Variable Response to Therapeutic Hypothermia Suggests Potential Role for NIRS in Guiding Individualized Care

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With the goal of therapeutic hypothermia (TH) to reduce neuronal metabolism, a bedside measure of neuronal metabolism may help guide individual care. A good marker of neuronal metabolism is the cerebral metabolic rate of oxygen consumption ($CMRO_2$), which can be measured using noninvasive near infrared spectroscopy (NIRS) methods. To determine if NIRS measures have the potential to individualize care, we set out to determine if therapeutic hypothermia resulted in similar $CMRO_2$ reductions in individual neonates with hypoxic ischemic injury (HII). **Design/Methods:** We enrolled seven term neonates with a diagnosis of hypoxic-ischemic encephalopathy who met hospital criteria for TH. To estimate CMRO2, cerebral blood volume (CBV), cerebral oxygenation (StO_2) and cerebral blood flow (CBF) were measured using frequency-domain near-infrared spectroscopy (FD-NIRS) and diffuse correlation spectroscopy (DCS). Measurements were performed at bedside in up to seven locations on the head during and after hypothermia therapy. Results were compared to averaged data from 10 normal term newborns. Additionally, we considered pattern and severity of injury on MRI obtained during and after hypothermia. **Results:** During controlled hypothermia, $CMRO_2$ and CBF were significantly lower compared to normal infants in five of seven subjects. In two infants, $CMRO_2$ was in the normal range during hypothermia while CBF was significantly elevated. When cooling was discontinued, $CMRO_2$ values remained below normal or approached normal in all but one subject. All seven infants had no obvious decreased diffusion on MRI and only minimal abnormalities at seven to ten days. **Conclusions:** In this pilot study, controlled hypothermia resulted in different $CMRO_2$ levels in different neonates with HII, suggesting its potential for individualized care.

Obstetric Outcomes in Cases of First Trimester Cystic Hygroma

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OBJECTIVE: To determine obstetric outcomes in pregnancies diagnosed with a cystic hygroma in the first trimester.

STUDY DESIGN: A multi-center retrospective study of 2842 records of patients with increased NT (≥2.5mm) and/or cystic hygroma that presented between 2000 and 2010 yielded 910 patients with a cystic hygroma. Patients had ultrasound examinations between 10 weeks 3 days and 13 weeks 6 days. Cystic hygroma was defined as "an enlarged hypoechoic space at the back of the fetal neck, extending along the length of the fetal back, and in which septations were clearly visible."

RESULTS: Obstetric outcome data were available for 712 of the 910 fetuses diagnosed with cystic hygroma. 436 (61.2%) underwent elective termination, 160 (22.5%) were born alive (9 of them with Down's syndrome), 107 (15%) miscarried before 24 weeks, 7 (1%) had fetal loss after 24 weeks and 2 (0.3%) suffered neonatal death. Of the electively terminated pregnancies, 367 had available karyotype data. Of those, 92 (25.1%) were found to have a normal karyotype while 275 (74.9%) had an abnormal karyotype. Of all genetic abnormalities in the terminated group, Trisomy 21 (37.1%) was the most frequently detected, followed by Trisomy 18 (24.7%) and Monosomy X (20%). Trisomy 13 was detected in 7.6% while Mosaicism and Triploidies were both diagnosed in 2.5%. 5.5% had other abnormal karyotypes.

CONCLUSION: Many pregnant women (61.2%) diagnosed with cystic hygroma terminate their pregnancy. A significant percentage (22.8%) of those terminations have a normal karyotype.

Turner's Syndrome is the Most Common Karyotype in Fetuses With Extremely Large Cystic Hygromas Diagnosed in the First Trimester.

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Objective: To evaluate the association between cystic hygroma size and the incidence of 45X karyotype.

Methods: We performed a multi-center retrospective chart review of all fetuses with increased nuchal translucency and/or cystic hygroma diagnosed between 2000-2010 at five institutions. Ultrasounds were performed between 10 weeks 4 days and 13 weeks 6 days. Cystic hygroma was defined as "An enlarged hypoechoic space at the back of the fetal neck, extending along the length of the fetal back in which septations were clearly visible." Patients were offered chorionic villus sampling or amniocentesis for karyotype, as well as targeted fetal anatomic and cardiac evaluations. For this analysis, only subjects with a cystic hygroma and known karyotype were analyzed. These subjects were divided into three groups based on the size of the cystic hygroma.

Results: A karyotype was available for 522 of the 910 fetuses diagnosed with a cystic hygroma.

	Euploid	Tr 21	Tr 18	Tr 13	45 X	Other	Total
≤ 4.9mm	156 (66.7%)	50 (21.4%)	8 (3.4%)	2 (0.9%)	4 (1.7%)	14 (6%)	234 (100%)
5 -7.9mm	59 (30.2%)	53 (27.2%)	39 (20%)	13 (6.6%)	22 (11.3%)	9 (4.6%)	195 (100%)
≥ 8mm	20 (21.5%)	14 (15 %)	12 (12.9%)	4 (4.3%)	38 (40.9%)	5 (5.4%)	93 (100%)
All	235 (45%)	117 (22.4%)	59 (11.3%)	19 (3.6%)	64 (12.3%)	28 (5.4%)	522 (100%)

($p<0.001$ for the comparison of 45X to Tr 21)

Conclusion: Overall, Trisomy 21 is the most common aneuploidy among fetuses with cystic hygroma. However, in those fetuses with a particularly large cystic hygroma diagnosed in the first trimester, 45X is the most common karyotype.

The Impact of Maternal Lipids on Cord Blood Lipids and the Incidence of Large for Gestational Age Newborns.

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Objective: Previous studies are limited regarding the influence of maternal lipids on fetal lipid levels. To evaluate a possible association between fasting maternal lipids with umbilical cord blood lipids and large for gestational age (LGA) newborns.

Study Design: We prospectively enrolled 106 women aged 18 to 40 years between 24 to 28 weeks gestation, scheduled for a 100 gram three hour oral glucose tolerance test (OGTT) to screen for gestational diabetes mellitus (GDM). Women with multiple gestations, history of diabetes mellitus, hypertension, lipid disorder, heart, thyroid or chronic renal disease and those later diagnosed with preeclampsia were excluded. Fasting levels of total cholesterol, triglycerides, high and low density lipoprotein (HDL and LDL) were measured at the time of OGTT. High levels of fasting maternal lipids were defined as values greater than the 75^{th} percentile. We performed multivariate linear regression for the cord blood lipid values and multivariate logistic regression for LGA controlling for maternal age and body mass index (BMI) at recruitment, gestational age, infant gender, infant birth weight and area under glucose curve from the OGTT.

Results: Women with high levels of fasting cholesterol did not have higher adjusted median cord blood total cholesterol as compared to women with low maternal cholesterol (117 mg/dl vs. 117.2, mg/dl p=0.97). Similarly the median cord blood triglyceride (27.2 mg/dl vs. 27.4 mg/dl, p=0.96), HDL (51.5 mg/dl vs. 47.6 mg/dl, p=0.35) and LDL (52.5 mf/dl vs. 53.2 mg/dl, p=0.93) levels did not differ between the two groups.. Women with high levels of fasting cholesterol did not have a statistically significant increase in risk for LGA (odds ratio (OR): 2.12, 95% confidence interval (CI): 0.50, 8.9), triglycerides (OR:0.86, 95% CI: 0.21,3.56), HDL (OR:1.14, 95% CI: 0.27,4.80) or higher LDL (OR:1.25, 95% CI: 0.29,5.49) as compared to women with low levels of cholesterol. We did not observe statistically significant effect modification by GDM status.

Conclusion: In this dataset, fasting maternal lipids measured during OGTT were not associated with cord blood lipids or LGA.

Does Suture Choice Matter for Elective Cerclage?

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OBJECTIVE: To compare Prolene versus Tevdek suture on pregnancy outcomes when used for an elective cervical cerclage.

METHODS: With Institutional Review Board approval, we conducted a retrospective cohort study involving pregnant women who underwent elective McDonald cerclage placement between June 2006 and December 2009. Medical records were reviewed for all women who underwent the procedure at 11 to 15 weeks of gestation at our institution. Procedure indications included: prior second trimester delivery (before 20 weeks), history of a prior preterm birth (between 20 and 37 weeks) or prior cerclage placement. Suture type was identified as either Tevdek (#9) or Prolene (#1). We calculated medians and interquartile ranges (IQR) for gestational age at delivery for both groups. Significant differences in gestational age at delivery were evaluated using the Wilcoxon rank-sum test. We also evaluated for differences in post-operative complications with the Fisher's Exact Test. Post-operative complications included: pull through, revision and/or cervical laceration. Statistical significance was set at $p<0.05$.

RESULTS: Of the 141 subjects who underwent cerclage placement at our institution, we conducted a sub-analysis with 54 women with an elective cerclage. Subject characteristics were similar between the two groups**.** The median gestational age at delivery was 37.4 weeks (IQR=19-40) for Tevdek and 39.0 weeks (IQR=18-41) for Prolene ($p=0.13$). The overall rate of post-operative complications did not appear to differ by suture (Tevdek 12.9%, Prolene 17.4%, $p=0.71$).

CONCLUSION: Although larger studies are needed, we found no difference in gestational length between Tevdek and Prolene suture type for elective cerclage. If these results are confirmed with larger studies, Prolene should be considered the suture of choice for elective cerclage placement since it has the advantage of ease of placement and removal.

Title: Improving Neonatal Transport with Real-Time Video Monitoring

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Telemedicine is the use of communication technology to improve patient care. To date, telemedicine has had a positive impact on health care delivery in specialties that rely on image-based diagnoses, such as radiology and cardiology, and in critical care specialties where real-time video of a patient can allow off-site experts to actively participate in patient management. We hope to bring the benefits of telemedicine to the field of neonatal transport medicine by adding real-time video monitoring. Neonatal transport medicine is well-suited for telemedicine since patient management is most effective when expert opinion based on clinical appearance is a critical part of an iterative decision-making process. In current practice, a neonatologist's assessment of critically ill neonates born in non-specialty institutions prior to and during transport is performed primarily with second-hand information. Real-time video monitoring allows neonatologists the ability to assess patient condition first-hand.

To monitor the patients, our team has created a novel video monitoring system. Since monitoring is needed when the system is both stationary and mobile, the system uses ubiquitously available cellular technology as the base communication layer. To provide the necessary bandwidth and reliability required by our application, our system opportunistically combines wireless data channels from different cellular providers. Unlike proprietary video monitoring systems, our system has lower operating costs, a continuously improving communication platform and widely available hardware components, making it both affordable and sustainable.

We have evaluated the technological capabilities of our system and are in the process of understanding the clinical utility of our system through a series of pilot studies and clinical trials. We believe that widespread deployment of our telemonitoring system will improve patient outcomes at hospitals where neonatologists are unavailable.

Recent Trends in Continuing Medical Education among Obstetrician-Gynecologists

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Objective: To assess current trends in continuing medical education (CME) among obstetrician-gynecologists in relation to the Maintenance of Certification (MOC) program.

Methods: A validated questionnaire was mailed to 1,030 randomly selected physicians of the American College of Obstetricians and Gynecologists (ACOG) in the United States, Puerto Rico and Canada. Participants were asked about current practices and opinions regarding CME activities. Responses were compared between members mandated for MOC (board certification 1986 or later; time-limited certificate) or not (board certification prior to 1986; non time-limited certificate).

Results: 520 (50.4%) surveys were completed. Respondents were more often male (57.1%), generalists (87.3%), in community-based (73.8%), group practices (77.2%) with mean (±SD) age 52.4 ± 9.9 years. Compared to physicians not requiring MOC and after adjustment for age, gender, years in practice, and practice-type, those mandated for MOC were more likely to pursue Annual Board Certification (ABC) articles as a moderate or large source of CME credits (OR 9.09, 95% CI 4.03-20.5). Conversely, MOC requirement led to decreased utilization of the national or international meetings (OR 0.31, 0.14-0.67) and self-selected CME materials (OR 0.29, 0.14-0.60). These differences were not due to generally changing attitudes towards CME activities. Physicians in both groups equally valued CME training (p=0.20), relevance of ABC articles (p=0.23), content of academic meetings (p=0.33), and usefulness of simulation drills (p=0.35).

Conclusion: Requirement of the MOC program has led to significant changes in CME choices by obstetrician-gynecologists. The changes in CME appear related to mandated obligations rather than personal preference.

Association of Higher Pre-Pregnancy BMI with Longer Femur Length at 16-20 Weeks

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Objective: To examine associations of maternal pre-pregnancy BMI with fetal biometry measures at the 16-20 week ultrasound.

Study Design: We studied 1,156 mother-fetus pairs in Project Viva, a prospective pre-birth cohort study. The main exposure was pre-pregnancy BMI, evaluated as a continuous (kg/m2) and categorical variable (BMI normal [<25.0]; overweight [25.0-<30.0]; and obese [≥30.0]). We used regression models adjusted for age, height, race, education, income, marital status, smoking, fetal sex, weight gain and gestational age at ultrasound.

Results: Mean (SD) pre-pregnancy BMI was 24.7 (5.2) kg/m2. In adjusted models, each 5 kg/m2 increase in pre-pregnancy BMI was associated with 0.36 mm (95% CI 0.21, 0.51) longer femur length. Overweight and obese participants, compared with normal weight participants, had longer femurs (0.68 mm [95% CI 0.31, 1.05] and 0.95 mm [95% CI 0.51, 1.39], respectively). BMI was not associated with fetal biparietal diameter, abdominal circumference, or estimated fetal weight. Maternal height (m) and gestational weight gain (kg/wk) were independently associated with longer femurs; smoking was associated with shorter femurs.

Conclusions: Greater pre-pregnancy BMI was associated with longer femur length at the 16-20 week ultrasound. Gestational weight gain and smoking during pregnancy are potentially modifiable factors that also influence early femur growth.

Complications Associated with Peripherally Inserted Central and Non-Central Catheters in the Newborn Intensive Care Unit

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Background: Peripherally inserted central catheters (PICCs) are utilized in critically ill newborns for stable intravenous access. Ideal tip position for a PICC is the superior or inferior vena cavae. In instances where central position can not be achieved, peripherally inserted non-central catheters (PINCCs) may still be utilized. Little data exists, however, as to their rate of associated complications.

Objective: To compare complication rates in PINCCs versus PICCs in a neonatal intensive care unit (NICU) and to evaluate the risk of a complication with duration of catheter use.

Design/Methods: Using an existing database, we identified all lines placed in the Yale NICU from July 2005 through August 2010. Data included demographics and catheter position, duration of use, and associated complications including associated bloodstream infections, phlebitis, infiltration, obstruction, and effusions. Unadjusted and adjusted complication rates were compared between PINCCs and PICCs. Risk factors for complications were assessed using Generalized Linear Equations (GEE) modeling, accounting for multiple catheter insertions per infant. Risk of complication by duration of catheter was further assessed use via Kaplan-Meier survival estimates.

Results: Data were available from 980 lines placed in 750 neonates. 91 were PINCCs and 889 PICCs. Neonates with a PINCC were of significantly higher gestational age (34 weeks *v.* 30 weeks; $p<0.0001$) and birth weight (2252 grams *v.* 1495 grams; $p<0.0001$). 44% of PINCCs had a major complication as compared with 25% of PICCs ($p=0.0001$), with the most common PINCC-related complication being infiltration. The overall, unadjusted complication rate among PINCCs was 51.7 per 1,000 line days and 15.9 for PICCs (rate ratio: 3.25; 95% CI: 2.32, 4.55). After adjusting for multiple confounders such as birth weight, the adjusted odds ratio for complications from GEE remained significantly higher for PINCCs (adj OR: 2.41; 95% CI: 1.34, 4.37). The median time to onset of a complication with the use of a PINCC was 11 days as compared with 45 days for PICCs ($p<0.0001$).

Conclusions: PINCCs are associated with a significantly higher rate of line-related complications as compared with PICCs. The median time to onset of a complication with the use of PINC is about 11 days. Particular care should be taken with the use of a PINCC beyond 10 days and subsequent removal or replacement should be considered.

The Ethics of Emerging Technologies and Transition to Accepted Practice: Intestinal Transplant for Short Bowel Syndrome

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Abstract

When considering the use of emerging technologies, counseling becomes complex when it is unclear whether the level of evidence is sufficient to transform the proposed therapy into accepted practice. This paper addresses the ethical issues underlying medical decision-making and counseling in the setting of emerging treatments, when long-term outcomes are still in the process of being fully validated. We argue that the ethical transition of emerging technologies, ideally from ethically impermissible to ethically permissible to ethically obligatory, depends primarily on two factors: outcome data (or prognosis) and treatment feasibility. To illustrate these points, we will use intestinal transplant for short bowel syndrome (SBS) as a specific example. After reviewing the data, this paper will identify the ethical justifications for both comfort care only (CCO) and intestinal transplant in patients with ultra SBS, and argue that both are ethically permissible, but neither is obligatory. The approach outlined in this paper will not only be valuable as ultra SBS outcomes data continue to change, but will also be applicable to other novel therapies as they emerge in perinatal medicine and in pediatrics.

Age-Related Type II Cell Behavior *in vitro*

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Background: Responses to injury are known to be developmental-age and context-specific for multiple tissues. Chronic lung disease (CLD) develops in immature lungs more rapidly than in the adult lungs and is associated with fibrosis. Fetal tissue is capable of injury repair without scarring and fibrosis. Fetal and adult T2 cells are known to require different culture conditions to keep their epithelial cell character *in vitro.* Differences in developmental-age related cell behavior might help discover treatment strategies for CLD. We showed that MLE12 cells, similar to primary adult type II (TII) cells, loose epithelial cell marker after Transforming Growth Factor beta (TGFβ)1 treatment. In contrast, TGFβ1 did not induce this response in fetal TII cells. ErbB receptors are important in lung development, injury, and cancer development and their expression pattern in TII cells is age-dependent.
Objective: We hypothesize that TII cells behave *in vitro* in a developmental age-related fashion.
Methods: MLE 12 cells and primary fetal and adult TII cells (>95% pure) were pretreated with cis-OH-proline to eliminate remaining fibroblasts, and epithelial and mesenchymal cell marker and ErbB receptor expression were studied in different culture conditions or following a 5-day treatment with 2.5 ng/ml TGFβ1.
Results: TTF-1 expression peaked shortly before birth, and adult type II cells kept their epithelial cell expression in HITES medium, while DMEM containing FCS, the ideal condition for fetal TII cells, would induce mesenchymal marker expression. In addition to cell marker expression, the response to TGFβ1 was age-related. TGFβ1 treatment induced epithelial marker and ErbB4 expression in fetal TII cells. ErbB4 overexpression decreased TGFβ1-induced upregulation of mesenchymal marker expression in adult TII cells.
Conclusions: These data suggest that there are developmental-age related differences in cell behavior and that ErbB4 regulates this age-related behavior in TII cells. Further analyses are required to fully understand the regulation of TII cell behavior and the role of ErbB receptors in the process.

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TTF1 and ErbB Receptors Might Regulate Cigarette Smoke- and Nicotine-Induced Lung Cell Remodeling

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RATIONALE: Cigarette smoke (CS)-exposure causes oxidative damage to the adult lung and leads to chronic injury and inflammation. Moreover, prenatal exposure to nicotine, which crosses the placenta, increases the risk of developing chronic lung diseases later in life due to premature signs of type II cell hyperplasia and ageing.

OBJECTIVE: To determine *in vivo* and *in vitro* differences of CS- and nicotine- exposure effects on the expression of TTF1 transcription factor and regulation of ErbB-receptors, important regulators in lung development and injury.

METHODS: Mouse lung epithelial type II (MLE12) cells were used for *in vitro* experiments. Wild-type C57Bl6 female mice were used for *in vivo* studies. Animals were exposed to CS for 4 weeks prior and during pregnancy. Macrophage accumulation in the lungs was used as an indicator of maternal CS-induced inflammation. Newborns weight was used as indicator of prenatal nicotine exposure. Adult and fetal lungs were collected on fetal D18 and at postnatal D1-6 and proteins analyzed by Western Blotting.

RESULTS: *In vitro* CS- but not nicotine-exposure increased TTF-1 expression, while phospho-AKT and AKT expression was increased with both treatments in a time- and dose- dependent manner. Increased macrophage accumulation was seen in lungs of smokers. Weight of nicotine exposed newborns was significantly smaller. In the *in vivo* setting, CS and nicotine increased TTF-1 expression in adult and newborn whole lung lysates, respectively. Interestingly, TTF-1 expression was dramatically reduced during pregnancy in the fetal and maternal lung independent of treatment. In adult lungs CS exposure led to an increase in ErbB2, ErbB4, and AKT.

SUMMARY: TTF1 and ErbB receptor signaling might play a role in CS- and nicotine-induced lung injury remodeling.

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DIFFERENTIAL EXPRESSION OF MMP-2 AND -9 AND THEIR INHIBITORS IN FETAL LUNG CELLS EXPOSED TO MECHANICAL STRETCH: REGULATION BY IL-10

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Background: Abnormal remodeling of the extracellular matrix (ECM) has been implicated in the pathogenesis of bronchopulmonary dysplasia. However, the contribution of lung parenchymal cells to ECM remodeling after mechanical injury is not well defined.

Objective: To investigate in vitro the release of MMP-2 and -9 and their respective inhibitors TIMP-2 and -1 in fetal type II cells and fibroblasts exposed to stretch and to explore the potential regulation by IL-10.

Methods: Mouse fetal type II cells and fibroblasts were exposed to 20% cyclic stretch for 48h to simulate injury. Activation of MMP-2 and -9 and their inhibitors TIMP-2 and -1 were analyzed by ELISA and Western blot, respectively.

Results: Mechanical stretch released active MMP-2 into the supernatant of fibroblasts and decreased TIMP-2, indicating that excessive stretch promotes MMP-2 activation by 2.5-fold, expressed as the MMP-2/TIMP-2 ratio. Incubation with IL-10 did not affect MMP-2 levels but decreased TIMP-2 levels by 44% in static monolayers, increasing the MMP-2/TIMP-2 ratio in stretched samples by 1.6-fold, a 64% reduction compared to samples without IL-10. Contrary to MMP-2, stretch decreased MMP-9 by 60% in type II cells whereas TIMP-1 was not affected. When IL-10 was added, TIMP-1 increased 2-fold in unstretched samples and decreased 50% in samples exposed to stretch. MMP-9 activity (MMP-9/TIMP-1 ratio) decreased by 50% after stretch. In samples with IL-10, this ratio increased by 50%.

Conclusions: Mechanical stretch differentially affects MMP-2/9 and their inhibitors in fetal lung cells. Although IL-10 has no direct effect on the release of MMPs, IL-10 can modulate ECM remodeling via TIMPs.

The influence of nuchal translucency thickness on the risk of structural abnormalities

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OBJECTIVE:
To determine the relationship between nuchal translucency (NT) thickness and the risk of fetal structural abnormalities.

STUDY DESIGN:
We performed a multi-center, retrospective cohort study of fetuses diagnosed with non-septate NT measurements $\geq$ 2.5 mm during first-trimester screening from 2000-2010. Medical records of these cases were reviewed to identify structural abnormalities.

RESULTS:
The rate of structural abnormalities increased with increasing NT size (Table 1). Among fetuses with NTs $\geq$ 3 mm with structural abnormalities, 44% had major cardiac anomalies, 15% had genitourinary abnormalities, and 27% had central nervous system abnormalities. Among fetuses with NTs of 2.5-2.9 mm with structural abnormalities, 13% had major cardiac anomalies, 31% had genitourinary abnormalities, and 21% had central nervous system abnormalities.

Table 1: The incidence of structural abnormalities based on NT size

NT size	N	Structural abnormalities
2.5 – 2.9 mm	575	6.7 %
$\geq$ 3 mm	298	25.2 %

$p<0.001$

CONCLUSION:
Increasing NT measurements, specifically with a NT $\geq$3 mm, are associated with an increased risk of structural abnormalities. The distribution of structural abnormalities differs based on size. Among those fetuses with NT $\geq$ 3 mm, cardiac anomalies are the most common abnormality. These findings may be helpful in counseling patients with abnormal NT findings on first trimester screening.

The impact of first trimester risk assessment on timing of aneuploidy diagnosis and termination of pregnancy

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OBJECTIVE:
Over the past decade there has been increasing availability and acceptance of aneuploidy screening using first trimester markers. We sought to evaluate the impact of first trimester risk assessment on the gestational age at time of invasive testing for and at termination of pregnancy for aneuploidy.

STUDY DESIGN:
All cases of aneuploidy diagnosed antenatally at a tertiary care referral center from January 2002 to December 2009 were included for analysis. Gestational age at time of invasive diagnostic procedure, indications for invasive testing, and gestational age at termination of pregnancy were collected. First trimester risk assessment was defined as first trimester serum screening or first trimester ultrasound. The association between gestational age at time of diagnosis and at subsequent termination of pregnancy was analyzed using Pearson's pairwise correlation coefficients. Linear regression was used to analyze continuous variables over time.

RESULTS:
272 patients had complete clinical data and abnormal fetal karyotypes. Of these patients, 181 (67%) underwent subsequent termination of pregnancy. Gestational age at time of invasive testing and gestational age at termination were significantly correlated ($p=0.002$). Gestational age at invasive testing and at termination of pregnancy decreased over time. This corresponded to a 7% increase per year in the proportion of cases of aneuploidy diagnosed by CVS rather than amniocentesis ($p=0.01$). Similarly, the proportion of aneuploidy cases diagnosed due to abnormal first trimester risk assessment significantly increased by 5% per year ($p=0.02$). From 2002-2009, the gestational age at time of invasive testing decreased by 2.3 days per year ($p=0.05$) and the gestational age at termination of pregnancy for aneuploidy decreased by 2 days per year ($p=0.07$).

CONCLUSION:
These findings demonstrate an intended goal of first trimester screening can be achieved. Increasing use of first trimester risk assessment is associated with an earlier gestational age at aneuploidy diagnosis and affords patients earlier options for termination of pregnancy.

Risk of early severe preeclampsia in singleton and twin pregnancies

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Objective: Preeclampsia is more common in twin, as compared to singleton pregnancies, however, it is unknown whether the severity and timing of disease varies by fetal number. We aimed to evaluate whether rates of early and late preterm birth for the indication of severe preeclampsia differ between singleton and twin gestations.
Study Design: This is a retrospective cohort study at a single institution including all deliveries from 2000-2009. Rates of delivery for severe preeclampsia (sPE) among infants born prior to 32 and 37 weeks gestation (GA) were compared, and diagnostic criteria for preeclampsia were compared between groups. Chi-squared tests were used for analysis.
Results: There were 6259 preterm deliveries, including 1399 twins, among 86,554 births. Examining delivery for sPE as a percentage of total births, early severe preeclampsia was significantly more common in twin compared to singleton pregnancies (2.4% vs. 0.4%, p< 0.001). This was also true for deliveries from 24-32 (0.8% vs. 0.2%, p < 0.001) and 32-37 weeks (1.7% vs. 0.3%, p ,0.001). In all gestational age categories, criteria for delivery including HELLP syndrome, abruption, and fetal indications were similar between groups. Among babies born < 32 weeks GA, delivery for sPE was equally common in singleton and twin pregnancies (136 and 25 deliveries, or 9% and 8%) Between 32 and 37 weeks GA, the rate of delivery for sPE was greater for singletons than twins (213 and 54 deliveries, or 7% vs. 5%, p=0.03).
Conclusions: Risk of premature delivery for severe preeclampsia is significantly greater in twin, as compared to singleton pregnancy, an effect seen particularly between 24-32 weeks. Preeclampsia diagnostic criteria were similar in all groups. These findings are of value in both antenatal surveillance and patient counseling.

Title: Blood Pressure (BP) Values in Preterm Infants ≤32 weeks GA During the First 4 Days of Life: A comparison.

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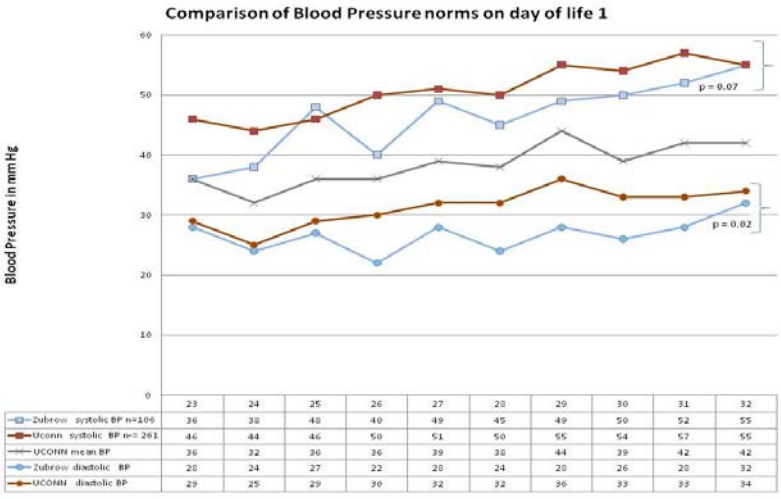
Background: The decision to treat hypotension in the NICU is often based on data derived from preterm infants born in the 1980s and early 1990s and who were not exposed to therapies such as prenatal steroids, surfactant and gentler ventilation modalities. Moreover, there were low numbers of infants <= 32 wk GA in those studies.

Objective: To study the current gestational age (GA) and postnatal age specific values for systolic (SBP), diastolic (DBP) and mean BP(MBP). To compare current values to previously reported values.

Design/Methods: This was a retrospective review of infants <=32 wk GA admitted to the Univ. of CT (UCONN) NICU from 2003-2007. A minimum of 25 infants were selected at each GA. Infants receiving vasopressors or steroids during the first 4 days of life were excluded. Perinatal and neonatal data was gathered from a database (NIS®). SBP, DBP and MBP on admission and at each 8-hour interval during the first 4 days of life were obtained by chart review. From the many sources studied (Versmold-'81, Heygi-'94, Lee-'99, Laughon-'07), GA and postnatal age based comparisons could only be made with data from Zubrow et al, '95. Statistical analyses were done using t-test and linear regression where appropriate.

Results: Of the 472 infants selected, 264 infants met inclusion criteria. Use of prenatal steroids in this sample was 80% and number of days on ventilator was 4.3±10 days(mean ±SD). At each GA from 23- 32 wk, SBP, DBP and MBP increased with postnatal age ($p < 0.001$). When compared with Zubrow's data, values from the current study were higher than those reported for all GA. A representative sample from postnatal age 1 day is shown.



	23	24	25	26	27	28	29	30	31	32
Zubrow systolic BP n=106	36	38	48	40	49	45	49	50	52	55
Uconn systolic BP n= 261	46	44	46	50	51	50	55	54	57	55
UCONN mean BP	36	32	36	36	39	38	44	39	42	42
Zubrow diastolic BP	28	24	27	22	28	24	28	26	28	32
UCONN diastolic BP	29	25	29	30	32	32	36	33	33	34

Conclusions: We found significantly higher blood pressure values for similar GA and postnatal age than those reported earlier in infants born at <= 32 wk GA. This may be due to higher use of prenatal steroids, surfactant and better ventilation strategies. There is a need for a multicenter study with a larger sample size to establish current BP norms.

Efficacy and Morbidity Following Bakri Use for Major Post-partum Hemorrhage

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Objective:
We sought to better understand the success rate and morbidity of Bakri balloon use for major postpartum hemorrhage (PPH), and to determine whether these factors are affected by uterine arterial embolization (UAE), prophylactic antibiotics, or duration of balloon placement.

Study Design
Retrospective cohort study of patients receiving Bakri balloon tamponade for transfusion-requiring PPH.

Results
68 women with transfusion-requiring PPH were treated with Bakri balloon tamponade from 2007-2009. In two cases (3%), the clinician was unable to place the balloon. Of the 66 women who had the balloon placed, five (7%) had continued hemorrhage requiring immediate laparotomy. Of the 61 stabilized patients, 19 underwent UAE while 42 were expectantly managed (EM). Of 45 women with no fever prior to Bakri placement, 28 (62%) were given prophylactic antibiotics. Median duration of balloon placement was 20.2 (25-75% = 13.8-25h). Three patients (7%) in the EM group had recurrent hemorrhage after the balloon was removed, while none re-bled after UAE (p=1.0). A new fever developed in 12 of 45 patients (27%) after Bakri placement. Those who underwent UAE had twice the rate of fever of those having EM (RR=1.96, 95% CI .77-5.0), and this association did not change after controlling for size of transfusion (adjusted RR = 2.16). The UAE group also had twice the rate of non-febrile morbidity (RR=2.06, 95% CI 0.99-4.31). There was no relationship between fever and duration of balloon placement. Median time to fever was 5 hours, and 11 of the 12 fevers occurred within 11 hours of balloon placement. Paradoxically, those placed on prophylactic antibiotics had three times the rate of fever (36% vs. 12%, RR=3.04, 95% CI 0.75-12.23), and this association persisted after controlling for size of transfusion (adjusted RR = 2.72).

Conclusion
With 7% immediate and 7% delayed failure rates, the Bakri balloon is a highly effective tool in managing severe post-partum hemorrhage. We found notable rates of both febrile and non-infectious morbidity (27% and 15% respectively). Fevers occurred relatively early after Bakri placement, and we found no evidence that prophylactic antibiotics decreased the rate of fever. Women undergoing UAE had twice the rate of morbidity, which did not reach statistical significance with our sample size. Further studies should define selection criteria for adjuvant UAE, given the success of the Bakri balloon when used alone.

MECHANISMS OF STRETCH-INDUCED DECREASE OF IL-10 PRODUCTION IN FETAL LUNG CELLS

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BACKGROUND: Although the mechanisms by which mechanical ventilation promotes bronchopulmonary dysplasia are not fully understood, an imbalance between pro- and anti-inflammatory cytokines seems to play a central role; in particular, the inability to maintain optimal IL-10 levels in response to an inflammatory injury. Previous studies from our laboratory showed that mechanical stretch of fetal rat type II cells decreased IL-10 production and the administration of IL-10 prior to stretch protected these cells from injury.

OBJECTIVE: Our primary aim was to analyze the mechanisms for inadequate IL10 production in fetal type II cells exposed to mechanical stretch.

DESIGN/METHODS: Fetal mouse lung type II cells were isolated at different gestational ages and cultured on silastic membranes precoated with fibronectin. Monolayers were then exposed to 20% cyclic stretch to simulate lung injury, using the Flexercell Strain Apparatus. Unstretched cells were used as controls. IL-10 release into the supernatant was analyzed by ELISA. IL-10 receptors gene expression was studied by real-time PCR. IL-10 signaling proteins were investigated by Western blot using phospho-specific antibodies.

RESULTS: First, we investigated IL-10 receptors gene expression during different stages of development (E17-E19) and found an increase with gestational age. 20% cyclic stretch of E18 type II cells for 24 hours decreased IL-10 in the supernatant by 58% compared to controls ($p<0.02$). Furthermore, mechanical stretch reduced IL10R1 gene expression by 60%, and IL10R2 expression by 42% when compared to controls ($p<0.0001$). Next, we analyzed signaling proteins from the IL-10 pathway and found that mechanical stretch decreased phosphorylation of JAK1, TYK2 and STAT3. Interestingly, administration of IL-10 increased activation of these proteins only during stretch, suggesting that under basal conditions the IL-10 pathway is maximally activated. Finally, mechanical stretch increased the transcription factor SOCS3 by 2-fold when compared to controls.

CONCLUSION: Our studies suggest that IL-10 expression is developmentally regulated. IL-10 receptor gene expression and associated kinases are decreased following mechanical stretch. Given that SOCS3 is a negative regulator for both pro and anti-inflammatory cytokines, we speculate that this transcription factor may play a central role in the decrease of IL-10 production by mechanical stretch. Currently, we are addressing this hypothesis using siRNA and transfection with adenoviruses

STRETCH-INDUCED DIFFERENTIATION OF FETAL TYPE II EPITHELIAL CELLS REQUIRES AN INTACT EGFR

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Background. The ErbB receptors family (ErbB1, ErbB2, ErbB3 and ErbB4) plays an important role in lung development. Previous studies from our laboratory have shown that stretch-induced differentiation of fetal type II epithelial cell is mediated via shedding of HB-EGF and TGF-α via the EGFR (ErbB1)-ERK pathway. Objective. To investigate whether other members of the ErbB family participates in stretch-induced differentiation. Design/Methods. Whole fetal lung and type II cells were isolated from wild-type and EGFR (-/-) mice on E17-19 of gestation. ErbB receptors abundance and ERK phosphorylation were investigated by Western blot. Fetal type II cell differentiation was assessed by surfactant protein C (SP-C) mRNA and protein levels. Release of ligands by stretch was investigated by measuring AP activity in the supernatant after transfection of type II cells by electroporation of plasmids encoding AP-tag ligands. Monolayers were exposed to 5% cyclic stretch to simulate fetal breathing movements, using the Flexercell Strain Apparatus. Results. In the whole fetal lung and isolated type II cells from EGFR (-/-) mice and as expected, no ErbB1 receptor protein was detected. ErbB2 and ErbB3 increased and ErB4 and SP-C protein decreased, when compared to wild-type mice. In type II cells isolated from wild-type mice, mechanical stretch activated ERK and increased SP-C mRNA and protein levels. In contrast, opposite results were observed in stretched cells isolated from knockout mice. 5% cyclic stretch of type II cells from wild-type animals shed mature HB-EGF and TGF-α into the supernatant, while in type II cells from EGFR(-/-), only HB-EGF was released. Conclusions. Despite some compensatory mechanisms in mice lacking the ErbB1 receptor, our data suggest that stretch-induced type II cell differentiation is almost exclusively mediated via the EGFR. This receptor seems also to regulate release of TGF-α by stretch.

Obesity in Pregnancy Alters Maternal Immune Function

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Objective: Obesity in pregnancy has long term implications for mother and fetus. Maternal obesity has recently been associated with increased endotoxemia, suggesting that obesity in pregnancy modifies maternal immune function. The objective of our study was to determine whether obesity in pregnancy alters T lymphocyte sub-populations and T cell function.

Methods: Pregnant women were recruited between 24 and 28 weeks of pregnancy in two groups based on pre-pregnancy BMI; obese (O) BMI > 30 (N=15) and lean (L) BMI 20-25 (N=15). Flow cytometric analysis was used to measure cell populations and intracellular cytokine expression. Proliferative ability of T cells was assessed with 3H- thymidine.

Results (data presented in table): Obese women had fewer CD8+ and CD4+/CD45RA+ cells compared to lean controls. A significant increase in B cell population was seen among the obese subjects. Obese subjects had impaired expression of interferon-γ and tumor necrosis factor-α in response to stimulation. In addition, obese pregnant women had significantly impaired cell proliferation in response to anti-CD3 ($p<0.05$ data not shown.) **Conclusions**: These marked differences in the immune response of obese and lean pregnant women may explain the increase in infectious morbidity in obese pregnancy and have implications for maternal and fetal health.

Table 1: Cell populations and cytokine response to stimulation (geometric mean)

	Obese (N=15) mean+/-s.d.	Lean (N=15) mean+/-s.d.	p value
CD4+	45.8% ±9.4	44.3% ± 12.7	NS
CD8+	16.4% ± 5.8	23.5% ±7.4	<0.05
CD4+/45RA+	35.9% ±7.7	44.8%± 10.8	<0.05
CD8+/CD45RA+	62.4% ±12.7	54.8% ±14.0	NS
CD4+/CD45RO+	50.0%± 11.4	60.3%± 20.7	NS
CD8+/CD45RO+	39.9%± 12.7	43.1%± 14.0	NS
NK cells	9.9%±4.6	8.8%±4.6	NS
B cells	21.9%±6.2	13.3%±5.3	<0.05
TNF α response to stimulation			
CD8+ cells	308.8±226.0	502.0±350.2	<0.05
CD4+ cells	292.0±281.5	550.9±396.0	<0.05
IFN γ response to stimulation			
CD8+ cells	415.3±242.9	573.2±261.6	<0.05
CD4+ cells	406.8±181.7	686±519.1	<0.05

The Influence of Plurality on Termination Decisions in Cases of Cystic Hygroma

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OBJECTIVE: To assess the relationship between plurality and obstetric outcomes in pregnancies diagnosed with cystic hygroma in the first trimester.

STUDY DESIGN: A retrospective multi-center study of 2,842 records of patients with increased nuchal translucency ($\geq$2.5mm) and/or cystic hygroma diagnosed between 2000 and 2010 at five institutions yielded 1872 patients with cystic hygroma diagnosed in the first trimester. Patients had ultrasound examinations between 10 weeks 3 days and 13 weeks 6 days. Cystic hygroma was defined as "an enlarged hypoechoic space at the back of the fetal neck, extending along the length of the fetal back, and in which septations were clearly visible." Outcomes were classified as termination (or selective reduction in the case of multiples), live birth, or fetal loss.

RESULTS: Of the 1578 singleton pregnancies, 559 (35.4%) resulted in elective termination, 129 (8.2%) resulted in fetal loss, and 890 (56.4%) were born alive. Of the 210 twin pregnancies, 67 (31.9%) were selectively reduced, 28 (13.3%) resulted in fetal loss, and 115 (54.8%) were born alive. Of the 84 pregnancies with three or more fetuses, 57 (67.9%) were selectively reduced, 7 (8.3%) resulted in fetal loss, and 20 (23.8%) were born alive (Table 1). Women carrying triplets or a higher order multiple pregnancy were more likely to terminate the affected fetus than women carrying twins or singletons ($p<0.0001$). Among women who chose not to obtain a prenatal karyotype of the affected fetus, 76.3% of women carrying triplets or higher-order multiples elected to terminate the affected fetus, compared to 22.6% of women carrying twins and 5.7% of women carrying a singleton gestation.

CONCLUSION: In the setting of a first-trimester diagnosis of a cystic hygroma, women carrying twins were no more likely to selectively terminate the affected fetus than women carrying a singleton pregnancy. The data suggest that women carrying high-order multiple pregnancies used the diagnosis of a cystic hygroma as an indication to reduce to a lower-order gestation - an option typically offered primarily to women carrying high-order multiples -- in addition to terminating a fetus at high-risk of abnormalities. This is not the case for women carrying twin or singleton gestations.

	Frequency (n)	Elective Termination	Fetal Loss	Live Birth
Singleton	1578	35.4%	8.2%	56.4%
Twin	210	31.9%	13.3%	54.8%
Triplet +	84	67.9%	8.3%	23.8%

Axon Regeneration in the CNS with Activated KRAS

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Background: Neurodevelopmental outcome is a major issue in Neonatology; despite greater plasticity in the newborn brain, we still see significant damage in both preterm and term infants from hemorrhage and hypoxia-ischemia. Unlike the peripheral nervous system, axons in the central nervous system do not regenerate after injury. This lack of regeneration is attributed to both the inhibitory extrinsic environment of the CNS and a diminished intrinsic regenerative capacity. Two major signaling pathways have been studied in association with regulation of axon growth: the PI3K/AKT pathway and the Ras-activated Raf/ERK kinase cascade. KRAS is an oncogene in the Ras family that is involved in regulating cell division; it produces a GTPase which activates the MAP kinase signaling pathway.

Objective: The aim of this study is to assess the impact that activating KRAS has on axon regeneration after optic nerve crush.

Methods: Because germline knockout of individual cell growth control genes can result in compromised viability in mice, we use intravitreal injection of adeno-associated viruses expressing Cre (AAV-Cre) in adult mice. This results in overactivation of KRAS in mature RGCs in vivo. Optic nerve crush is performed 2-3 weeks later; after another 2-3 weeks the mouse is sacrificed and examined for RGC survival and axon regeneration.

Results: KRAS mutant mice show increased axon regeneration after injury when compared to controls. Neuronal survival was not affected, indicating that the increase in regenerating axons is not due to an increase in RGC numbers.

Conclusions: KRAS overexpression in adult RGCs and subsequent activation of the downstream MAP kinase pathway leads to increased axon regeneration after optic nerve crush injury. Understanding the impact of this intrinsic growth control pathway will generate greater understanding of the CNS's response to injury and could lead to future therapeutic approaches to promote axon regeneration.

Online Developmental Questionnaires For Preterm Infants After NICU Discharge: Parental Preference And Ability To Participate

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Background: Very preterm infants require close developmental surveillance after hospital discharge. Online parent reported developmental questionnaires might be a useful supplement to in-person assessment, but the preference and ability of preterm infants' parents to complete them is unknown.

Objective: 1)To describe the preference of preterm infants' parents to complete developmental questionnaires online vs. on paper; 2)to describe the parents' degree of internet and email access; and 3)to examine correlates of preference and access.

Design/Methods: As part of a study to assess a developmental questionnaire in a preterm infant-follow up clinic, we asked 241 families about internet and email access, sociodemographic characteristics, and preference for completing the questionnaire online vs. on paper. We collected child health data from the medical record and compared parent preference and access by sociodemographic and child characteristics using χ^2 and t-tests.

Results: Median(range) gestational age was 27(25-30) weeks and birth weight was 954(750-1200) g. 98% of parents had internet access, 95% had email access; and 70% preferred completing a developmental questionnaire online vs. on paper or were indifferent. Less maternal education (83% v. 98%, $p<0.01$ for less than a high school education), lower family income (77% v. 95% , $p <0.01$, for less than $20K/year) and Hispanic ethnicity(90% vs. 98%, $p<0.02$) were associated with less internet and email access but sociodemographic characteristics were not associated with a preference for online questionnaires. Families of children receiving early intervention (EI) were less likely to prefer online questionnaires than families not receiving EI (68 vs. 88%, $p=0.03$).

Conclusions: Most families attending a high-risk preterm infant follow-up clinic had internet and email access, and preferred completing developmental questionnaires online to on paper. Sociodemographic disparities were evident in access, but *not* in preference.

Title: The Effect of Massage on NICU Network Neurobehavioral Scale for Methadone Exposed Infants, a Randomized Controlled Trial

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Background: NICU Network Neurobehavioral Scale (NNNS) was developed for NIH to see the effect on prenatal drug exposed infants. It was designed to provide neurologic integrity and behavioral function. It has summary scores on habituation, nonoptimal reflexes, asymmetrical reflexes, hypertonicity, excitability, quality of movement, attention, handling, lethargy and stress/abstinence. There has not been NNNS for the effect of massage on Methadone exposed infants.
Objective: To evaluate the neurobehavioral response to message for Methadone exposed infants by using NNNS.
Design/Methods: Methadone exposed infants, who were treated with Morphine and then loaded with Phenobarbital were randomized to receive massage and standard care (M/SC) or standard care alone (SC) once a day and 5 days a week at gestation age of 35-6 weeks (PT) and 37-42 weeks (FT). Administrators of NNNS were blinded to the type of therapy before morphine, after the loading of Phenobarbital before randomization began, and then after 3, 5, 7, 10, 15, 21, 28 treatments or before discharge. Statistical analyses of repeated assessments are by general linear modeling. Differential effect of group was assessed through developmental trajectories over time.
Results:
1. Morphine and Phenobarbital improved regulation, quality movements and excitability for FT. They did not improve stress/abstinence scores on NNNS.
2. For PT, M improved attention and lethargy. $P<0.05$ for M vs. SC.
3. Hypertonicity was improved in FT-M but not in PT-M.
4. Quality of movements, regulation and excitability were improved among FT-SC but not for FT-M group.
5. Although overall stress/abstinence scores were not improved in all 4 groups, subscores of autonomic, physiological and skin were significantly improved for FT-M group, and CNS and state among FT-SC. PT-M improved physiological ($P=0.0014$) and had a trend for autonomic ($P=0.054$) and GI ($P=0.08$).
Conclusion:
1. The effects of Morphine and Phenobarbital could not be separated due to our protocol.
2. Medications did not affect the stress/abstinence scores on NNNS.
3. Improved quality of movements, regulation and excitability among FT-SC suggest that M may stimulate them rather than calming them during first 7 treatments. Since M improved attention after 7 treatments, it may be more efficacious if the test is given from the second week of life.
4. M improved response to audio and visual stimulation with better attention for FT and PT.
5. M has positive effect on the autonomic nervous system.

TITLE: FETAL ABDOMINAL WALL DEFECTS: NEONATAL OUTCOMES BY MODE OF DELIVERY

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OBJECTIVE: To compare neonatal outcomes for fetuses with gastroschisis and omphalocele by mode of delivery.

METHODS: A retrospective review of maternal and neonatal charts from January 2008 to January 2009 was performed to obtain the mode of delivery and neonatal outcomes for infants with abdominal wall defects. Results were deidentified and compared for multiple short-term neonatal outcomes including length of stay, neonatal sepsis, length of mechanical ventilation, avulsion injuries, ischemic bowel, small bowel obstruction, necrotizing enterocolitis, Apgar scores, and mortality rates.

RESULTS: A total of 75 fetuses born with omphalocele or gastroschisis were identified. Infants with gastroschisis had a cesarean in 49/54 (91%) and vaginal delivery 5/54 (9%). Mean length of stay was 45.8 days for cesarean and 54.8 days for vaginal. Neonatal sepsis occurred in 10.2% by cesarean and 20% vaginally. Mean ventilator time was 7.6 days for cesarean versus 15.4 days for vaginal. Birth injury occurred in only one case, a cesarean. Obstruction was noted in 12.2% for cesarean, 20% for vaginal. Necrotizing enterocolitis noted in 6.1% in cesarean, none for vaginal. Apgar scores were similar for both groups. No neonatal deaths noted. For omphalocele, 14/21 (67%) had a cesarean and 7/21 (33%) had a vaginal delivery. Mean length of stay was 42.1 days for cesarean delivery and 18.7 days for vaginal delivery. Neonatal sepsis occurred in 21.4% for cesarean and none for vaginal. Days on the ventilator were a mean of 7.9 for cesarean and 1.0 for vaginal delivery. Ischemia, rupture of omphalocele, and obstruction all noted on 7.1%of cesarean, none for vaginal. No necrotizing enterocolitis was noted in either. Apgar scores were similar for both groups. One neonatal death was noted in a patient with hydrops fetalis.

CONCLUSIONS: Though not statistically significant, this study shows a trend of decreased length of stay, neonatal sepsis, days of ventilation for cesarean delivery with gastroschisis. For omphalocele, it shows a trend toward the benefit of vaginal delivery from decreased length of stay, ventilation, obstruction, ischemia and rupture of omphalocele. This data shows clear trends; however larger numbers would potentially allow statistical significance and should be addressed.

Title: Eliciting Physician and Nursing Perceptions about Initiation of Minimal Enteral Feedings (MEF) in Very Low Birth Weight (VLBW) Infants.

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Introduction/Background: Recent American Academy of Pediatrics recommendations to enhance nutritional management of VLBW infants have included early introduction of MEF and efforts to standardize nutritional practices. Studies show a large variation in enteral nutrition management within and between NICUs.

Goal: The goal of our study was to elicit physician and nursing perceptions about initiation of MEF in VLBW infants to understand why 'consensus' early feeding guidelines were not being followed.

Methods: A qualitative research design was conducted in 2 phases. Phase I involved 26 non-participant observations of morning rounds. Phase II involved 26 in-depth, semi-structured interviews of members of the NICU healthcare team. Sample: All 12 attending MDs were invited via email; 10 participated. 21 nurses were selected using stratified randomization from 7 groups based on years of experience; 9 participated. 7 of 23 NNPs were randomly selected & interviewed. Data Anayses: Data were collected beyond thematic saturation. The transcripts were coded & analyzed according to Miles & Huberman (1994). Themes were developed based on the responses to the interview questions relating to perceptions that influenced the healthcare team's decision to initiate MEF in VLBW infants. Data from observations & interviews were triangulated with chart reviews.

Results: Preliminary data suggest that despite unanimous agreement with the concept of MEF by all the respondents, there was a poor & inconsistent understanding of the benefits of MEF. Most expressed that MEF could not be started until the infant was 'clinically stable'; but, there was significant variation in the interpretation of & the concerns for the definition of clinical stability, feeding intolerance and fear of NEC. Most respondents said they hesitated to initiate MEF with formula & preferred to wait extra days for breastmilk. Major reasons that prevented medical staff from initiating MEF in first 3 days of life were prophylactic indomethacin to prevent IVH, omission of presentation of MEF on rounds & high ventilator settings. The need for more education was voiced by all respondents.

Conclusion: There is a need for ongoing education & open discussions to improve understanding of the benefits of MEF, & specifically that the risk:benefit ratio for MEF favors benefit.

Maternal Cell Microchimerism in the Fetus

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Background: Maternal cell microchimerism (MCM) is defined as the presence of maternally derived cells in fetuses. Maternal cells, which travel to the fetus through the placenta, are present in the human fetal blood beginning at 13 weeks gestation and persist into adulthood. Studies show that these maternally derived cells are associated with autoimmune disorders. It is unclear whether they cause disease or participate in the repair of injury. MCM has been studied in post-natal mice, in which organ-specific MCM was present in brain, heart, lung, kidney, liver, spleen, and small bowel. Heart and lung had the highest numbers of maternal cells. The development of organ-specific MCM in the fetus in utero has not been studied.

Objective: To establish the frequency and quantity of organ-specific MCM in fetal tissues.

Design/Methods: MCM was studied using a green fluorescent protein (gfp) mouse model. Hemizygous gfp positive C57Bl/6 females were bred with wild-type males. Timed-pregnant females were sacrificed at E18. Fluorescent maternal cells in brain and lungs of wild-type pups were quantified using FACS (fluorescence-activated cell sorting) analysis.

Results: The distribution of MCM showed that fetal brain contains 4 times as many maternally-derived gfp positive cells than fetal lungs at E18 of gestation.

Conclusions: In contrast to the post natal distribution of MCM, MCM is skewed to the brain in late gestation fetuses. This raises important questions of the fate of maternal cells in late gestation and after delivery. Further, the function, and fate of maternally derived cells in the fetal and neonatal brain, specifically in the setting of injury, requires study. (Support: NIH HD 049341 and Ikaria's Advancing Newborn Medicine Grant Program for Fellows in Neonatology)

Auditory neural maturation, indexed by brainstem auditory evoked response (BAER), is associated with reduced apnea, bradycardia and blood-oxygen desaturation in preterm infants

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Objective: The present study investigated the relationship between brainstem auditory evoked responses (BAERs), which provide an index of myelin development and brain maturation, and the frequency of infant apnea, bradycardia and blood-oxygen desaturation in preterm infants.

Methods: A prospective study was performed in 13 preterm infants (10 female; 6 non-white) at UMass Memorial Healthcare NICU. Infants' mean GA=30.4wks (SD 2.98), mean GA weight=1444 (SD 571), mean Apgar score at 5 minutes =7.2 (SD 2.5). Infants with chromosomal disorders, congenital malformation, culture-proven sepsis, CNS congenital or perinatal infection, intraventricular hemorrhage>grade II, periventricular leukomalacia, hypoxic-ischemic encephalopathy, cord PH<7, and Apgar score less than 5 at 5min were excluded. Bilateral monaural BAERs were assessed using 65dB nHL click stimuli at a repetition rate of 21/second. BAERs were performed at mean 2.6wks after birth and repeated at 1-2 week intervals. BAERs were analyzed with masked knowledge of infant demographics and previous BAER results. BAERs were categorized on a 4 point scale based on identification and replication of BAER waveforms I, III and V, reflecting maturation of peripheral auditory nerve through brainstem; response type 1 represented the most mature response and type 4 represented the least mature response (Amin, 1999).

Results: To date 13 infants participated in up to 5 sessions, with 35 sessions included in analysis. Data were analyzed by comparing infants studied at the following PCA: Group 1: <28 wks (n=2; mean=27.2 wks, 735g); Group 2: 28-29wks (n=4; 29.1wks, 790g); Group 3: 30-33wks (n=15; mean=32.6wks, 1324g); Group 4: 34-37 wks (n=14; mean=35.3 wks, 1923g). BAERs for all infants in Group 1 were type 4 on the maturation scale (no identifiable BAER). In Group 2, there were 3 infants that were type 2 and 1 infant type 3. In Group 3, BAERs for 5 infants were type 2 and for 10 infants were type 1. BAERs for all infants in Group 4 were type 1 (most mature). Spearman's rho correlations revealed more mature BAERs were associated with older PCA ($r=-0.719$, $p<0.001$) and greater weight ($r=-0.662$, $p=0.001$). Immature BAERs were associated with increased apnea ($r=0.540$, $p<0.001$), blood-oxygen desaturation ($r= 0.549$, $p=0.001$) and bradycardia ($r=0.635$, $p<0.001$). Increased frequency in apnea, blood oxygen desaturation and bradycardia were each also associated with prolonged Wave V latency (see Figure 1). PCA and study weight were each inversely related to Wave V latency ($r=-0.620$, $p<0.001$; $r=-0.570$, $p<0.001$, respectively); neither were related to Wave I or Wave III.

Conclusion: In addition to corroborating findings that mature BAERs are associated with infant age, weight and reduced apnea, the present study found that BAER maturation is related to reduction in bradycardia and blood-oxygen desaturation. Latency of Wave V was correlated with apnea, bradycardia, and blood-oxygen desaturation suggesting that separate indices of cardio-respiratory are each related to central brainstem maturation. Further exploration of these relationships is underway.

Title: Improving Triage Decisions For Infants Born At 35 weeks Gestation

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Background: Infants born at 35 wks gestation are at increased risk for short term morbidities. Correct triage to Level 1 (L1) vs >Level 1 (>L1) setting balances medical, family and resource utilization.

Objective: To compare initial delivery room (DR) triage (L1 vs >L1 setting) to ultimate level of services received, and to determine clinical factors associated with need for >L1 services.

Design/Methods: Multicenter retrospective analysis of infants born 1/2007-12/2008 at 35 0/7-35 6/7 wk by best OB estimate in 5 hospitals with varying levels of care. Infants with major congenital anomalies or requiring CPR in the DR were excluded. Prenatal, intrapartum and postnatal maternal and infant data were collected. Highest level of care required for each infant was determined using AAP 2004 definitions. Univariate and multivariate regression analyses were performed with $p<.05$ considered significant.

Results: Of 431 infants meeting inclusion criteria, 338 (78%) required L1 services and 93 (22%) required >L1 services (Table 1). 228/231 (98.7%) initially triaged to L1 setting received only L1 services and 90/200 (45%) initially triaged to >L1 setting received >L1 services. In multivariate regression analysis (Table 2), maternal fever, C-section without labor, Apgar<9 at 5 min, DR blow-by oxygen, and DR bag mask ventilation were associated with need for >L1 services. ROC curve area for this model was 0.81 (0.765, 0.864). Gender, black race, antenatal steroid exposure, SGA/LGA vs AGA, maternal diabetes or preeclampsia, multiple gestation, and general anesthesia were not associated with the need for >L1 services after adjusting for factors in this model.

Conclusions: A minority of 35 wk infants required >L1 services and almost all of these were identified in the DR. A large proportion of infants triaged to >L1 setting never required >L1 services. These multicenter results document a need for improved triage of 35 wk infants and provide a potential tool for this purpose. Prospective validation of this model is warranted.

Table1: Initial Triage decision versus services received

	Services Received	
	L1	>L1
Triage to L1 Setting	228	3
Triage to >L1 Setting	110	90
Total	338	93

Table 2: Results of multivariate regression modeling predicting the need for >level 1 services

	OR	95% CI	P
Black race	0.36	0.16, 0.84	0.017
Apgar 5 <9	2.76	1.42, 5.36	0.003
Blow by O_2	2.00	1.16, 3.44	0.012
Bag-mask ventilation	6.11	3.47, 10.74	<0.001
CS no labor	2.06	1.09, 3.90	0.026
Maternal fever	7.46	1.08, 51.52	0.041

ErbB4 Drives the Age-Related Type II Cell EMT Behavior

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Background: Epithelial- Mesenchymal Transition (EMT) is a biological process where epithelial cells acquire a mesenchymal cell phenotype. EMT is activated in association with tissue repair and remodeling after injury in many organs including the lung. In adult lungs, EMT is associated with the progression of fibrosis. In contrast, fetal tissue is capable of wound repair without scarring or fibrosis. We previously showed that MLE12 cells, similar to primary adult type II (TII) cells, undergo EMT after Transforming Growth Factor beta (TGFβ)1 treatment. In contrast, fetal rat d21 TII cells did not undergo EMT with TGFβ1. ErbB receptors are important in lung development, injury, and cancer development. Their expression pattern in TII cells is age-dependent. Their regulation in the EMT process is not known.

Objective: We hypothesize that ErbB4 drives the age-related regulation of TII cell EMT.

Methods: Primary isolated fetal d21 rat TII cells (>95% pure) were pretreated with cis-OH-proline to eliminate remaining fibroblasts, followed by a 5-day treatment with 2.5 ng/ml TGFβ1. MLE-12 cells were used as an adult TII cell model. Epithelial and mesenchymal cell markers and ErbB receptor expression were studied.

Results: TGFβ1 significantly increased Vimentin and N-cadherin and reduced epithelial marker Cytokeratin 18 in MLE12 cells while non significant changes seen in fetal type II cells. TGFβ1 treatment increased epithelial marker ZO-1 in fetal TII cells.

The table below shows the TGFβ1 treatment effects on ErbB receptors phosphorylation and protein content:

	MLE12 cells	Rat Fetal type II cell
ErbB2 receptor	A trend to increased receptor phosphorylation and protein	Decreased receptor phosphorylation (to 70%: $p< 0.01$) and protein expression (to 81%; $p< 0.05$)
ErbB4 receptor	Decreased receptor phosphorylation (to 68%; $p< 0.05$) and protein (to 85%; $p< 0.05$)	A trend to increased receptor phosphorylation and high increase in protein amount (to 130%; $p< 0.05$)

Preliminary data of ErbB4 overexpression in MLE12 cells show decreased upregulation of Vimentin, N-Cadherin and ErbB2 by TGFβ1.

Conclusions: These data suggest that ErbB4 drives the age-related induction of EMT in TII cells. Further analyses are required to fully understand the function of ErbB receptors regulation in TGFβ1-induced EMT in TII cells.

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Thicker Nuchal Translucency Is Associated with Greater Risk of Abnormal Fetal and Neonatal Outcomes Among Fetuses with First Trimester Cystic Hygroma

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OBJECTIVE: To assess the relationship between thickness of nuchal translucency and outcomes in first trimester fetuses with cystic hygroma.

STUDY DESIGN: Multicenter, retrospective cohort study from 2000 to 2010 of fetuses with ultrasound diagnosed cystic hygroma and nuchal translucency measurements between 10 weeks 3 days and 13 weeks 6 days gestation.

RESULTS: Nuchal translucency measurements were available for 318 (50%) of 631 fetuses with cystic hygroma. The median nuchal translucency thickness was 4.4mm (range 1.4-12mm). A karyotype was available for 238 fetuses of which 106 (44.5%) were abnormal. Anatomical information was documented for 140 fetuses and 40 (28.5%) had a major structural abnormality. Of the 87 gestations not aborted and with follow up information, 25 (28.7%) resulted in fetal or neonatal loss. After adjusting for maternal age, race, and multiple gestation, every 1mm increase in nuchal translucency thickness increased the odds of an abnormal karyotype by 44% (adjusted OR=1.44; 95% CI: 1.24-1.69, $p<0.001$), the odds of a major structural abnormality by 21% (adjusted OR=1.21; 95% CI: 1.00-1.46, $p=0.048$), and the odds of a fetal or neonatal death by 2-fold (adjusted OR=2.06; 95% CI: 1.35-3.13, $p=0.001$).

CONCLUSION: Cystic hygroma diagnosed in the first trimester is associated with a high risk of abnormal karyotype, major structural anomaly, and fetal or neonatal death. The risk of these outcomes increases with greater thickness of the nuchal translucency.

Obesity In Pregnancy Alters Maternal Micronutrient Balance

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Background: Obesity is associated with oxidative stress which impacts maternal and fetal health. We have previously shown in an animal model of diet induced obesity that maternal antioxidant supplementation ameliorates gene changes, oxidative stress and adiposity found in offspring of obese pregnancy.

Objective: The objective of this translational study is to determine whether obesity during pregnancy alters the balance of key micronutrients in mothers.
Methods: Women were recruited for the study between 24 and 28 weeks of pregnancy in two groups based on pre-pregnancy BMI; obese (OB) BMI > 30 (N=12) and lean controls (C) BMI 20-25 (N=10). Blood was drawn from mothers between 24-28 weeks of pregnancy and cord blood is being collected at delivery. Vitamins A, C and E were measured by HPLC. Vitamin 25(OH) D was measured by RIA. Zinc was measured by spectrophotometry. Red blood cell folate was measured by chemiluminesence. Students T test was used to determine difference between groups and significance. Oxidized and reduced glutathione is being measured in maternal blood and all of these assays are being repeated in cord blood as mothers deliver.
Results: Levels of RBC folate, vitamin C and vitamin E were significantly lower ($p<0.05$) in obese compared to lean pregnant women. Levels of vitamins A and D approached significance (see table 1 for results.) There was no difference in zinc levels between groups. There is no reported difference in prenatal vitamin intake between groups.
Conclusions: These results indicates that the oxidative stress of obese pregnancy is associated with reductions in levels of micronutrients, particularly those involved in maintaining anti-oxidant defenses. The resultant pro-inflammatory milieu could influence the developing fetal epigenetic code. Restoring this balance could prevent changes in offspring.

Table 1: Micronutrient status from obese and lean pregnant women

	RBC folate (ng/ml)	Vitamin A (ug/dL)	Vitamin C (mg/dL)	(1,25)OH Vitamin D (ng/ml)	Vitamin E (ug/dL)	Zinc (ug/dL)
Lean (N=9)	1423.4+/-300.5	62.6+/-9.9	1.4+/-0.3	39.0+/-9.2	3254.8+/-986.0	61.1+/-6.1
Obese (N=10)	970.7+/-174.2	46.1+/-12.6	0.088+/-0.2	30.25+/-8.2	2277.9+/-322.4	60.5+/-4.3
P value	<0.05	0.06	<0.05	0.08	<0.05	NS

Correlation of the anteroposterior diameter of the fetal renal pelvis in the second and third trimester with neonatal outcome.

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OBJECTIVES: The aim of this study was to evaluate the need for postnatal follow up and treatment--scintigraphy and surgery--in relation to the grade of fetal renal increased pelvic anteroposterior dilatation (APD) found on second and third-trimester ultrasound examination. Also to determine the most efficacious fetal renal pelvis antero-posterior diameter (APD) cut-offs in the second (2^{nd} Tr) and third (3^{rd} Tr) trimester to predict neonatal nephro-uropathy requiring surgery (Surg).

METHODS: Seventy-four consecutive fetuses with a diagnosis of persistent hydronephrosis who had an antenatal pediatric urology consult between 01/2007 and 01/2010 were enrolled in the study. Each fetus had hydronephrosis which persisted until the referral to the Perinatal-Pediatric Urology Clinic. The children were allocated to three groups based on pelvic anteroposterior diameter (APD) detected on second and third-trimester ultrasound. In the second trimester APDs of 5-8.9 mm, 9-14.9 mm and > or = 15 mm were classified as mild, moderate and severe hydronephrosis, respectively. In the third trimester APDs of < 7mm, 7-9.9 mm, 10-14.9 mm and > or = 15 mm were classified as resolved, mild, moderate and severe hydronephrosis, respectively. We used student "t" test for continuous, Chi square for categorical variables and we developed Receiver operating characteristic (ROC) curves by group. A $p < 0.05$ was deemed significant.

RESULTS: Of the 74 enrolled, 53 had postnatal follow up. Tables 1 and 2 show a comparison of the grade of fetal hydronephrosis with postnatal evaluation.The mean (+/- SD) APD in the 2^{nd} Tr was 8.0 (+/- 3.5) and in the 3^{rd} Tr 14.7 (+/-10.1). Comparing Surg vs Observ, the mean (+/-SD) APD in the 2^{nd} Tr was 7.4 (+/- 3.1) Observ and 11.1 (+/- 4.5) Surg ($p = 0.01$) and in the 3^{rd} Tr it was 12.1 (+/- 7.2) Observ and 28.3 (+/- 12.2) Surg ($p < 0.0001$). The area under the ROC curve (AUC) and tests of efficacy for predicting neonatal surgery are seen in Figure 1.

CONCLUSIONS: Neonatal nephro-uropathy requiring surgery is best predicted at a 3^{rd} Tr APD threshold of 15 mm. Fetuses with isolated hydronephrosis in the 2^{nd} Tr should be followed with an APD in the 3^{rd} Tr. Because the grade of fetal hydronephrosis does not reliably identify fetuses at increased risk of postnatal complications, even in the mild group, all fetuses with antenatal hydronephrosis need a postnatal evaluation.

Nurse-Patient Ratio (NPR) Remains Significantly Associated With Achievement of Oxygen Saturation (SpO_2) Goals in Preterm Infants After Changes in O_2 Clinical Practice

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Background: Previously, we reported that NPR was significantly associated with achievement of SpO_2 goals in a NICU before instituting clinical practice changes (CPC) to optimize O_2 management. It is unclear whether NPR remains associated with achievement of SpO_2 goals after such CPC. Objective: To examine the relationship between patient factors, NPR, and proportion of time SpO_2 target 85-93% was achieved (TA), proportion of time with hypoxemia (SpO_2 <80%, Hpo) and with hyperoxemia (SpO_2 >97%, Hpr) in VLBW newborns after O_2 CPC. Design/Methods: We linked medical records and nurse-patient assignment data with continuous SpO_2 data from birth to 36 wk postmenstrual age (PMA) for VLBW infants inborn from Mar-Dec 2009, after O_2 CPC including policy revision, staff education, and audits. Proportion TA, Hpo, and Hpr while on supplemental oxygen were determined for multiple 6 hr monitoring periods (MPs) characterized by one nurse, respiratory support mode, and oximeter high alarm setting. Factors associated with TA, Hpo, and Hpr were identified in cross-classified hierarchical regression to adjust for clustering of MPs within patients and nurses. Results: We analyzed 892 MPs from 23 infants with mean (SD) bwt 916 (249) g. Mean (range) PMA for MPs was 30.2 (23.7-35.9) wk. 85 nurses provided care. For all MPs, median TA was 39%, Hpo 9.7%, and Hpr 6.9%. In regression analysis, NPR of 1:1 (vs. 1:2 or 1:3) was associated with a 20% increase in TA for infants on mechanical ventilation (Table 1), and a 3% decrease in Hpo for all respiratory modes (Table 2), after adjusting for alarm setting and markers of illness severity. TA worsened with advancing PMA despite adjustment for NPR. No significant association between NPR and Hpr was found. Conclusions: Fewer patients per nurse remained associated with improved SpO_2 target achievement and reduced hypoxemia after clinical practice changes to optimize O_2 management. Optimal O_2 management may require limiting nurse-patient ratio and/or use of technologies such as automated FiO2 adjustment.

Table 1: Cross classified random effects model of factors influencing SpO_2 target achievement while on oxygen therapy

	Coefficient	SE	p
Adjusted overall mean	0.452	0.023	<0.001
PMA, per week	-0.023	0.003	<0.001
Nurse caring for 1 patient (vs. >1)	-0.028	0.015	0.063
Mechanical ventilation (MV), nurse caring for ≥2 patients	-0.122	0.028	<0.001
nurse caring for only 1 patient	0.075	0.026	0.005
CPAP	-0.064	0.014	<0.001
Oximeter alarm 95% (v. 100%)	0.043	0.010	<0.001
Regular diuretic therapy	-0.035	0.012	0.005
Systemic steroid therapy	-0.061	0.011	<0.001

Table 2: Cross classified random effects model of factors influencing time with SpO2 <80% while on oxygen therapy

	Coefficient	SE	p
Adjusted overall mean	0.074	0.008	<0.001
Nurse caring for 1 patient (vs. >1)	-0.027	0.005	<0.001
Oximeter alarm 95% (v. 100%)	0.046	0.004	<0.001
Pulmonary acuity score*	0.078	0.010	<0.001

*Madan A, Pediatrics 2005

Improved identification of pregnancies at risk for stillbirth with ultrasound based estimates of individualized fetal growth potential

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Objective

Unrecognized growth restriction (IUGR) may result in preventable stillbirth. We evaluated whether individualized fetal growth potential norms based on maternal and fetal determinants of birth weight better identify growth restriction in pregnancies resulting later in stillbirth, compared to customized or standardized ultrasound based growth curves.

Study Design

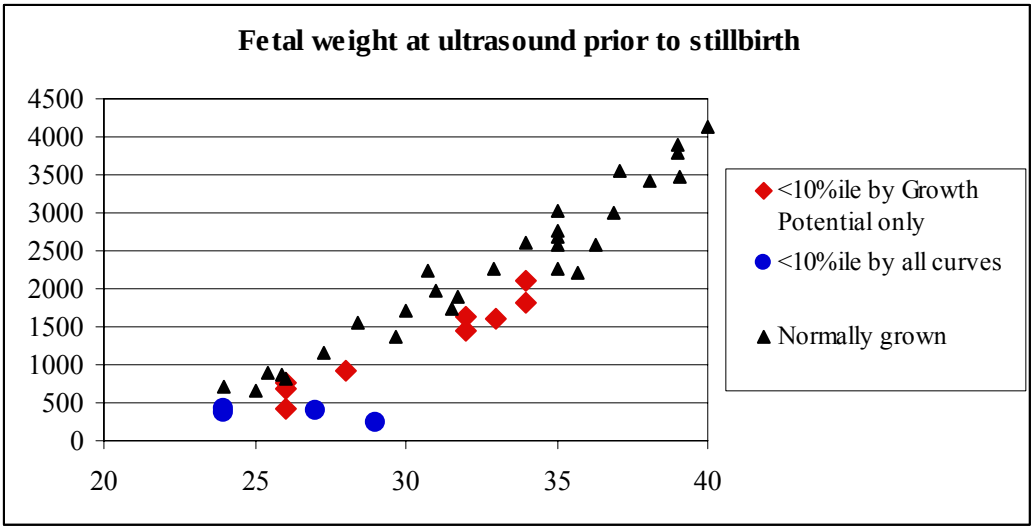
All pregnancies resulting in stillbirth between 2001-2009 at a single institution were reviewed to identify those that had had an ultrasound performed within one month of demise. Non-anomalous singleton pregnancies with viable fetuses at ultrasound performed after 24 weeks gestation, and with demise unrelated to pregnancy complication or acute maternal illness, were analyzed. Growth centile at ultrasound examination was calculated using customized (Doubilet), standardized (Hadlock), and growth potential norms, and growth restriction was defined as <10%ile. Growth potential centile was calculated using maternal race, height, weight, gravidy and parity, and fetal sex, estimated weight, and gestational age. McNemar's and Wilcoxon rank-sum tests were used for analysis.

Results

Among 43 stillbirths meeting inclusion criteria, growth restriction was diagnosed by traditional ultrasound growth curves as well as growth potential norms in 9% (4) of pregnancies. Growth potential norms identified IUGR in an additional 23% (9) of fetuses that eventually died (p=0.003, Kappa=0.39, 95% CI 0.10-0.67). Median gestational age at diagnosis by traditional ultrasound was 25.5 weeks, and in cases diagnosed by growth potential was 27.6 weeks (NS). Diagnosis of growth restriction was unrelated to maternal body mass index, race, gravidy or parity, or fetal sex.

Conclusions

Individualized fetal growth potential norms may better identify growth restriction than do traditional ultrasound-based growth curves, allowing increased fetal surveillance, and potential prevention of stillbirth. One limitation of the study is the small sample size, however, that may make these findings of increased clinical consequence.



Do septations matter? An enlarged cystic hygroma is more likely to predict aneuploidy than a nuchal translucency of the same size.

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OBJECTIVE: To assess the relationship between nuchal translucency (NT) size, cystic hygroma size, and the risk of aneuploidy.

METHOD: We conducted a retrospective chart review of all fetuses diagnosed with a nuchal translucency greater than 2.5 mm and/or a cystic hygroma at five institutions between 2000 and 2010. Ultrasounds were performed between 10 wks 4 days and 13 wks 6 days. Cystic hygroma was defined as "an enlarged hypoechoic space at the back of the fetal neck, extending along the length of the fetal back in which septations were clearly visible." Amniocentesis, chorionic villus sampling, pathology or postnatal testing identified fetal karyotype.

RESULTS: Of the 2,842 total cases that were reviewed, 945 fetuses had a cystic hygroma, while 1,630 did not. Data were missing for 267 subjects. Dimensions of the NT and the cystic hygroma, as well as karyotype, were available for 544 subjects with a cystic hygroma and 649 subjects without a cystic hygroma.

2.5-4 mm	Euploid	Aneuploid	Total
Cystic Hygroma	120 (69.4%)	53 (30.6%)	173 (100%)
No Cystic Hygroma	451 (79.3%)	118 (20.7%)	569 (100%)

(p=0.007)

> 4 mm	Euploid	Aneuploid	Total
Cystic Hygroma	122 (32.9%)	249 (67.1%)	371 (100%)
No Cystic Hygroma	49 (61.2%)	31 (38.8%)	80 (100%)

(p<0.001)

More euploid fetuses with an enlarged NT and/or cystic hygroma were male (61.5%) than female (38.5%). Gender data were not available for aneuploid fetuses.

CONCLUSION: Analyses of the FaSTER and FMF data found that subjects with an enlarged NT measurement above 4 mm have very similar prognoses, whether or not a cystic hygroma is identified. Although the availability of karyotype data for more subjects with cystic hygroma than for enlarged NT may bias our results, our data suggest that the finding of a cystic hygroma increases the risk of aneuploidy, particularly for those subjects with a NT measurement greater than 4 mm.

An Illness Acuity Score for VLBW Infants with Bronchopulmonary Dysplasia (BPD) on Nasal Cannula Supplemental Oxygen (NCO2)

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Background: Pulmonary acuity scores may be used to stratify infants needing respiratory support. There are no such tools specific to VLBW infants with established BPD on NCO2.

Objective: To develop and provide initial validation for an illness acuity score specific to VLBW infants with established BPD on NCO2.

Design/Methods: This was a retrospective analysis of data collected during room air challenges (RACs) of infants on NCO2 in a level 3 NICU. Infants were born 2004-2008, with bwt <1500 g, gestation <31 wks and in NCO2 for ≥28 days. RACs were performed weekly as routine care when infants reached 34 wks PMA, were stable with a persistent NCO2 requirement and were able to take a minimum of 15ml/kg per oral feed. RACs were performed in a state of rest followed by a period of agitation first on NCO2, then in RA, followed by a PO feeding challenge in RA. RACs have 4 potential outcomes: fail in NCO2, fail in RA, fail at feeding or pass. RACs were randomly divided into cohorts for derivation (1/2) and validation (1/2). In the derivation cohort, we created a hierarchical ordinal regression model based on RAC outcome and converted the resulting regression coefficients and thresholds to an illness acuity score. The score was tested in the validation cohort and compared to an existing pulmonary acuity score derived from infants on all methods of respiratory support.

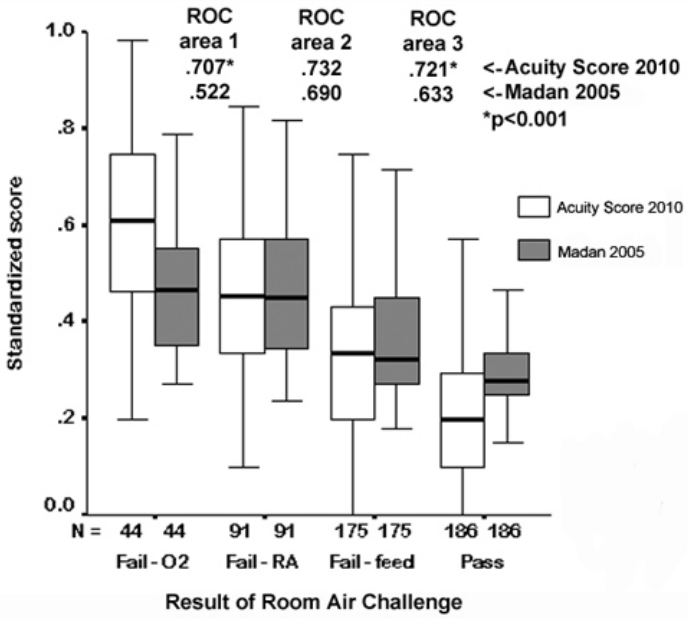
Results: In the derivation cohort, 492 RACs were performed at 33-51 wks postmenstrual age on 206 infants 899±251 g bwt, 26.9±1.8 wks gestation, 53% male, with 85% receiving antenatal steroids. Pulmonary factors associated with RAC outcome in hierarchical ordinal regression were converted to an acuity score (Table). In the validation cohort which consisted of 496 RACs, the score showed significantly ($p<0.05$) improved ROC curve areas and calibration compared to the existing score (Figure).

Conclusions: For a specific group of VLBW infants ≥34 wks PMA with established BPD requiring NCO2, this illness acuity score showed superior discrimination and calibration at 4 distinct clinical levels of pulmonary illness severity compared to a more general score. This score may be useful for research and clinical management of VLBW infants with established BPD on NCO2 in the NICU and following discharge. Multicenter prospective validation is warranted.

Table: Score Components

	Points Assigned
Currently on inhaled steroids	
No	0
Yes	7
pCO_2	
<47 mm Hg	0
47 – 54.9 mm Hg	5
55+ mm Hg	10
Nasal cannula flow	
≤ 0.5 lpm	0
0.51 - 1 lpm	6
>1 lpm	21
Effective FiO_2	
≤ 0.25	0
0.26 - 0.5	5
>0.5	6
Highest resting respiratory rate	
≤ 65 bpm	0
>65 bpm	7

Figure: Score Performance



Title: Efficacy of Als3p-specific Monoclonal Antibody in a Mouse Model of Neonatal Candidiasis

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Background: *Candida albicans* is the leading fungal pathogen causing invasive disease in premature infants. Despite treatment with antifungal agents, these infections lead to high mortality and neurodevelopmental impairment among survivors. Novel therapeutic strategies are needed to treat these infections.

Objective: To evaluate the therapeutic potential of a monoclonal antibody (mAb) against the *C. albicans* adhesin, Als3p, in a neonatal mouse model for disseminated candidiasis.

Design/Methods: Two-day-old BALB/c mouse pups were given a lethal dose of *C. albicans* by intraperitoneal injection, and randomized to receive anti-Als3p antibody or sterile saline. Control animals received anti-Als3p antibody only. Pups were examined every 3-8 hours for death and were euthanized if moribund. Surviving pups were euthanized at 72 hours after injection and organs were harvested. Kidney, lung and brain were homogenized at time of death and plated to assess fungal burden.

Results: Infection with *C. albicans* in animals receiving saline (n=8) led to a median survival of 34 hours. A single dose of anti-Als3 mAb given 1.5 hrs after infection (n=12) led to increased survival to a median of 55 hours ($p = 0.07$). Median colony counts (in colony forming units (CFU)/organ) in the kidney were 1110 [600-4100]* in the treatment group vs. 5250 [3325-36,000]* for *C. albicans* alone. Colony counts for lung tissue were comparable in both groups, 1340 [535-3055]* in the treatment group vs. 1450 [300- 3075]* in *C. albicans* only group. Uninfected pups injected with anti-Als3 mAb alone remained healthy until study endpoint. Death due to candidiasis in infected animals was confirmed by colony counts of homogenized kidney, lung, and brain tissue. *inter-quartile range

Conclusions: Although limited by small sample size, a single dose of anti-Als3 mAb given to neonatal mice infected with *C. albicans* shows a trend toward reduced mortality. Targeted immunotherapy may be a useful approach for translation to human neonates.

ADAM17 Is Critical For Stretch-Mediated Differentiation Of Fetal Type II Epithelial Cells

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Rationale. Mechanical forces are essential for normal fetal lung development. However, the mechanisms by which strain promotes lung development are not well characterized. Previous studies from our laboratory showed that stretch-induced differentiation of fetal type II epithelial cells is mediated via release of the EGFR ligands HB-EGF and TGF-alpha. Here, we investigated how stretch-induced release of ligands is regulated. We hypothesized that is mediated via ADAM17/TACE.

Methods. Fetal mouse type II epithelial cells were isolated on E17-18 of gestation (canalicular and saccular stages) and exposed to physiological levels of mechanical strain using the Flexercell Strain apparatus. TACE activation was investigated using a fluorescence FRET substrate. Release of ligands by stretch in the presence or absence of the TACE inhibitor IC-3 was analyzed by measuring alkaline phosphatase in the supernatant after cells were transfected by electroporation with plasmids encoding HB-EGF and TGF-alpha. Type II cell differentiation was assessed by SP-B/C mRNA expression

Results. 2.5% continuous stretch activates TACE by 2-3-fold after 1-5 min on E17-18 cells, respectively. 5% intermittent stretch stimulates TACE by 3.5-fold on E17 but not on E18 cells. Stretch-induced release of mature HB-EGF and TGF-alpha was inhibited in samples incubated with IC-3. Furthermore, stretch-induced upregulation of SP-B/C mRNA was decreased in the presence of the metalloproteinase inhibitors heparin, phenanthroline or GM6001 or the specific TACE inhibitor IC-3. Currently, we are confirming these results in TACE knockout mice

Conclusion. Activation of TACE depends on gestational age and stretch protocol. Stretch-induced release of EGFR ligands and type II cell differentiation is mediated via TACE. These studies provide novel mechanisms on how mechanical forces may promote lung development.

Nonalcoholic fatty liver is associated with gestational diabetes mellitus

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Background: National data demonstrates that there is an association between nonalcoholic fatty disease increasing BMI, ranging from 5.3% of adults with normal BMI (18-24.9kg/m2) to 16.8% among adults with BMI >35 kg/m2. Nonalcoholic fatty liver disease is present in 50-75% of adults with established diabetes mellitus type 2. Several small studies have also demonstrated that that elevated alanine aminotransferase (ALT), as a marker for NAFLD, is predictive of later development of DM2. There is currently no data regarding whether, in the window of pregnancy, a similar association is present between baseline elevated ALT and development of gestational diabetes (GDM).

Objective: 1.) Identify an association between elevated (ALT), a marker for nonalcoholic fatty liver disease and body mass index (BMI) in pregnancy. 2.) Identify any association between elevated ALT and development of GDM.

Study Design: This was a retrospective chart review of pregnancies where liver function tests were obtained for any reason and where BMI was documented. Women were excluded if they had documented alcohol abuse, viral hepatitis, and other pregnancy specific hepatic pathologies. Elevated ALT was defined as ALT>31 IU/L. The patients were stratified according to normal (BMI <25kg/m2), overweight (BMI 25-29.9kg/m2), and obese (BMI >=30kg/m2) at the beginning of pregnancy.

Results: After limiting the available data set by the above criteria there were 267 eligible pregnancies in 2008 and 2009. In contrast to previous studies, there was no difference in prevalence of elevated ALT between the three weight groups (p=0.81 chi square test p=0.5 r=-0.39 Spearman rank correlation). However, there was an increased rate of GDM among women with elevated ALT in both normal and overweight women. Women who have elevated ALT were three times more likely to have GDM compared to women who have normal levels, p=0.017 OR 2.948. (95% CI 1.209-7.193)

Conclusion: There was an association between elevated ALT and GDM, independent of BMI. Women with elevated ALT were three times more likely to develop GDM, consistent with a preexisting impaired glucose tolerance. ALT, as a marker for NAFLD, may prove to be a helpful and inexpensive marker in identifying women at risk for GDM.

Maternal body mass index is associated with 25 (OH) vitamin D levels in the first trimester

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Objective

We hypothesize that maternal BMI is associated with 25 (OH) vitamin D (25-OH-D) levels and prevalence of vitamin D deficiency in the first trimester.

Methods

We studied 455 women with singleton pregnancies followed prospectively from the initiation of prenatal care through delivery. Maternal BMI was calculated from self-reported height and weight obtained at the first prenatal visit (mean 10 weeks). Plasma 25-OH-D concentrations were measured in the first trimester using a commercial assay (DiaSorin Inc., Stillwater, MN). Maternal race and prenatal vitamin (PNV) use were assessed by questionnaire. We modeled 25-OH-D levels as a function of maternal BMI using multivariate linear regression, and the odds of 25-OH-D deficiency (<20 ng/mL) using multivariate logistic regression, controlling for age, race, parity, season of conception and prenatal vitamin use.

Results

The mean (SD) BMI was 26.6 $\pm$ 6.6 kg/m^2. First trimester 25-OH-D levels were in the insufficient range on average, with a mean (SD) 25-OH-D level of 22.8 $\pm$ 8.7 ng/mL. Women with a BMI $\geq$ 30 kg/m^2 were more likely than women with a normal BMI (<25 kg/m^2) to be African American (21% vs. 8%, p=0.0005), and were less likely than women with a normal BMI to be taking a PNV prior to pregnancy (42% vs. 59%, p=0.004). BMI was inversely associated with 25-OH-D, independent of covariates (-0.21 ng/mL per kg/m^2, p=0.0006). Compared to women with a normal BMI, women with a BMI $\geq$ 30 kg/m^2 had a two-fold increased odds of vitamin D deficiency in the first trimester (adjusted OR 1.95, 95% CI 1.14, 3.34).

Conclusions

Maternal BMI is inversely related to 25-OH-D levels in the first trimester, independently of race, season of conception and prenatal vitamin use. Providers should be aware that maternal obesity is associated with an increased risk of vitamin D deficiency in the first trimester.

The association of first trimester body mass index with preeclampsia phenotype

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Objective

We investigated the hypothesis that maternal body mass index (BMI) is associated with the type and severity of preeclampsia (PE).

Methods

We studied 2450 singleton pregnancies followed prospectively from the initiation of prenatal care through delivery at three urban academic centers. BMI was calculated from self-reported height and weight measured at the first prenatal visit (mean 10 weeks gestation). PE was defined by ACOG criteria and each case was reviewed by a senior investigator. We modeled the odds of chronic hypertension, gestational hypertension, mild preeclampsia, severe preeclampsia, and HELLP syndrome as a function of BMI using logistic regression. To evaluate the impact of BMI on PE severity, we modeled gestational age as a function of BMI among women with PE using linear regression and controlling for age, parity, race, smoking, chronic hypertension and diabetes.

Results

Mean BMI in the 198 women with preeclampsia was higher (31.0 ± 8.4 kg/m^2) than in women without preeclampsia (25.9 ± 5.9 kg/m^2) ($p<0.0001$). The odds of preeclampsia increased with increasing BMI (table). In particular, women with a BMI $\geq$40 kg/m^2 had increased odds of chronic hypertension, mild and severe preeclampsia as well as severe preeclampsia prior to 34 weeks' gestation (OR 10.8, 95% CI 2.4, 49.0). Unlike other hypertensive disorders of pregnancy, HELLP syndrome was not associated with maternal BMI. Among women with PE, BMI was not predictive of gestational age at delivery (-0.009 week per kg/m^2, $p=0.75$).

Conclusions

Maternal BMI is linearly associated with risk of PE, but not HELLP syndrome. Although there is an increased risk of both mild and severe PE among obese women, BMI is not predictive of gestational age at delivery, suggesting that the severity of PE is not affected by maternal BMI.

First Trimester BMI (kg/m^2)	<25	25-<30	30-<35	35-<40	≥40
Any preeclampsia	1	2.1 (1.4, 3.2)	3.6 (2.4, 5.5)	5.1 (3.1, 8.5)	9.9 (5.9, 16.6)
Chronic hypertension	1	2.5 (1.6, 4.0)	4.6 (2.8, 7.5)	7.2 (4.1, 12.7)	11.2 (6.2, 20.0)
Gestational hypertension	1	1.6 (1.0, 2.4)	1.7 (1.0, 2.9)	2.9 (1.6, 5.4)	2.0 (0.9, 4.4)
Mild preeclampsia	1	2.2 (0.9, 5.4)	3.5 (1.4, 8.9)	5.9 (2.1, 16.4)	4.3 (1.2, 15.9)
Severe preeclampsia	1	2.0 (1.3, 3.1)	3.3 (2.1, 5.4)	4.1 (2.3, 7.4)	10.7 (6.2, 18.5)
Severe preeclampsia ≤34 weeks	1	2.8 (0.7, 10.3)	6.6 (1.8, 23.4)	7.2 (1.6, 32.6)	10.8 (2.4, 49.0)
HELLP	1	1.8 (0.7, 4.4)	2.0 (0.7, 5.7)	0.9 (0.1, 6.7)	1.3 (0.2, 10.0)

ErbB4 Regulates TTF-1 Effects on Surfactant Protein B Promoter

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Background: Surfactant protein B (Sftpb) is critical for postnatal lung function. Lung development is a finely tuned arrangement of biological events that involve the regulation of many signaling pathways. Neuregulin (NRG) and the ErbB receptors as well as thyroid transcription factor-1 (TTF-1) play an important role in this process. TTF-1 controls the expression of surfactant proteins by binding to their promoter sequence. Down-regulation of ErbB4, the signaling receptor for NRG, inhibits fetal surfactant synthesis. Activated ErbB4 receptor is cleaved at the cell membrane and its intracellular domain (4ICD) translocates to the nucleus to directly interact with transcription factors to regulate gene expression. So far, nothing is known about ErbB4 interactions with TTF-1.

Objective: We hypothesize that ErbB4 regulates TTF-1 effects on Sftpb expression in type II epithelial cells.

Design/Methods: Mouse lung epithelial cells (MLE-12) were treated with NRG. ErbB4 and TTF-1 interactions were studied by co-immunoprecipitation and confocal microscopy. The cells were transfected with full-length ErbB4 (pHer4 GFP), an ErbB4 mutant lacking the nuclearlocalization signal (pHer4 GFP-muNLS1), or a TTF-1 construct. The effect on cell viability, Sftpb expression, TTF-1 expression and *Sftpb* promoter regulation was analyzed. Primary fetal ErbB4 depleted type II epithelial cells from $HER4^{heart}$ (-/-) mice were transfected with pHer4 GFP and treated with NRG. TTF-1 mRNA expression was analyzed.

Results: ErbB4 and TTF-1 co-precipitated each other and NRG induced the nuclear translocation of 4ICD, and its co-localization with TTF-1 in the nucleus. Co-expression of ErbB4 and TTF-1 inhibited cell viability, and stimulated Sftpb expression and *Sftpb* promoter activity. This was even further increased by NRG treatment. NRG stimulated TTF-1 expression in ErbB4 overexpressing MLE-12 and primary $HER4^{heart}$ (-/-) cells.

Conclusions: ErbB4 regulates the TTF-1 expression and its effects on Sftpb. ErbB4 might be an upstream regulator and transcriptional co-factor of TTF-1 in the developing lung.