SAFETY OF PROTEIN ADMINISTRATION TO EXTREMELY LOW BIRTH WEIGHT INFANTS

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BACKGROUND: Malnutrition in the early postnatal period may have detrimental effects on growth and development. Increasing amino acid (AA) administration in preterm infants improves nitrogen retention, prevents loss of lean protein mass, and increases levels of serum amino acids. AA provision to extremely low birth weight (ELBW) infants in the immediate postnatal period is often not equivalent to that required for fetal growth, due to concerns of high levels of blood urea nitrogen (BUN) and metabolic acidosis. One retrospective review showed no association between serum BUN and protein intake; no studies have assessed association between acidosis and protein intake. **OBJECTIVES**: The purpose of this study is to determine the correlation between protein intake in the first week of life and serum BUN and acidosis. We hypothesize that there is no correlation between amount of AA administered in the first week of life to ELBW infants and serum bicarbonate (HCO3) or BUN levels. **STUDY DESIGN**: This is a retrospective review of 122 neonates 400 to 1000 grams birth weight admitted to Women & Infants Hospital NICU from 8/1/06 to 10/31/08 who received early hyperalimentation (HAL). Laboratory and nutritional data from postnatal days 1 to 7 was collected. A random coefficient model was used to estimate the relationship of AA intake in the first week of life with BUN and HCO3. **RESULTS**: There were 496 separate BUN and 505 separate HCO3 values analyzed. The range of protein intake was between 0 and 4 g/kg/day in the first week of life. The average BUN on day of life 1 was 18.7 mg/dl. For every 1 g/kg of protein given on day 1 there was an increase of 5 mg/dl in BUN ($p<0.0001$). There was a relative decrease in BUN values by 1.4 mg/dl/day on day 2 to 7 ($p<0.0001$). There was no significant association between protein intake and HCO3 in the first week of life. **CONCLUSIONS**: In ELBW infants who are predominantly nourished with HAL in the first week of life, AA administration is not associated with metabolic acidosis. The association of protein load with BUN is initially positive, which may reflect a catabolic state in the immediate postnatal period. The relationship of protein with BUN decreases with time, potentially as the neonate develops a positive nitrogen balance.

Acute Lung Injury and ErbB4 Signaling in the Developing Lung

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Background: Inflammation and hyperoxia contribute to acute lung injury in preterm infants. ErbB4 plays an important role in fetal lung development. Pulmonary ErbB4 deletion in a cardiac rescue mouse model (HER4^{heart}) results in delayed fetal lung development and alveolar hypoplasia in postnatal animals. We have shown that inflammation alters ErbB receptor amounts in the fetal lung. However, the role of ErbB receptor signaling in acute lung injury is unknown. *Objective:* To study ErbB receptor signaling with hyperoxic and inflammatory lung injury in the developing lung. *Methods:* First, pulmonary ErbB receptor protein expression was studied in fetal and adult lungs from HER4^{heart} (-/-). Second, pregnant HER4^{heart} (+/-) mice were treated with LPS (100g/kg, intra-amniotic) at d17 of gestation. Lungs were isolated 24h later for ErbB receptor analyses. Third, fetal E17 lung fibroblasts, epithelial type II (T2) cells, and lung organ cultures were isolated wild type (WT) lungs and cultured for 48h in RA or 95% oxygen. ErbB receptor expression was studied. Surfactant disaturated phosphatidylcholine synthesis (DSPC) was measured in T2 cells and lung organ cultures. *Results:* First, in adult HER4^{heart}(-/-) lungs, ErbB1, 2, and 3 receptor protein and phosphorylation were downregulated. At fetal E17 and E18 only ErbB2 expression was decreased. Second, intrauterine LPS treatment increased ErbB1, 2, and 3 receptor expression in WT animals. This was blunted in HER4^{heart} (-/-) lungs. Third, hyperoxia decreased expression of all four ErbB receptors in WT lung fibroblasts. Decreased ErbB2 and 3 was also seen in fetal WT T2 cells as well as decreased surfactant synthesis. However, in WT organ culture, ErbB4 receptor expression was increased after hyperoxia injury. The hyperoxia-induced decrease in surfactant synthesis was overcome in the lung organ cultures. *Conclusions:* ErbB4 not only plays a critical role in lung development, but also in protective remodeling after inflammatory or hyperoxic lung injury. Mesenchymal-epithelial interactions are critical in remodelling after injury. Therapeutically enhancement of ErbB4 expression might prevent some of the lung injury seen in the preterm born infant exposed to inflammation and/or hyperoxia. (Support: NIH HL 37930, Peabody and Gerber Foundation, Susan B Saltonstall Funds, DFG Da378/3-1 and 3-2)

Comparison of Methicillin-Resistant and Methicillin-Sensitive *Staphylococcus aureus* Infections in the Neonatal Intensive Care Unit

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Background: *Staphylococcus aureus* infections are a common source of hospital-acquired infection (HAI) in neonatal intensive care units (NICUs). Although many centers have screening and isolation policies for the containment of methicillin-resistant *Staphylococcus aureus* (MRSA), such approaches are not usually applied to methicillin-sensitive *Staphylococcus aureus* (MSSA). Little is known about the relative impact of MRSA and MSSA infections among NICU patients.

Objective: To compare the clinical characteristics and outcomes associated with MRSA and MSSA infections in a tertiary care NICU with a screening and isolation policy for MRSA.

Design/Methods: Case-control study conducted at the Brigham and Women's Hospital NICU from 8/2000-6/2008. During this period, all neonates were screened weekly for MRSA colonization. Beginning in 2004, the screening culture results included identification of MSSA colonization. All infants > 72 hrs of age with blood-culture proven MRSA or MSSA HAI were identified by search of the hospital microbiology database. Cases were infants with MRSA-HAI. Three control infants with MSSA-HAI infections were matched to each MRSA case by gestational age (GA) and year. The clinical characteristics of each infant were recorded and compared. Continuous variables were assessed by t-test; dichotomous variables by chi-square analysis.

Results: Eight cases of MRSA-HAI (0.06 cases/1000 patient-days) and 64 cases of MSSA-HAI (0.45 cases/1000 patient-days) were identified during the study period. During 2005-2007, 1.3% of all NICU admissions became colonized with MRSA; 17% became colonized with MSSA. The mean GA for both MRSA and MSSA infants was 26.9 wks. There were no significant differences between the MRSA and MSSA infants in day of life at onset of infection or in clinical status at onset of infection. Two MSSA infants and one MRSA infant died. There were no significant differences in measures of morbidity attributed to infection and no difference in total length of stay. The mean number of days of bacteremia was significantly different: 6 (range 1-15) for MRSA and 2 (range 1-6) for MSSA (p= 0.0095).

Conclusions: Although MRSA HAI was associated with longer periods of bacteremia, both MRSA and MSSA HAI occurred at similar times and both resulted in significant morbidity and little mortality. NICU infants may benefit from efforts to control MSSA colonization and infection similar to those used for MRSA.

Title: Fetal Type II Cells Do Not Undergo Epithelial- Mesenchymal Transition

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Background: Adult alveolar type-II (T2) cells undergo Epithelial-Mesenchymal Transition (EMT) after TGFβ treatment and express phenotypes of mesenchymal cells. Most regeneration processes in adult tissue are associated with progression of fibrosis. However, fetal tissue is capable of wound repair without scars and fibrosis. Both adult and fetal T2 cells are multipotent, showing some stem cell characteristics. Adult T2 cells are capable of both self-renewal and serving as progenitors for type-I (T1) cells. Fetal T2 cells function as distal airway epithelial progenitor cells. It is not known if fetal T2 cells express stem cell markers or undergo EMT.

Objective: We hypothesize that fetal T2 cells express stem cell markers and in contrary to adult T2 cells do not undergo EMT in response to TGF-β1.

Design/Methods: Isolated fetal d21 rat T2 cells (>95% pure) were pretreated with cis-OH-proline to eliminate remaining fibroblasts, followed by 2.5 ng/ml TGF-β1 or in combination with 10ng/ml epidermal growth factor (EGF) treatment. Cells were harvested after 7d of culture (5d treatment) for Western blot analysis, immunhistochemistry, RT-PCR and flow cytometry. Additionally, MLE-12 cells were cultured and treated with TGF-β1 for the same time period.

Results: TGF-beta decreased SP-C protein content in fetal T2 cells, but did not change the % of SP-C-immunopositive cells. EGF inhibited TGF-β1 induced decrease in SP-C, but did not affect the % of SP-C positive cells. TGF-β1 and EGF did not induce expression of mesenchymal markers vimentin, desmin, and collagen type I or the T1 cell marker AQP5 (none are expressed in fetal T2 cells at baseline). A high percentage of untreated fetal T2 cells express stem cell markers CD90 and CD73. This was markedly decreased after TGF-β1 treatment. The MLE-12 cells showed an increase in the expression of mesenchymal markers after TGF-β1 treatment, similar to other adult type II cells.

Conclusions: TGF-β1 treatment does not induce fetal T2 cells to undergo EMT despite decreasing CD90 and CD73 expression. These data imply a mechanism whereby fetal tissue is able to repair without scars and fibrosis perhaps through their retention of stem cell characteristics.

Title: Racial Disparities and Overall Low Rates of Providers Recommending Folic Acid During Primary Care Visits for Young, Non-Pregnant Women in the US.

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Background: Folic acid (FA) use started prior to pregnancy confers a decreased risk of neural tube defects, and may decrease the risk of preterm birth. Because approximately 20-50% of pregnancies are unplanned, the American College of Obstetricians and Gynecologists and the Institute of Medicine have published guidelines and policies that state that all woman of childbearing age should take daily 400 mcg of FA, the amount contained in a standard multivitamin (MVI).

Objective: Our aim was to determine whether healthcare providers recommend FA or FA-containing MVIs to their non-pregnant, female patients of childbearing age and whether a racial disparity exists in this anticipatory guidance.

Design/Methods: This is a cross-sectional study using data from the Center for Disease Control and Prevention's National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey (NHAMCS) (2005 and 2006). Among non-pregnant, female patients of childbearing age (15-44), the proportion of preventative health visits during which a provider ordered MVI or FA supplements was determined. Next, the rates of MVI/FA orders were compared among visits for non-Hispanic White women and their non-White counterparts. Analysis was conducted using SAS-callable Sudaan to account for survey design and to obtain population estimates.

Results: There were 3,923 preventative care visits for non-pregnant women of childbearing age, representing 14.6 million visits nationally. Overall, 4.15% of visits for non-pregnant women of childbearing age included ordering MVI/FA supplements, as opposed to 42% of visits for pregnant women. Among visits in non-pregnant women, the rates were 4.72% for White women, 0.92% for Black women, and 13.5% for Asian women. (Chi Square p=0.0053.)

Conclusions: Preventative care visits represent an important venue for anticipatory guidance regarding the benefits of FA for women of childbearing age, but appear to be under-utilized in all women and especially in Black women. Although these data count number of visits and not individual women, they do suggest racial disparity in preventative care that could, in turn, affect disparities of health outcomes such as neural tube defects and preterm birth.

A Meta-Analysis of High vs Low Oxygen Saturation and Severe Retinopathy of Prematurity

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Abstract

Background: Some studies suggest that high oxygen saturation increases the risk of severe retinopathy of prematurity (ROP), while others suggest that high oxygen saturation reduces the risk at late post menstrual age (PMA).

Objective: To perform a systemic review and meta-analysis including studies that report severe ROP incidence of newborn infants with high or low oxygen saturation measured by pulse oximetry.

Methods: Data Sources: Studies were identified through a Pubmed search of the literature using the Mesh terms "retinopathy of prematurity" and "oxygen therapy". All identified papers were cross-referenced for studies missed with the Pubmed search. Data extraction: Information from individual studies was extracted by 2 independent extractors using standardized forms. Study selection: We performed meta-analyses on 6 initially identified publications addressing the association between severe ROP and oxygen saturation measured by pulse oximetry. Statistical analyses were performed with Stata using a random effect model to calculate the summary effect estimate. To examine possible publication bias funnel plot was visually inspected. We compared high oxygen saturation range from 89%-99% with low oxygen saturation range 70%-96%.

Results: High oxygen saturation in the first postnatal weeks was associated with a 2.3-fold increased risk of threshold ROP (95% CI 1.6-3.5) in four of the 6 studies. Two of the 6 studies addressed the association between oxygen saturation and threshold ROP at >35 weeks postmenstrual age (PMA) and suggested a decreased risk for progression to severe ROP (RR 0.7, 0.5-1.07).

Conclusion: Meta-analysis confirms that high oxygen saturation during the first neonatal weeks is associated with a significantly increased risk of threshold ROP, while it might be associated with a risk reduction when administrated at PMA >35 weeks. There might be room for additional clinical studies into this potentially protective mechanism.

Impact of Routinely Offering Cystic Fibrosis Screening in Patients Undergoing Genetic Counseling for Other Indications.

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Objective: To evaluate the impact of offering cystic fibrosis (CF) carrier testing at a time of genetic counseling for other indications on testing acceptance and carrier identification.

Study Design: A retrospective chart review was conducted at a single maternal-fetal medicine practice on all women undergoing genetic counseling for indications other than CF, from October 1, 2007 through September 30, 2008. All women were offered CF carrier testing if no prior testing had been performed. Charts of previously untested women were reviewed for response to offered testing, results of accepted testing, and impact of carrier status on further paternal and prenatal CF evaluation.

Results: 1098 women underwent genetic counseling for indications other than CF during the study period. Of these, 357 (33%) had prior CF carrier testing, and 15 carriers had been identified. An additional 131 women accepted testing at the time of genetic counseling and 9 more carriers were identified. This resulted in 488 (44%) of patients seen for genetic counseling being tested ($p<.0001$). Seven of nine (78%) newly identified carriers had partners that underwent carrier testing, none of whom were carriers.

Conclusion: Routinely offering CF carrier testing during prenatal genetic counseling for other indications significantly increases testing acceptance and improves carrier identification. More study is needed to understand why most patients continued to decline testing.

Title: The Impact of Maternal Characteristics on the Moderately Premature Infant

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Background: Moderately premature infants, defined as those born between 30 0/7 and 34 6/7 weeks gestation, comprise 3.9% of all births in the United States and 32% of all preterm births. This group has a relatively low morbidity and mortality, although substantially increased compared to infants at term. A portion of these infants require tertiary level care and thus would be transferred out if born at a hospital that is unable to properly manage that severity of illness.

Objective: The primary aim of our study is to determine the impact of maternal characteristics and antenatal medical management on the early neonatal course of the moderately premature infant. The secondary aim is to create a clinical prediction rule to determine which infants require intubation and mechanical ventilation in the first 24 hours of life. Such a prediction rule could impact the decision to transfer maternal-fetal patients prior to delivery to a facility that houses a Level III NICU, where optimal care could be provided without the requirement for a neonatal transfer.

Methods: We undertook an analysis of a cohort of infants in the Moderately Premature Infant Project (MPIP) database. MPIP is a multi-center cohort that contains prospectively collected data in combination with a retrospective chart review and post-discharge telephone interviews. MPIP includes 850 infants born at gestational age 30 0/7 to 34 6/7 weeks, with birth weight between 1,500 grams and 2,499 grams, who were discharged home alive from the study hospital. We used bivariate and multivariate analysis to build a logistic regression model in order to identify maternal characteristics associated with the primary outcome, administration of surfactant.

Results: In multivariate modeling, we identified three predictors for administration of surfactant, including birth by Cesarean section (OR=1.52 [1.04, 2.22]), use of magnesium sulfate (OR=1.68 [1.14, 2.47] and race (OR not shown); and three factors which were protective, including older gestational age (OR=0.5, [0.43, 0.58]), female gender (OR=0.58 [0.41, 0.84]), use of betamethasone (OR=0.53, [0.34, 0.84]). The clinical prediction rule correctly discriminated between infants who received surfactant versus those who did not in 77% of cases.

Conclusions: The six antenatal risk factors identified are associated with a requirement for Level III NICU care as defined by the need for surfactant administration. Future analysis will involve the examination of a broader spectrum of antenatal characteristics and revalidation of the prediction rule in a separate cohort.

Maternal Perinatal Methadone Maintenance and the Incidence of Fetal Talipes Equinovarus (Club Foot): A Retrospective Case Series

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ABSTRACT

Objective: Our intent was to analyze the incidence of fetal clubfoot in women on methadone maintenance at Boston Medical Center and to determine if this incidence is increased in comparison to the general population.

Methods: A retrospective chart review was performed to identify fetuses diagnosed with club foot between 2000 and 2007 on fetal anatomy surveys. An additional retrospective chart review was performed in order to identify women who had received perinatal methadone maintenance for narcotic addition between 2000 and 2007. Patients who were both on methadone maintenance and noted to have fetal club foot on ultrasound were identified. All in-utero diagnoses were confirmed postnatally. The incidence of fetal club foot was then calculated and compared to the published incidence in the general population, i.e. 1 in 1000.

Results: 17 fetuses were identified with either unilateral or bilateral club foot. 13 patients were excluded due to no exposure to perinatal methadone. During this time period, 175 women were identified as having been exposed to methadone during their pregnancy. Of these women, 4 had fetuses diagnosed with club foot. The incidence of club foot in this population was 4/175 (20/1000 95% CI: 6/1000 - 60/1000). When compared to the incidence in the general population, the incidence of clubfoot among methadone users in pregnancy is highly significant (p=0.0001).

Conclusion: In our patient population, the use of methadone maintenance in pregnancy may be an additional important factor in the etiology of fetal club foot. Larger studies are required to ascertain whether this is a true association or merely a statistical finding in order to best counsel patients.

Effect of Duration of Second Stage of Labor and Mode of Delivery on Neonatal Complications among Preterms

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Objective: To study the effect of the duration of the second stage of labor and mode of delivery on the incidence of intraventricular hemorrhage (IVH) among infants weighing ≤1500 gm or ≤30 weeks of gestation.

Study Design: We conducted a retrospective chart review of a subset from the Vermont Oxford database at Baystate Medical Center. Maternal characteristics and duration of the second stage were abstracted from medical records. A total of 401 singleton deliveries between 01/03 and 06/08 without major congenital malformation were included in the study.

Results: There were 253 cesarean sections and 148 vaginal deliveries. The mean duration of the second stage of labor was 14.4 min (SD=14.6 min). There were 37 newborns with IVH in the cesaeran section group and 57 newborns with IVH in the vaginal delivery group. Multivariate odds ratio was calculated adjusting for gestational age and antenatal steroids. The overall association between duration of second stage of labor and IVH (OR=1.01; 95% CI: 0.98, 1.03) was non-significant. However, when analysed using linear splines, there was a significant increase over time for the risk of IVH before 10 min (OR=1.15; 95% CI: 1.03, 1.29), but the risk was non-significant beyond the first 10 minute period (OR= 0.98; 95% CI: 0.76, 1.26).

There were 57 newborns with IVH in cesarean group, 18 of which had grade III/IV IVH. There were 61 newborns with IVH in the vaginal group of which 10 had grade III/IV IVH. Compared to the cesarean section group, the vaginal delivery group had a significantly increased risk for IVH (OR=1.96; 95% CI:1.25, 3.08). However, the risk of grade III /IV IVH was not significantly different between the two groups (OR=0.84; 95% CI: 0.37, 1.90).

Conclusion: The mean length of the second stage of labor is very short in infants weighing ≤1500 gm or ≤30 weeks of gestation. An increase of all types IVH over time for the first 10 min of the second stage of labor suggests that the duration of this stage of labor may contribute to the development of IVH. The risk for any grade of IVH increased significantly with vaginal delivery but a significant association was not detected in the clinically important grade III /IV IVH. Further studies with larger numbers of cases of IVH are required to fully explore these associations.

NeoQIC: the Neonatal Quality Improvement Collaborative of Massachusetts

Munish Gupta, Beth Israel Deaconess Medical Center, and Alan Picarillo, UMass Memorial Medical Center, on behalf of the NeoQIC Steering Committee.

Description: NeoQIC is a voluntary organization of health care providers and institutions throughout Massachusetts that seeks to promote quality improvement in neonatal intensive care through joint projects and initiatives built upon the open sharing of information and practices. A regional neonatology quality improvement collaborative for Massachusetts was first proposed in 2002, and the concept was reintroduced in 2006. The first formal NeoQIC meeting was held in September 2007. Membership in NeoQIC currently consists of all ten of the level III NICUs in Massachusetts. Nine of the units are Vermont-Oxford Network (VON) members, and the tenth is a referral center without a delivery service. In 2006, NeoQIC hospitals delivered 34,398 infants (44% of the state total), and 826 very low birth weight infants (79% of the state total).

Accomplishments and Results: Four NeoQIC meetings have been held since 2007; at each, we have had greater participation from member NICUs and greater enthusiasm for NeoQIC projects. It seems we have achieved 'buy-in' from all members. We have agreed upon core principles of the organization, including transparent data sharing, and have outlined them in a memorandum of understanding. We have defined the administrative structure of the organization, and begun to secure funding.

We have also begun focused joint quality improvement projects examining blood stream infections and retinopathy of prematurity (ROP). Through analysis of VON data, we have noted significant variability in outcome rates among the state NICUs; in 2007, late-onset infection rates ranged from 5% to over 25%, and ROP rates ranged from 17% to nearly 60%. We are in the process of collecting information on practice variances and process measures to help identify opportunities for improvement.

Future Plans: Future plans for NeoQIC include current and new quality improvement projects, development of a shared database to support quality improvement efforts, inclusion of level II special care nurseries and the perinatal community, and collaboration with neighboring states within New England.

TITLE: Pain Following Vaginal and Cesarean Delivery: A Prospective Evaluation

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OBJECTIVE:

To determine the symmetry and intensity of postpartum pain at rest and with activity and to evaluate modifying factors.

STUDY DESIGN:

A seven item visual analog pain scale (VAS) was created by modifying the validated Surgical Pain Scale, (SPS) created by McArthy et al. Consenting women were administered the scale each day postpartum and asked to assess the symmetry, intensity and unpleasantness of pain in the previous 24 hours, at rest and with activity. Chart review was performed to evaluate demographics and clinical factors that might influence pain. Univariate and multivariable analysis was performed, a $p < 0.05$ was considered significant.

RESULTS:

Of the 126 women enrolled, 78 underwent vaginal delivery (VD) and 48 cesarean delivery (CD). Women with CD were significantly older and had greater BMI. There was no difference in gestational age, induction rate, history of chronic pain/narcotic use, and infant birth weight. Table 1 describes the pain scores. There was little difference in pain at rest on postpartum day 1 (PPD 1), otherwise women with CD experience more pain and required more narcotics. In addition, women with CD were more likely to experience asymmetric pain, with neither side predominating. Of the factors potentially influence pain; none were significant in women with VD. In women with CD, ketoralac (Toradol) for 24 hours was associated with significantly less pain and a prior vaginal delivery with increased pain.

TABLE- 1

Cesarean vs Vaginal	Vaginal	Cesarean	p-value
PPD 1 pain at rest	3.5	3.7	0.71
PPD 2 pain at rest	2.4	3.8	0.041
PPD 2 pain with activity	4.5	7.5	0.00
PPD 2 Pain Assymetry	8.9%	41.5%	0.00

CONCLUSION:

CD is associated with greater and more asymmetric pain than VD, with neither side predominating. Systematic evaluation of factors associated with postpartum pain is needed for both modes of delivery to aid in counseling patients about difference in the postpartum experience of CD versus VD.

Title: Development of YAP and γ-Secretase in ErbB4-receptor Signaling Pathways during Fetal Lung Type 2 Cell Maturation

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Background: We have shown the significance of ErbB4 receptors for fetal lung type 2 (T2) cell maturation, but ErbB4 signal transduction in T2 cell maturation is not understood. One important ErbB4 signal mechanism is ErbB4 cleavage at the cell membrane by γ-secretase, an enzyme complex whose active component is Presenilin-1 (PSEN-1). The cleaved intracellular fragment associates with chaperone proteins including YAP (Yes associated protein) and moves into the nucleus where it regulates gene expression. The cell- and development-specific expression of PSEN-1 and YAP in fetal lung, and their role in ErbB4 signaling, is unknown.

Objective: We studied the developmental distribution and amount of PSEN-1 and YAP in fetal lung T2 cells and the effect of stimulation with the ErbB4 ligand Neuregulin (NRG).

Design/Methods: We used T2 cell cultures of gestations e16, e17 and e18. Cells were untreated (control) or stimulated with NRG (30nM) for 5 min. Western blots of whole cell lysates and subcellular fractionations were used to show gestational regulation of, and effects of NRG on PSEN-1 and YAP amount and distribution. Co-immunoprecipitation in e17 and e18 T2 cells using anti-YAP and anti-PSEN-1 antibodies was done to identify interactions with ErbB4.

Results: Subcellular fractionation showed cytosolic but not membrane location of YAP. We observed a strong increase of YAP in the cytosol of e18 T2 cells over e16 and e17. NRG stimulation increased the YAP amount in e17 and e18 T2 cells. PSEN-1 was present in both the membrane and cytosol fractions and was strongly increased in e18 compared to e16 and e17 in both fractions. The membrane/cytosol ratio of PSEN-1 also increased with gestation. NRG increased PSEN-1 in e16 and e18 T2 cells . Co-IPs showed ErbB4 association with both YAP and PSEN-1 which increased with NRG.

Conclusions: YAP and PSEN-1 are expressed in fetal lung T2 cells, where they increase in amount as term approaches. Co-imunoprecipitations indicate that PSEN-1 and YAP interact with the ErbB4 receptor and this interaction is stimulated by NRG. These results suggest that PSEN-1 and YAP are important in ErbB4 signaling and trafficking during lung maturation.

Title: Cervical tissue engineering using silk scaffolds and human cervical cells

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Objective: Our objective was to explore the possibility of using a tissue engineering approach to investigate collagen remodeling in cervical tissue.

Methods: Cervical cells were cultured from explants of cervical stroma obtained from premenopausal women undergoing hysterectomy for benign disease. Cells were culture expanded in media containing DMEM with 10% FBS and 1% antibiotics. Cells from passage 4-6 were used for experiments. Silk fibroin protein was purified from the *Bombyx Mori* silkworm and processed into porous silk sponges with dimensions 10 x 30 x 1 mm (500 um pore size). To promote cell attachment and proliferation, the scaffold was collagen coated. A cell suspension ($20x10^6$ cells/ml) was applied to the scaffold in a drop-wise fashion (750 ul/scaffold). Scaffolds were cultured for 8 weeks in a humidified incubator at 37 ^oC, 5% CO_2 / 95% air in media supplemented with 0.2 M ascorbic acid 2-phosphate. Scaffolds were assessed for cell viability (Live/Dead assay, Invitrogen), ECM morphology ($H_{\&}E$) and collagen content (hydroxyproline assay).

Results: Cells remained viable during the course of the experiment. Histology of formalin-fixed, paraffin-embedded scaffolds revealed ECM with morphology similar to native tissue. Collagen content (% dry weight) was significantly decreased compared to native tissue.

Conclusions: Human cervical cells cultured on a silk scaffold synthesize an ECM with morphological features and biochemical content similar to native ECM. Tissue engineered cervical-like tissue may be a useful model system for studying ECM remodeling in the cervix.

PROTECTION OFFERED BY MATERNAL HYPERTENSION FOR SEVERE INTRAVENTRICULAR HEMORRHAGE (IVH) IN VERY LOW GESTATION INFANTS (≤ 28 WK) IS INDEPENDENT OF EXPOSURE TO MAGNESIUM SULFATE (MGSO4) AND ANTENATAL STEROIDS (ANS)

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Preeclampsia in the mother has been associated with lower risk of intraventricular hemorrhage (IVH) in preterm infants; but it is not clear if this is in relation to maternal hypertension (HTN) per se or some other aspect of preeclampsia or its management. The **aim** of this study is to determine the relationship between maternal hypertension and severe IVH and examine the effects of MgSO4 and ANS administration on this association in very low gestational age (VLGA) infants born at ≤ 28 completed weeks of gestation.

Methods: A retrospective analysis based on a multivariate logistic regression model was conducted on 1144 VLGA infants admitted to the University of Connecticut Health Center between 1991 and 2007. Maternal HTN of any etiology including pregnancy-induced hypertension (PIH), preeclampsia, HELLP syndrome and pre-pregnancy chronic hypertension complicating pregnancy were determined based on obstetric or peri-partum diagnoses in the maternal charts. IVH was assessed based on the highest grade of IVH on any one side.

Results: Maternal HTN was associated with preterm birth in 15.8% of VLGA infants. Severe IVH (Grade 3-4) was diagnosed in 11% of VLGA infants with decreasing incidence (30% decrease/wk) with each increasing week. VLGA infants born of pregnancies with new onset of HTN including preeclampsia, PIH and HELLP syndrome were significantly protected from severe IVH (n=132; OR 2.8; 95% CI 1.2-6.5). Interestingly, mothers with pre-pregnancy chronic HTN were even better protected and none of the 76 VLGA infants from these pregnancies had severe IVH. Combining all causes of HTN also showed a significant protective effect on the occurrence of severe IVH (n=181; OR 4.1; 95% CI 1.8-9.6). This relationship remained significant even after controlling for GA at birth. Use of MgSO4 was not associated with decrease in incidence of severe IVH. In a logistic regression model incorporating maternal HTN of any cause, GA at birth, infant sex, use of ANS and MgSO4, maternal HTN remained protective of severe IVH(OR 2.8; 95% CI 1.2-6.6) and MgSO4 or ANS showed no significant relationship.

Conclusion: The protective effect of both pre-pregnancy and pregnancy-onset hypertension on severe IVH in the VLGA infants is probably due to maternal HTN per se and is not significantly affected by the use of magnesium sulfate or antenatal steroids in management of pregnancy prior to delivery. The physiological basis of this association remains to be investigated.

Title: Effect of Massage on Methadone Exposed Infants

Authors: Yun J Lee, Barry Lester, Mary Roberts, Pauline Wright, Joseph McNamara
Institution: Women and Infants' Hospital, Brown University

Background: There has not been a study on the effects of massage for infants withdrawing from methadone exposure although it improved weight gain and behavior for preterm infants.

Objective: To see the utility of massage for neonates withdrawing from methadone exposure.

Methods: Infants born at 35 weeks or later are enrolled as preterm(PT:35-6 weeks) or full term(FT:37-42 weeks) at 2 sites. Infants requiring morphine to captured dose are given Phenobarbital loading of 10 mg/kg twice, and then are randomized for clinical trial either to massage+SC(M) or standard care(SC) alone. Phenobarbital was maintained at 2.5mg/kg twice a day. Data are analyzed on LOS, peak daily total NAS scores, The rate of decrease on morphine dose and NICU Network Neurobehavioral Scale(NNNS) summary scores. Statistical methods are general linear modeling, survival analysis and hierarchical linear modeling.

Results: N=52. Demographics: both groups are compatible in numbers of male, GA, BW, HC, Apgars, 2 NAS Scores before morphine, maternal age, parity, education level, smoking, use of other drugs and dose of methadone. 1. Overall LOS was related to methadone dose($P<0.008$). LOS significantly shorter for PT on massage group with covariates of maternal methadone dose and total morphine dose. 2. The rate of decrease on morphine was faster for massage group ($P<0.056$) for FT and PT combined. 3. There was no difference on peak daily total NAS scores. 4. There was no difference between M and SC on NNNS summary scores with covariate on sites. There were site differences on habituation, arousal, excitability and stress/abstinence.

Conclusions: Massage shortened LOS for PT. The rate of decrease on Morphine was more rapid for M than SC group. LOS was related to maternal methadone dose. We need larger numbers on PT for reliable NNNS scores.

Urinary Vascular Endothelial Growth Factor (VEGF): Correlation with Mechanical Ventilation and Bronchopulmonary Dysplasia (BPD) in Infants Born Before 29 Weeks Gestation.

Bernadette M Levesque, MD[1], Sonia Hernandez-Diaz, MD, DrPH[2], Richard Parad, MD[1,3], Michele Phillips, RN[3], Munish Gupta, MD[1,4], Donald E Ingber, MD, PhD[5] and Linda J Van Marter, MD, MPH[1,3]. [1]Division of Newborn Medicine, Children's Hospital Boston; [2]Department of Epidemiology, Harvard School of Public Health; [3]Division of Newborn Medicine, Brigham and Women's Hospital; [4]Division of Newborn Medicine, Beth Israel Deaconess Medical Center and [5]Vascular Biology Program, Children's Hospital Boston [all located in Boston, MA].

Background: BPD is caused by abnormal pulmonary vascular and parenchymal development that results, in part, from exposure of the immature lung to mechanical ventilation. Hallmarks of BPD include deficient alveolarization and impaired angiogenesis. VEGF is a critical regulator of angiogenesis and VEGF inhibition reduces alveolarization and results in BPD-like pathology in neonatal mice. Preterm infants with BPD have lower levels of VEGF in their tracheal aspirates and lung tissue, but VEGF regulation in the lung is not fully understood. Mechanical ventilation is a major risk factor for BPD and, in many cell types, VEGF production is mechanically regulated. VEGF can be measured in the urine and reflects ongoing VEGF production and/or release. **Objective:** Our hypothesis is that mechanical ventilation might contribute to the development of BPD by modulating VEGF production and/or release. Specifically, we explored whether urinary VEGF levels are lower in premature infants receiving mechanical support and if this reduction correlates with later development of BPD. **Design/Methods:** This is a case control study nested in a population-based cohort of infants born at <29 weeks gestation. Urine samples and clinical data were collected from preterm infants born at Brigham and Women's Hospital. VEGF was measured using ELISA (R&D Systems) and results were normalized for total urinary protein (BioRad). **Results:** 153 urine samples obtained from 53 patients during the first month of life were analyzed. Urinary VEGF/protein increases with increasing gestational age (P=0.02) and with increasing postnatal age (P=0.0003) during the first week and month of life respectively. Urinary VEGF/protein is lower in infants requiring mechanical ventilation during the first week (P<0.0001) and month (P=0.05) of age, but was not affected by fraction of inspired oxygen. Mechanical ventilation is associated with a higher incidence of BPD in the cohort, and urinary VEGF/protein trends lower over the first month of age in infants who develop BPD (P=0.06). **Conclusions:** Urinary VEGF/protein levels among infants born before 29 weeks gestation correlate with gestational and postnatal age. Urinary VEGF levels are generally lower among infants who are mechanically ventilated and in those who go on to develop BPD. NIH PO1HL67669-01 & 2T32HD07466-09.

Delivery Room Bubble Continuous Positive Airway Pressure (bCPAP), Strict Intubation/Extubation Criteria, and Avoidance of Nasal Cannula (NC) Oxygen (O_2) in Infants Born Before 33 Weeks Gestation: Impact of a Quality Improvement (QI) Initiative.

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Background: Ideal management of premature infants with respiratory distress syndrome remains an area of controversy, but available data support minimizing mechanical ventilation (MV) and supplemental O_2 whenever possible. **Objective:** The goal of our QI initiative was to reduce MV and supplemental O_2 in infants born at CSEMC at <33 weeks gestation. **Design/Methods:** Our QI initiative had 5 components: 1) exclusive use of bCPAP, 2) provision of bCPAP in the delivery room as a first mode of support for all spontaneously breathing but distressed infants ≥26 weeks gestation, 3) strict intubation criteria, 4) strict extubation criteria, and 5) avoidance of NC supplemental O_2 in infants <35 weeks post-menstrual age (PMA). Infants born at <26 weeks gestation were given prophylactic surfactant in the DR (no change). We compared management and outcomes of babies born during the 12 months before and after these changes went into effect. We excluded outborn infants, those exposed to prolonged oligohydraminios or significant in-utero blood loss, and infants with major congenital anomalies. Data collection without signed parental consent was approved by the CSEMC IRB. **Results:** 62 of 76 infants born before 1/14/2007, and 60 of 74 infants born after 1/14/2007 were included. There were no significant demographic differences between the groups. Compliance with the 5 elements of QI initiative was 100%, 95%, 97%, 83%, and 88% respectively. In infants born between 26 and 33 weeks gestation (n=59 before, n=56 after), need for intubation in the first 72 hrs life was reduced from 51% to 11% (P <0.000001) and surfactant use was reduced from 47 to 14% (P <0.0001). In infants born <33 weeks gestation (n=62 before, n=60 after), days of MV decreased from 7 to 2 (P=0.005), days of CPAP increased from 6 to 12 (P=0.001), and days of supplemental O_2 decreased from 18 to 9 (P=0.07). There were no differences in PMA on final day off CPAP or in total length of stay. Percent of infants with hypotension (<24 hrs age) was reduced from 33 to 15% (P=0.03), but there were no difference in other complications of prematurity. **Conclusions:** Implementation of this 5-element QI initiative reduced the need for MV, surfactant administration, and hypotension among infants born at <33 weeks without any adverse consequences.

LAPAROSCOPIC VS. OPEN TRANSABDOMINAL CERCLAGE: SURGICAL OUTCOMES AND COST ANALYSIS

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Objective: In 2007 our institution began offering the laparoscopic placement of abdominal cerclages in addition to traditional placement via laparotomy. We present here the first comparison of outcomes and costs.
Methods: We performed a retrospective cohort study comparing laparoscopic cerclage (n=10) to abdominal cerclages placed via laparotomy (n=17). Our surgical endpoints included complications, OR time, estimated blood loss (EBL), and length of stay (LOS). Our financial outcomes included medication, OR/recovery time, equipment, and admission costs. All costs were inflated to 2008 dollars and reflect true cost rather than charge.
Results: Table 1 displays our results. As shown, the average surgical time and EBL were comparable between the two groups. However, the length of stay was significantly shorter for women undergoing laparoscopic procedures (the majority of which were outpatient procedures). There were 2 surgical complications, both in the laparoscopic group. These were fundal perforations with the uterine manipulator that were easily repaired without significant clinical implication. The average costs were significantly lower in the laparoscopic group ($4,071 as compared to $5,986).
Conclusions: The laparoscopic placement of abdominal cerclage offers similar surgical outcomes at lower costs largely due to a reduced post operative length of stay. This innovation offers greater flexibility in the surgical scheduling and treatment of cervical insufficiency. Based on our findings, we believe that in experienced hands the laparoscopic approach should be offered as the primary means for placement of interval transabdominal cerclage.

Table 1: Mean Surgical and Cost Outcomes for Abdominal Cerclage Placed Laparoscopically versus via Laparotomy (Standard Deviation)

	Laparoscopy	**Laparotomy**	**P-Value**
Age	37 (3.6)	33 (5.3)	0.025
Parity	0 (0.5)	0 (0.4)	0.203
OR Time (min)	62 (15)	63 (13)	0.899
EBL (cc)	34 (12)	42 (32)	0.411
LOS (nights)	0.22 (0.44)	1.8 (0.56)	<0.001
Average Cost			
All Medication	57 (26)	163 (64)	<0.001
Analgesia	22 (17)	68 (36)	<0.001
OR/Recovery	1535 (335)	2147 (628)	<0.001
Equipment	2117 (1012)	1496 (437)	0.117
Hospital Stay	1060 (274)	1777 (813)	<0.001
Total	4071 (1586)	5986 (1825)	0.010

Cost in 2008 dollars; p-values based on 2 tailed t-test with unequal variance

Title: Maternal sFlt and PlGF levels predict preeclampsia in the HIV+ population

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Background: Untreated HIV+ gravida have a lower risk of preeclampsia(PE), but the use of highly active antiretroviral therapy(HAART) may increase this risk. We hypothesize that the association between the angiogenic markers, sFLT and PlGF, and the risk of PE will be limited in HIV+ patients, particularly those on HAART.

Methods: We performed a nested case-control study using data and blood samples collected from visits at gestational ages18±2, 25±2, and 34±2 by the Women &Infants Transmission Study(WITS). 62 cases of PE were matched by year to 122 non-PE controls. Samples were processed using an Abbott Diagnostics prototype assay.

Results: Cases tended to be; older(29.2 vs 27.3, *p*=.01), nulliparous(28.4% vs 17.3%, *p*=.05), deliver earlier(36.2 vs 37.8 wks, *p*<.01), and chronically hypertensive(15.2% vs 1.2%, *p*<.01) but did not differ by race, education, BMI, pre-existing/gestational diabetes, or CD4 count. Logistic regression indicated associations between preeclampsia and obstetric risk factors but not CD4 count or HAART status.

	OR	CI	p-Value
Age	1.1	1.0-1.1	.01
Nulliparity	1.9	1.0-3.6	.04
Chronic Hypertension	14.1	3.1-64.6	<.01
CD4	1.0	0.99-1.0	.64
HAART	1.2	0.7-2.0	.53

Comparing cases to controls, mean sFlt concentrations(pg/ml) were not different at 18 weeks(5.6 vs 6.7 *p*=.30). By 25 weeks, levels increased(9.6 vs 6.8 *p*=.02) and increased further by 34 weeks(29.2 vs 12.2 *p*<.01). PlGF concentrations(ng/ml) were similar at 18 weeks(88.8 vs 116.2 p=0.19) and at 25 weeks(525.2 vs 678.5 p=0.12) but were lower by 34 weeks(393.9 vs 808.31 p=.01). Neither HAART(OR 0.8, CI 0.4-1.9, p=.76) nor CD4 count(OR 0.9, 0.9-1.0, *p*=.43) predicted PE. In multivariate modeling controlling for maternal age, nulliparity, and chronic hypertension we observed:

	Upper quartile sFlt			Lower quartile PlGF		
Week	OR	CI	p-value	OR	CI	p-value
18	0.5	0.1-2.1	0.38	0.9	0.2-3.4	0.86
25	2.0	0.7-5.3	0.17	1.6	0.6-4.34	0.33
34	3.4	1.12-9.6	0.02	3.3	1.1-9.5	0.03

Conclusion: sFlt and PlGF are predictive of PE in the HIV+ gravida despite the lower risk of PE in this population. The predictive ability of these analytes was unaltered by CD4 count or HAART.

Title: Antenatal Indomethacin is Associated With Spontaneous Intestinal Perforation (SIP)

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Background: We experienced an alarming increase in SIP in our unit prompting a review of potential causes.

Objective: To study perinatal risk factors associated with SIP in premature infants ≤28 wk gestational age (GA).

Design/Methods: This was a retrospective case-control study using NICU clinical data base, supplemented with review of records. Data were searched for all cases of SIP or perforation in infants born at ≤28 weeks of gestation admitted to our NICU between Dec 2006 and June 2008. Infants diagnosed with NEC or other gastrointestinal abnormalities were excluded. Each case was matched with 2 controls based on GA at birth. We studied antenatal factors including use of indocin, MgSO4, antibiotics, steroids, preterm labor, pregnancy induced hypertension, premature rupture of membranes, chorioamnionitis, funisitis, twins or singleton births. The postnatal factors reviewed included gender, birth weight, race, resuscitation at birth, use of normal saline bolus, use of pressors, steroids, indomethacin and caffeine prior to SIP. Univariate and multivariate logistic regression was used for analyses.

Results: There were 11 cases of SIP and 22 controls. On univariate analysis, SIP was significantly associated with infants of twin gestation (87% vs 16%, p=0.0005). All infants who had SIP were exposed to indomethacin either antenatally or postnatally. However, infants whose mother received a high cumulative dose of indomethacin prior to delivery (mean ±sd, 60 ±118 vs. 213 ±230 ; p=0.016) were at most risk for SIP. SIP was also more common in whites compared to non-whites (50% vs 13%, p=0.03). Use of MgSO4, prenatal antibiotics, antenatal steroids or maternal diagnoses of PIH, PROM, chorioamnionitis or funisitis were not significantly associated with SIP. Postnatal use of pressors, caffeine, steroids and indocin were also not related to SIP. On multivariate logistic regression analysis of significant factors, twin gestation and cumulative antenatal indomethacin dose remained highly significant predictors of SIP ($p < 0.05$). Area under the ROC curve using these two variables was 89%. Infants who received a bolus of normal saline within the first 24 hours of life were highly represented in the SIP group but this finding did not reach statistical significance (p=0.08).

Conclusions: The combination of high cumulative dose of antenatal indomethacin with twin gestation was highly correlated with SIP in our cohort. This finding needs further detailed investigation.

How Do Gestational Age and Gender Affect miRNA Expression Profiles in Developing Lung?

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Background: MicroRNAs (miRNAs) play important roles in regulation of many biological processes, including organ morphogenesis and maturation with recent direct links between miRNAs, development and disease. Dicer, a key enzyme in miRNA processing is necessary for normal airway branching morphogenesis. However, little is known about the mechanistic role of miRNA regulation of lung development.

Objective: Test the hypothesis that the miRNA expression profile during pseudoglandular to saccular stage fetal lung development is gestation- and gender-dependent.

Design/Methods: We used TLDA low density real time qRT-PCR arrays (Applied Biosystems) to profile the known mouse miRNA genome (376 miRNAs) in male and female fetal mouse lungs of gestational days E15-E18, an interval spanning the transition from late pseudoglandular to early saccular stage with the development of surfactant synthesis.

Results: miRNA expression patterns were different in males and females. In males, most miRNA species increased between E15 and E16, then decreased on E17 to near E15 levels, followed by an increase on E18. The female expression profile was more heterogeneous compared to males. The majority were shifted one day earlier, i.e. decreased from E15 to E16, increased at E17, then decreased at E18. A subset followed the male pattern. Finally, select few miRNAs had unique profiles in males and females of continued increase or decrease in expression with advancing gestation. Evaluating these patterns could predict potential important molecular targets (TargetScan).

Conclusions: miRNAs are differentially regulated during development and between sexes. Differential miRNA expression by gender may regulate the gender differences in structural and functional development. Our data provide a valuable resource to further enhance the understanding of miRNA control of lung development and lung maturation.

Prediction of Preterm Birth and Low Birth Weight from First Trimester Screening

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OBJECTIVE: To evaluate receiver operator curves for nuchal translucency and its relation to preterm birth and low birth weight.

STUDY DESIGN: We performed a retrospective analysis on all first trimester screenings performed at Hartford Hospital from December, 2003 through March, 2008. The selected date range included all fetuses currently born at Hartford Hospital where first trimester data was available.

RESULTS: We evaluated 2605 first trimester screens for increased nuchal translucency of 3mm or more and found no relationship to preterm birth or low birth weight. ROC curves for increased nuchal translucency and preterm birth showed an area under the curve of 0.53, while for low birth weight the area under the curve was 0.57 as shown in Tables 1 and 2 respectively.

Table 1: ROC Curve for PTB

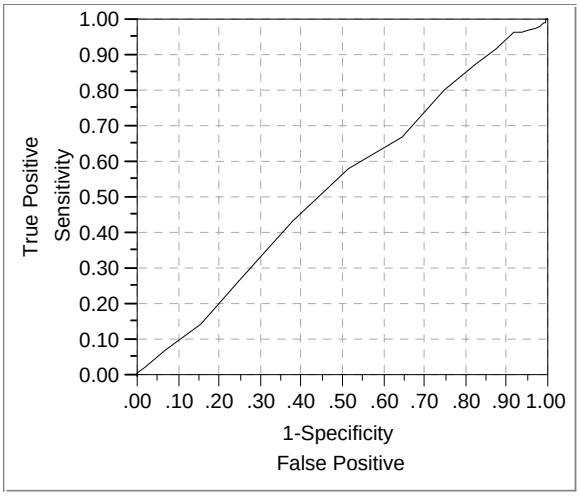
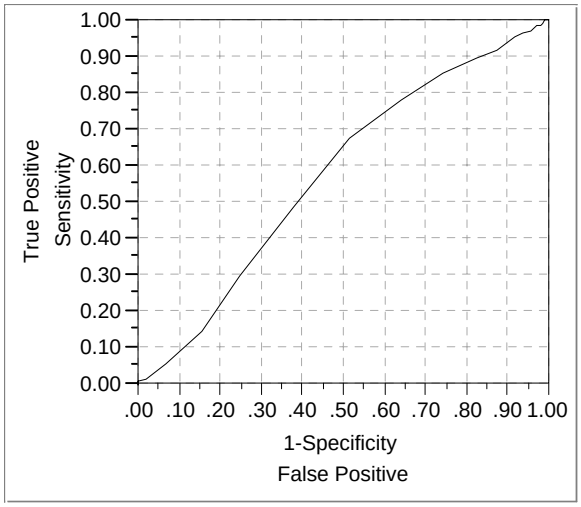


Table 2: ROC Curve for LBW



CONCLUSION: An increased nuchal translucency in our study population did not show an increase in incidence in preterm birth or delivery of a fetus with low birth weight. These findings at the time of screening would not be an indication for increased surveilance for these outcomes.

Title: Three-dimensional ultrasound for visualization of cervical change in the presence of a cerclage.

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Background: The rationale for cervical cerclage is to provide cervical support in the setting of cervical insufficiency, although the manner by which cerclage provides support is not well understood.

Objective: To develop a method to visualize sonographically-based, three-dimensional (3D) cervical change in the presence of a cerclage.

Study design: A longitudinal study was performed in a cohort of patients with cervical insufficiency and cerclage placement. 3D transvaginal scan was performed at the same time as a clinically indicated measurement of cervical length. Solid model construction followed a three step protocol. First, a 3D volume was obtained using a Philips IU22 3D9-3V transducer. Second, the sonographic data was transferred to mechanical design software to construct anatomic models (SolidWorks, Concord MA). Third, solid models from multiple time points were superimposed to visualize 3D cervical change.

Results: Eight patients with a cerclage (5 emergent, 3 prophylactic) were studied. The mean gestational age of the first scan was 21.2 weeks and the mean number of scans was 2. Of the eight patients studied, 1 patient demonstrated significant cervical shortening. There was no cervical change noted in the other 7 patients. The cervical length changed from 16mm residual closed length below the cerclage at 22 weeks to 11mm residual closed length by 26 weeks. As the cervix shortened, changes in the lower uterine segment, cervical stroma and cervical mucosa with respect to the position of the cerclage were observed.

Conclusion: We present a method of constructing ultrasound guided solid anatomic models to demonstrate 3D cervical change in patients with a cerclage. A better understanding of 3D anatomic changes in the setting of cerclage combined with mechanistic studies of cervical biomechanics may help elucidate the structural basis of cerclage support or failure.

Risk factors for presumed versus definite early and late neonatal bacteremia in extremely low gestational age newborns (ELGANs)

Sonal Patel*, Olaf Dammann, Cami Martin , Elizabeth N. Allred, and Alan Leviton for the ELGAN study investigators (Tufts Medical Center)

Background: Neonatologists separate bacteremia into early and late, reflecting the perception that early-onset bacteremia is acquired during labor and delivery and late-onset bacteremia is acquired in the NICU. Culture proven bacteremia continues to be the gold standard. Neonatologist's perception of "presumed bacteremia" might be inferred from the prolonged administration of antibiotics despite negative cultures. **Objective:** We sought to explore differences in risk patterns for presumed versus definite bacteremia, both with early and late onset. **Design/Methods:** The sample for this study consists of the 1106 ELGANs who survived until day 28. We defined early bacteremia as a positive bacterial culture in the first week and late bacteremia as a positive culture in week 2, 3 or 4. Presumed bacteremia was defined as antibiotics for more than 72 hours despite negative blood cultures. **Results:** Unless stated otherwise, the antecedents and correlates identified below for each form of bacteremia convey information about increased risk. Early presumed bacteremia (n=390): Maternal vaginitis, longer duration of intubation and presence of CSF infection. Early definite bacteremia (n=72): Maternal vaginitis, cervical insufficiency, fetal indication for delivery, prolonged rupture of membranes (>72hrs), and umbilical cord vasculitis. Late presumed bacteremia (n=166): Isolation of mycoplasma from the placenta and placental infarcts, reduced risk. Late definite bacteremia (n=286): Tracheal infection, necrotizing enterocolitis, persistent ductus arteriosus, chronic lung disease, and pulmonary hemorrhage. Reduced risks of all categories of bacteremia were associated with advanced gestational age and higher birth weight. Finally, infants with definite bacteremia had distributions of days of ventilation and oxygenation similar to those of infants with presumed bacteremia, both early and late. **Conclusion:** In general, low gestational age and birth weight are risk factors for all forms of neonatal bacteremia. By and large, the antecedents for early bacteremia are maternal and pregnancy characteristics. Neonatal co-morbidities are the main antecedents/correlates of late bacteremia.

Title: Effect of delivery prior to 36 weeks' gestational age on outcome of patients with gastroschisis

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Background: Optimal timing of delivery for infants with a prenatal diagnosis of gastroschisis is a subject of debate. Because exposure to amniotic fluid is believed to be injurious to the fetal bowel, premature delivery has been proposed as a method of minimizing bowl injury and improving neonatal outcome. Although inconsistent, most recent studies demonstrate that premature delivery of infants with gastroschisis does not improve outcome.

Objective: To evaluate the effects of delivery prior to 36 weeks' gestational age (G.A.) on outcome of infants with a prenatal diagnosis of gastroschisis.

Methods: We performed a retrospective chart review of infants with a prenatal diagnosis of gastroschisis born and/or treated at Tufts Medical Center, Brigham and Women's Hospital, Massachusetts General Hospital, and Children's Hospital Boston between 1990 and 2007. We compared the mortality rate and length of hospital stay among two groups of patients: those delivered before 36 completed weeks and those delivered at or after 36 weeks 0 days.

Results: Death prior to hospital discharge occurred in 5 of 33 neonates delivered prior to 36 completed weeks' G.A. (15%) and in none of the 52 neonates delivered at or after 36 weeks 0 days (0%), P = .007. Hospitalization longer than 30 days occurred in 25 out of 48 (52.1%) neonates delivered at or after 36 weeks' G.A., and in 18 out of 26 (69.2%) neonates delivered before 36 weeks G.A. While not statically significant (P = .0768), this finding represents a trend consistent with others' findings.

Conclusion: In this dataset, delivery prior to 36 weeks' G.A. was associated with death and extended hospitalization among newborns with the prenatal diagnosis of gastroschisis.

Title: Accuracy of Ultrasound to Predict Estimated Weight in Fetuses With Gastroschisis

Sonia Ranganath, MD,[1]* Sara Durfee, MD,[3, 5] Daniel Katz,[4, 5] Courtenay Pettigrew,[1] Russell Jennings, MD,[2] Jeffrey Ecker, MD,[4, 5] Michael House, MD,[1] Carol Benson, MD,[3, 5] Adam Wolfberg, MD, MPH.[1,2,5]

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Objective: To determine whether biometry-based systems for estimating fetal weight are as accurate for fetuses affected with gastroschisis as they are for normal fetuses. We hypothesized that because Hadlock's formula relies on the abdominal circumference as a biometric variable, estimations of fetal weight may be less reliable in fetuses with abdominal wall defects.

Study Design: We performed a retrospective chart review of all fetuses prenatally diagnosed with gastroschisis at three Boston institutions from 1990 to 2007. Charts were reviewed for clinical and ultrasound data. Estimated fetal weight (EFW) at the prenatal sonogram closest to delivery was compared to birth weight, using a correction factor of 30g/day to account for interval growth. All sonograms used in our calculations were done within 2 weeks of delivery.

Results: 118 patients with gastroschisis were identified. 69 patients had an ultrasound with a calculated EFW within 7 days of delivery; 92 had an ultrasound with 14 days. Ultrasound biometry underestimated birth weight by 7.0% and 5.9%, respectively. The average gestational age at birth was 35.7 and 36.0 weeks in the 7-day and 14-day groups, respectively. The average birth weight was 2310 grams +/- 556 grams and 2358 grams+/-554 grams respectively.

Conclusion: Biometric measurements consistently underestimate the weight of fetuses with gastroschisis.

Effect of O_2-Exposure on Developmentally Regulated Hox Genes in Key Stages of Lung Morphogenesis and Alveologenesis

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Preterm infants at 23-30 wks gestation are exposed to O_2 during critical periods of lung development (late canalicular/early saccular stages) when Hox transcription factors, Hoxb5 and Hoxa5 uniquely control airway and alveolar morphogenesis. Despite pivotal roles for Hoxb5 and Hoxa5 in normal human and mouse lung morphogenesis, O_2-effects on their expression and regulation and whether O_2-induced lung injury is dependent on changes in these Hox proteins is unknown. We hypothesize that Hoxb5 and Hoxa5 expression patterns will be differentially altered by modest O_2 exposure thereby arresting airway and alveolar development. **Design/Methods**: E14 whole fetal mouse lungs were cultured from Day 0-2 (D0-2) in 0.21 FiO_2 (RA) advancing lung development to late canalicular/early saccular stage followed by random assignment to 0.40 $Fi0_2$ (O_2Gp) or continued RA for D2-4. Daily lung surface area (ΔSA) quantified visual interpretation of lung airway and explant growth. After 4 days, lungs were processed for Hoxb5 immunohistochemistry and Hoxb5 and Hoxa5 Western blots with densitometry. Morphometric point counts on histologic sections quantified airway, mesenchyme and epithelial cell volume in RA and O_2Gp lungs. **Results**: All lungs exhibited airway branching and lung growth (↑ΔSA) over D0-2 in RA . RA lungs had continued airway growth from D2-4 but O_2Gp had significantly decreased and regressed growth from D2-3 (ΔSA, 16 ±26 μm RA vs −19.1 ±6.2 μm, O_2Gp, $P < 0.01$) and from D3-4 (ΔSA, 54.2 ± 21μm vs −36 ±7μm, O_2Gp, $P<0.0001$). RA lungs had strongly positive Hoxb5 mesenchymal cells around peripheral airways and alveolar ducts with cuboidal epithelium whereas O_2Gp had less intense and more diffuse Hoxb5 mesenchymal staining around immature airways with columnar epithelium. O_2Gp airway and epithelial cell volume significantly decreased whereas mesenchymal cell volume significantly increased. Hoxb5 protein levels were significantly decreased in O_2Gp to 55% of RA lungs whereas Hoxa5 protein levels were unchanged. **Conclusions**: O_2-exposure during critical stages of lung development alters Hoxb5 spatial and cellular expression and protein levels in association with arrest and regression of airway structural maturation and lung growth but does not alter Hoxa5 levels. We speculate that altered developmental regulation of Hoxb5 is part of the mechanism contributing to O_2-induced lung injury in preterm infants.

Title: Nurse Patient Load And Achievement Of Oxygen Saturation (SpO2) Targets In Premature Infants

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Background: Premature newborns often experience SpO2 levels outside policy-specified target range, which may increase morbidity. Nurse workload may affect oxygen management. Objective: To examine the relationship between nurse patient load and proportion of time premature infants achieve SpO2 within policy-specified target range; and identify factors associated with target range achievement (TRA) adjusted for nurse patient load. Design/Methods: We linked daily nurse patient assignment data with downloaded continuous SpO2 data for infants <29 weeks gestational age (GA) admitted to a single NICU 1-6/2008. SpO2 target range was 85-92%. Proportion TRA was described for monitoring periods (MP) of ~6 hr duration on supplemental oxygen and characterized by a single nurse and single method of respiratory support (HFOV, SIMV, CPAP or NC). MPs after mature eye exam or laser ablation were not included. Nurse's patient load and other duties, infant characteristics, and respiratory support were defined for each MP. Factors associated with TRA were identified using cross-classified random effects regression models to adjust for clustering of MPs within nurses and infants. Results: We analyzed 1019 MPs totaling 5568 hours from 14 infants having median (25, 75%) birth weight 823 (575, 1040) g and gestational age 26.9 (25.2, 28.5) wk. Mean (range) postmenstrual age (PMA) for all MPs was 31.6 (24.1-40.7) wk, with 80 MPs recorded on HFOV, 142 SIMV, 398 CPAP, and 399 NC. 87 nurses provided care. Median TRA for all MPs was 16.1% (8.7, 27.3). TRA was significantly greater with higher respiratory support (Figure). With regression modeling, earlier PMA was significantly associated with higher TRA, and lower nurse's patient load was significantly associated with higher TRA only among patients on HFOV (Table). Conclusions: Decreased nurse patient load may be associated with improved TRA. This effect may vary with level of respiratory support. TRA worsened with advancing PMA, consistent with lack of consensus on duration of SpO2 targeting in premature infants. Further research on this issue is warranted.

Figure: Target Range Achievement, by Respiratory Support

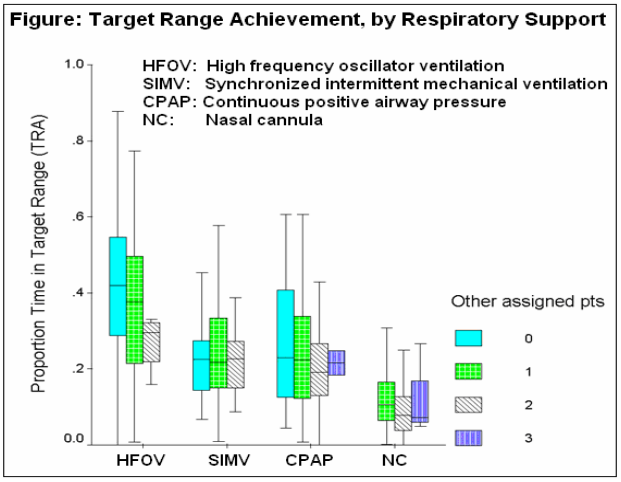

Table: Cross-Classified Random Effects Model

	Coefficient	SE	P-value
Adjusted overall mean TRA	0.172	0.032	<0.001
PMA	-0.022	0.001	<0.001
FiO2>0.5, compared to <0.5	0.044	0.019	0.023
HFOV, with 0 other assigned patients	0.108	0.031	0.001
with 1 other assigned patient	-0.069	0.036	0.054
with 2 other assigned patient	-0.131	0.056	0.019
SIMV	-0.062	0.012	<0.001

Amplitude Electroencephalogram (aEEG) Findings in Infants with Broncho-Pulmonary Dysplasia (BPD)

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BACKGROUND: Infants with BPD are at risk for poor neurodevelopmental outcomes. Tests to determine which infants with BPD are at risk for poor outcome are needed.

OBJECTIVE: To determine if there are differences in the aEEG of infants with and without BPD.

DESIGN/METHODS: This is a cross sectional study of infants who were ≤ 27 gestational age (GA) at birth and did (n=10) or did not develop BPD (n=10). Infants with grade III/IV intra-ventricular hemorrhage, cystic peri-ventricular leukomalacia, and major anomalies were excluded. BPD was determined by a room air challenge test performed at 36^0-36^6 weeks. aEEG tracings were recorded at 36^0-36^6 weeks for 6 hours using the BrainZ BRM3. aEEG parameters from a cross cerebral channel were evaluated using offline software Analyze(BrainZ). Projected sample size is 15 infants per group. Demographic, perinatal, neonatal morbidities, and aEEG variables were compared between groups.

RESULTS: Infants with BPD had lower GA and birth weight, and a higher male predominance (25^0±0.9 weeks, 651±211 grams, 70%) compared to non-BPD infants (26^1±1.1 weeks, 826 ±158 grams, 25%, all $p< 0.05$). BPD infants had a longer duration of ventilation and more post-natal steroid use for blood pressure or ventilator dependence (45±22days, 70%) compared to non BPD (7±10 days, 0% all $p< 0.01$). There were no differences in race, culture positive sepsis, patent ductus arteriosus, necrotizing enterocolitis, or days to full feeds. At aEEG acquisition, BPD infants had lower weight, smaller head circumference and a greater use of diuretics and caffeine (1680±474 grams, 29.7 cm, 40%, 60%) compared to non-BPD (2223±379 grams, 31.4 cm, 0%, 11%, all $p<0.04$)

In between sleep wake cycles, BPD infants had a larger aEEG bandwidth (9.7±1.9 vs. 7.4±1.3 mcv, $p< 0.01$) and higher lower border voltage (8.8±0.9 vs. 7.9±0.7 mcv, $p< 0.02$) compared to non BPD infants. Increased inter-cycle bandwidth correlated with a higher lower border voltage, $r^2=0.76$, $p<0.001$. During sleep wake cycles BPD infants had larger bandwidth (15.4±2.7 vs. 12.2±2.1 mcv, $p<0.01$) but similar lower border voltage (6.2±0.9 vs. 6.0±1.1 mcv) compared to non BPD infants. Infants with BPD tended to have less sleep wake cycles per hour (0.6±0.1 vs. 0.53±0.09, $p=0.07$) compared to non BPD infants.

CONCLUSION: Infants with BPD have differences in their aEEG tracings compared to infants without BPD at 36 wks. Differences may reflect altered brain maturation, gender effects, medication effects, or brain injury. Additional infants are needed to confirm these preliminary findings.

Prototype device for non invasive measurements of cervical collagen.

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Introduction: In the United States preterm labor is the major cause of infant morbidity and mortality. Screening and identifying those at risk is crucial to improving neonatal morbidity and mortality. Currently fetal fibronectin fFN measurements in cervicovaginal secretions in conjunction with sonographic cervical lengths length measurements are the most clinically useful and cost effective tests used to identify those at risk. However, other tests and markers are currently being evaluated. One of these tests is measurement of auto fluorescence from the cervix reflecting collagen content. The non invasive device Collascope™ described by R. Garfield has been shown to predict labor in animal and human models and may prove to be a useful tool in the future. However, the Collascope™ is bulky, expensive, and therefore, not practical. It was developed in early 90s, but still did not find any practical applications. The Nitride Materials and Devices group at the Center for Advanced Materials (University of Houston) has focused its research efforts on the development of advanced optoelectronic devices based on III nitrides and other wide bandgap semiconductor materials. The technology used for the epitaxial growth of III nitrides ultimately allows for integration of all sensor components into a miniature (in the order of few millimeters) single, solid-state device. Light Emitting Diodes (LEDs), Photodiodes (PDs) and their combinations are currently being developed in the group for various advanced applications. Research team from University of Houston is currently working in collaboration with Baystate Medical Center on effort to miniaturize the portable system that would allow for time-resolved measurements (TRM) and steady state (SS) measurements using our miniature sensors based on solid-state LEDs and PDs.

Materials and Methods: We have fabricated an experimental sensor setup based exclusively on solid-state components. This setup consists of a GaN based ultraviolet (UV) LED from Sensor Electronic Technology Inc, SC (model number UV TOP335SET3), and a conventional silicon based photodiode. As a first step we measured fluorescence of a sample prepared from animal tissues (a beef meat layer placed between two sapphire slides).

Results: The spectral response measured by using the silicon photodiode from the samples excited by the UV LED, indicated an appropriate collagen fluorescence emission peak at the wavelength of λ=473 nm.

Conclusion: The preliminary results indicate that alternative methods to measure real time fluorescence of collagen using inexpensive and miniature solid state optoelectronic components based on wide bandgap semiconductor materials are feasible.

Ibuprofen (Ibu) vs Indomethacin (Indo) For Patent Ductus Arteriosus (PDA): Meta-Analysis of Studies Using Historical Controls

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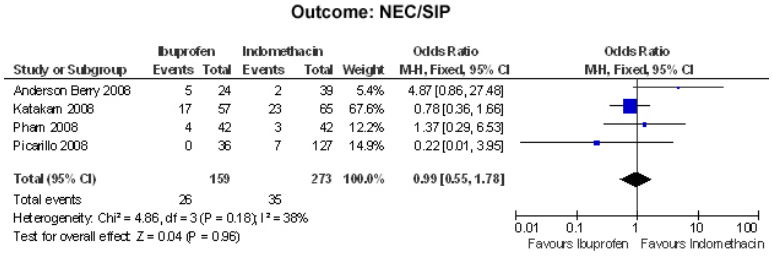
Background: Ibu and Indo have similar efficacy for PDA treatment in premature infants, but may have different effects on risk of necrotizing enterocolitis (NEC), spontaneous intestinal perforation (SIP) or chronic lung disease (CLD). Recent nonrandomized single center studies compare PDA treatment with Ibu to historical controls treated with Indo. **Objective:** 1) to summarize the experience of NICUs using Ibu as primary PDA treatment; 2) to analyze data comparing nonrandomized historical cohorts treated with Indo to infants treated with Ibu. **Methods:** Nonrandomized cohort or case-control studies comparing PDA treated with Ibu to historical cohorts treated with Indo were selected if published or presented at regional or national conferences. Data were excluded if both Indo and Ibu were used. Treatment outcomes and complications of prematurity were analyzed with RevMan v5. Heterogeneity was assessed using the I^2 test. **Results:** Five studies were analyzed. Mean birth weight ranged from 853-1036 gms, SD 248-351 gms. Gestational age ranged from 26-27.6 weeks, SD 1.97-2.6. Four studies examined survival, PDA closure, ductal ligation, IVH ≥grade 3, and NEC/SIP. Three analyzed SIP as an independent outcome; 2 examined CLD. Renal effects were evaluated by 2 studies and could not be combined due to inconsistent measurement. Moderate but not significant heterogeneity was observed among other outcomes. No significant differences between Ibu and Indo were identified with respect to NEC, SIP and CLD as well as survival, PDA closure, ductal ligation and IVH. **Conclusions:** This analysis does not demonstrate a significant difference between Indo and Ibu with regard to efficacy or short-term outcomes. These results are consistent with meta-analysis of randomized controlled trials (Ohlsson 2008) which showed similar efficacy of treatment and did not demonstrate a significant difference in development of IVH, NEC/SIP or CLD. Continued monitoring of outcomes of infants treated with Ibu is warranted.

Effect of Ibuprofen vs Indomethacin

	Ibuprofen		Indomethacin		OR, 95% CI
	n (%)	Total	n (%)	Total	
Survival	127 (77)	164	230 (87)	264	0.69, (0.39,1.21)
PDA Closure	153 (74)	206	221 (72)	306	0.99, (0.65,1.52)
PDA Ligation	43 (27)	159	67 (25)	273	1.23, (0.78,1.95)
IVH Grade 3 or 4	20 (13)	159	25 (9)	273	1.25, (0.66,2.38)
NEC/SIP	26 (16)	159	35 (13)	273	0.99, (0.55,1.78)
CLD/BPD	22 (37)	60	74 (45)	166	0.86, (0.46,1.62)



Proton Spectroscopy of the Fetal Brain: An Assessment of Clinical Feasibility in 22 Cases

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Background: Modern 1.5 Tesla MRI scanners offer the ability to extract water suppressed proton spectra from selected ~ 4 to 8 ml volumes of interest in only minutes. In the setting of the fetal brain, however, motion and maternal fat deposits present technical challenges which can degrade spectral quality. In this work we assessed the ability of state-of-the-art scanners to acquire diagnostic quality water suppressed single voxel spectra from fetal brain acquired in ~ 90 s acquisitions in N patients.

Methods: Pregnant women (N = 22) received MR abdominal examinations with a 1.5 T Phillips system. Each study included single-shot T2-weighed turbo-spin echo images and at least one single voxel proton spectroscopic interrogation of 4 to 8 ml voxels within the fetal brain (TR/TE/NEX = 1500 ms/144 ms/64, ~ 95 s acquisitions). Spectra were processed with manufacturer supplied software which included spectral fits of the major metabolites Cho, Cr, and NAA and tabulated ratios Cho/Cr and NAA/Cr. The quality of each spectrum was rated as 1, 2 or 3 where 1 = diagnostic quality spectra with accurate metabolite ratios, 2 = spectra that would require further post-processing (filtering, phasing, etc) by an experienced spectroscopist to extract metabolite information with confidence, and 3 = diagnostically useless spectrum.

Results and Discussion: Of a total of 26 spectra examined, 7 (27 %), 15 (58 %) and 4 (15 %) scored 1, 2 and 3, respectively. High Cho/Cr (> 4) were found in the diagnostic quality spectra as expected for this population and variable levels of the inverted lactate doublet were also observed. The majority of spectra (57 %) were deemed useful though requiring further processing than available with the automated version of the manufacturer supplied software. Only 15 % were deemed of no diagnostic utility either due to motion or fat contamination.

Conclusion: Single voxel proton spectroscopy is feasible in the clinical setting to evaluate the fetal brain.