimulating specific erbB-dimers. It is not known how dimerization, cellular localization, and co-localization of dimers are regulated in fetal type II cells.

Objective: We hypothesized that different ligands initiate different erbB receptor dimerization, localization and co-localization patterns in mouse epithelial type II cells.

Design/Methods: We used MLE-12 cells, a mouse alveolar type II cell line, as a model. Cells were cultured either in culture dishes or on glass cover slips. The cells were stimulated for 2min with EGF (100ng/ml) or NRG (33 nM). Co-immunoprecipitation (Co-IP) was prepared for each erbB receptor. For fluorescent microscopy, cells were incubated with erbB antibodies, followed by fluorescent-tagged 2° antibody. Receptor localization and co-localization were determined by confocal microscopy.

Results: Co-IP resulted in dimerization patterns that preferentially included erbB4. ErbB4 was the only receptor that showed a mixed pattern of autophosphorylation and phosphorylation in response to stimulation. Confocal microscopy studies showed a predominant localization of erbB1 in the cytoplasm, while erbB2 and ErbB3 almost exclusively localized to the nucleus. In contrast, erbB4 again exhibited a mixed pattern between cytoplasm and nucleus. EGF and NRG stimulated a more diffuse staining of erbB1 and 4 in the cytoplasm.

Conclusions: Among all four erbB receptors expressed by fetal lung epithelial cells, erbB4 appears to play a unique role. First, erbB4 might be the universal dimerization partner. Second, erbB4 might be rather mobile, moving between cell membrane and nucleus. Due to these unique capabilities, erbB4 may play a major role in the signalling of fetal surfactant synthesis. (Funded by NIH, Charles Hood and Peabody Foundation, and HiLF).