“COMPASSIONATE CARE” A NEW PROGRAM BEING OFFERED AT CARITAS ST ELIZABETH’S HOSPITAL.

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The modern challenge facing care givers of patients with pregnancies complicated by lethal or serious abnormalities has to be met with a multi-disciplinary approach. Although uncommon, some patients knowing they carry a fetus with a major defect chose to continue and ultimately deliver near or at term.

We offer a unique environment for the patient allowing her both to carry the pregnancy, but also to get caring prenatal care. The team consists of Obstetricians, Perinatologists, nursing staff both obstetrical and neonatal, Neonatologists, social services and a Chaplain. Each individual case will be seen by one or more care givers at varying times. Family intervention and support as a group involves most members of the team.

Case report: Mrs. X. was a self referral carrying a fetus with a diagnosis of acrania. She was 28 weeks pregnant and transferred her care to us, initially insisting on a Caesarean section. We performed an ultrasound and counseled her. She met with some of the team on the first day and returned for weekly visits after that. She was seen by the NICU staff, the social worker and the chaplain. After many visits we developed a plan which included normal vaginal delivery, comfort care for the baby including breast feeding if possible,no interventions other than covering the bare brain. She delivered vaginally after a 3 hour induction (miso/pit) and the baby lived 18 hours. The patient returned for her 6 week visit and was relatively well, planning for the next pregnancy.

The scope of patients we have seen included: Thanatophoric dwarfs, trisomy 18 & 13, Acrania, several patients with PPROM before 20 weeks. Many patients are at risk for intra and post-partum complications including pre-eclampsia, hemorrhage, post-partum atony, sepsis and post-partum depression. We aim to prepare the patient for the outcome expected and support her and her family throughout the pregnancy and the postpartum period.

INCREASED EXPRESSION/ACTIVATION OF MATRIX METALLOPROTEASE-9 (MMP-9) IN HYPEROXIC INJURY IN DEVELOPING LUNG

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Background: Bronchopulmonary dysplasia (BPD) annually affects >10,000 VLBW infants. A major morbidity component of BPD is oxidant injury-induced remodeling of extracellular matrix (ECM).

Objective: Hyperoxia promotes MMP-9 expression/activation causing abnormal ECM remodeling and altered lung morphometry.

Design/Methods: 3-day-old wild type (WT) and MMP-9 (-/-) mice were exposed to 95% oxygen and room air for 1 week. Lungs were isolated and inflation fixed with 4% paraformaldehyde at 20cm H_2O pressure. Paraffin embedded 5-micron sections were stained with hematoxylin for morphometric analysis. Images of 5 non-overlapping fields were grabbed at 20X magnification eliminating airway and vascular structures from the analysis and processed with Scion image analysis software (Scion Corp). Mean linear intercept (MLI; a measure of alveolar diameter which is inversely proportional to the alveolar surface area), radial alveolar count (a measure of acinar alveolarization), and the RAC/MLI ratio were studied. MMP-9 expression in room air and hyperoxia-exposed WT mice was examined by Western blot and immunohistochemistry.

Results: MMP-9 was significantly increased in lungs of WT mice exposed to hyperoxia compared to controls. Immunohistochemistry showed increased MMP-9 in the mesenchyme and alveolar epithelium of hyperoxia-exposed lungs. Hyperoxia-exposed WT mice has less gas exchange surface area compared to room air-exposed mice. Lungs from hyperoxic MMP-9 (-/-) mice had a larger gas exchange surface area compared to the lungs from hyperoxic WT mice.

Conclusions: MMP-9 plays an important role in oxygen-induced lung injury. Blocking MMP-9 activity may lead to novel therapeutic approaches to prevent BPD. Supported by HL67089 and HL37930.

Longitudinal Characterization of Continuous Regional Cerebral Oxygen Saturation (rSO2) for Preterm Infants

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Background: Optimal ranges of oxygenation in premature infants are not known. Assessments of regional oxygenation correlated with routine clinical factors may be used to ascertain oxygen status and delineate the most appropriate ranges of oxygen therapy.

Objective: To evaluate the longitudinal relationship between rSO2, systemic oxygen saturation (SpO2), gestational age (GA), and chronologic age (CA), in premature infants during their first 14 days of life.

Design/Methods: Prospective, observational, cohort study of premature infants born 24 through 31 6/7 wks GA admitted to the BIDMC NICU. On day of life 1, 3, 7, and 14, rSO2 measured via near-infrared spectroscopy (NIRS, INVOS 5100), was continuously recorded along with simultaneous continuous systemic oxygenation (SpO2, Masimo Radical) for six hour blocks each day. Patient characteristics were recorded.

Results: 17 infants were analyzed.

rScO2 and SpO2 by Groups

		GA group		
GA (wks)	24-28, n=12293	28-31, n=55501	>31, n=21289	All
Mean rSO2	76.1(7.7)	76.3 (8.7)	74.4 (10.6)	75.8 (9.1)
Mean SpO2	96.3 (3.2)	97.3 (2.9)	98.4 (1.8)	97.4 (2.9)
		CA group		
CA (days)	1, n=7882	3, n=19464	7, n=34023	14, n=17781
Mean rSO2	81.6 (6.8)	78.9 (8.6)	77.6 (7.3)	71.2 (9.8)
Mean SpO2	95.9 (3.2)	96.6 (3.1)	97.5 (2.2)	98.3 (2.5)

Using the generalized estimating equations (GEE) method for correlated, repeated data, univariate analysis revealed significant independent relationships between rSO2 and SpO2 (0.25, p=0.0002), as well as CA (-2.93, p=0.001). rSO2 was not related to GA (0.86, p=0.195). A longitudinal multivariate GEE model was created expressing the relationship between rSO2, SpO2, GA, and CA. Each 1 percent increase in rSO2 was significantly associated with: a 0.3% increase in SpO2; a 3 day decrease in CA; and a 1.4 wk increase in GA.

Correlations with Continuous rScO2

	GEE Longitudinal model			
Variables	rSO2	SpO2	GA	CA
Parameter estimates, 1 DF	---	0.27 p<0.0001	1.44 p=0.009	-2.97 p=0.013

Conclusions: Our final model shows us that higher rSO2 is significantly associated with higher SpO2 and gestational age, while significantly associated with lower CA. The importance and uniqueness of this finding is the *longitudinal* characterization of *continuous* regional cerebral oxygen saturation with SpO2, GA and CA in preterm infants.

Pulse Oximetry Index (POI) in Preterm Infants: Relationship with Outcomes

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Background: Oxygenation index (OI=(FiO2xMAP)/PaO2) is used in critically ill patients to assess oxygenation (PaO2) at a given level of respiratory support. **POI**, defined as ***(FiO2 x Respiratory Support) / SpO2***, is a proposed noninvasive measure to assess neonatal oxygenation at a given level of support using pulse oximetry SpO2.

Objective: Determine POI for 1st week of life (POI-wk1) in preterm babies and explore its relationship to gestational age (GA), death, ROP, BPD@36 wk (if FiO2>21%); days on FiO2>21% (DOO2) and mechanical ventilation (DOMV).

Design / Methods: Retrospective study of babies born GA 24<31 wks from Nov 2004–Oct 2005 and admitted to BIDMC NICU. Data were downloaded from secure medical record and ROP databases. Respiratory variables included hourly (by date, time) FiO2, SpO2, mean airway pressure (MAP), and respiratory support (RS). RS levels had prospectively assigned weighted values: none or nasal cannula (NC) =1; CPAP=1.5 + (MAP/10); mechanical ventilation (MV) =2.0 + (MAP/10). Median POI-wk1 calculation was based on each baby's hourly POI x first 7 days.

Results: Characteristics of 110 babies: mean(SD) GA=28(2) wk, BW=1.1(0.3) kg; male (55%). Table 1: POI-wk1 by GA and outcomes. POI-wk1 correlations (r) with GA: -0.38, p<0.0001; DOO2: 0.45, p<0.0001; DOMV: 0.33, p<0.001. Each 0.1 increment in POI-wk1 increased GA-adjusted odds for death by 51% (p<0.04) and BPD@36wk by 51% (p=0.0004). Each 0.1 increment in POI-wk1 increased unadjusted odds for ROP by 22% (p<0.04) and GA-adjusted odds for ROP by 10% (but not statistically significant, p=0.36).

Conclusions: POI-wk1 is related inversely to GA and positively to death, BPD@36wk, DOO2, and DOMV. Difference between unadjusted and GA-adjusted odds for ROP may relate to small number of ROP events and GA range. Future studies include validation of POI-wk1 as a marker of oxygenation severity and refinement of POIs per time interval that are optimal to predict neonatal outcomes.

POI-1wk by GA and outcomes		
	N	**POI-1wk median(IQR)**
GA(wk) All	110	0.55(0.34,0.67)
24<28	34	0.61(0.56,0.69)
28<31	56	0.38(0.34,0.61)
Survived	106	0.43(0.34,0.63)
Died	4	0.83(0.65,1.07)
No ROP Data	31	0.42(0.34,0.61)
No ROP	45	0.37(0.34,0.62)
ROP<Prethreshold	31	0.59(0.36,0.64)
ROP≥Prethreshold	3	0.93(0.87,1.08)
No BPD@36wk	78	0.38(0.34,0.59)
BPD@36wk	32	0.63(0.56,0.71)

Airway Pressure Release Ventilation Improves Ventilation/Oxygenation using lower Peak Inspiratory Pressures in Premature Neonates with Respiratory Failure.

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Neonates with severe pulmonary disease requiring conventional mechanical ventilation (CMV) may require high airway pressure and FiO2. We describe our experience with a new form of mechanical ventilation, airway pressure release ventilation (APRV on an Evita XL, Drager®, Lubeck, Germany), used as a rescue ventilation mode in premature newborns with respiratory failure. APRV applies a prolonged elevated airway pressure (P_{hi}) for a time interval (T_{hi}) to maintain adequate lung volumes and promote alveolar recruitment, analogous to continuous positive airway pressure or high frequency oscillatory ventilation. APRV adds a time-cycled "pressure release" phase (P_{lo}), commonly to 0 cm H_20, for a brief time interval (T_{lo}), usually 0.2 seconds, to facilitate CO_2 removal. The baby's spontaneous respirations are utilized at an optimized lung volume, while pressure release provides a second mechanism for CO_2 removal. We report our experience with APRV rescue in 7 premature infants with severe pulmonary disease.

Results: We utilized APRV ventilation in 7 patients with a birth weight 788 ± 73 (mean ± SEM), and gestational age 25.2 ± 0.4. The patients were supported with CMV or high frequency ventilation with peak inspiratory pressure 22.6 ± 1.5 cm H_20 at a post natal age 21.0 ± 4.2 days when APRV was started. Baseline pCO_2 was 62.9 ± 2.6 mmHg and FiO_2 68.3 ± 8.8 %. After institution of APRV, the pCO_2 declined by 11.8 ± 3.0 mmHg ($P = 0.01$) and FiO_2 declined by 29.9 ± 9.6 % ($P = 0.03$), while P_{hi} decreased by 9.6 ± 1.1 cm H_20 ($P< 0.01$), over the course of 9.7 ± 3.2 hours. Anecdotally, one patient who was deemed clinically unstable on high frequency JET ventilation was stabilized on APRV.

Discussion: We report a small case series of extremely premature infants with respiratory failure who were successfully managed using APRV. APRV achieved adequate mechanical ventilation in these infants, lowering pCO_2 and FiO_2, while lowering the peak inspiratory (P_{hi}) pressure, with the potential reduction in barotraumas and volutrauma. Further studies will be needed to assess its efficacy of the new mode of mechanical ventilation and to determine whether a higher continuous airway pressure (P_{hi}) affects other on morbidities of prematurity.

Successful Control of Methicillin-Resistant *Staphylococcus Aureus* (MRSA) Colonization Using Surveillance Cultures in a Newborn Intensive Care Unit (NICU)

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Background: MRSA colonization and infection is an increasingly recognized problem in NICUs. **Objective:** To assess the effectiveness of a comprehensive screening and isolation program for controlling MRSA colonization for all patients admitted to a large tertiary NICU after 9/00, and to describe the patient characteristics of infants with MRSA colonization and invasive disease. **Design/Methods:** All NICU infants were screened weekly by nasal/rectal swabs for MRSA. Colonized patients were isolated and cared for as a cohort. Data collection included demographics, clinical course, and age at colonization of culture-positive infants from the start of screening to 12/05. We also recorded the antibiotic (abx) resistance pattern of all MRSA isolates to assess whether it was consistent with hospital-acquired or community-acquired (CA) MRSA. **Results:** During the study period, 6265 infants were admitted to the NICU. Sixty-nine infants had positive screening cultures for MRSA; 40 of these were identified in the first two years of the surveillance program. The number of cases fell by 50% in each of the subsequent two-year periods (incidence of MRSA colonization in 2000: 32/1000 vs 2005: 2.8/1000, $p<0.01$).The median gestational age at birth for colonized infants was 30 weeks [range 23-40, IQR 26,32]. Median postnatal age at the time of the first positive culture was 11 days [range 1-88, IQR 6,20]. Ten of the 69 colonized infants developed invasive infection; infected infants were of lower GA (median 26 weeks) than colonized ones ($p<0.01$). Of the cases in 2000 and 2001, 29/40 had identical abx resistance patterns, suggesting that these represented a single MRSA strain. This strain was not identified after 2001, but multiple different strains were identified thereafter. Only 8/69 (11%) of the isolates had abx resistance patterns consistent with CA-MRSA. **Conclusions:** A program of weekly surveillance cultures to detect MRSA colonization and isolation of affected infants successfully controlled its spread and resulted in a significant decrease in the colonization burden in our NICU. Routine screening and isolation of colonized or infected infants should be considered to help control the spread of antibiotic resistant infections in NICUs.

Title: **Use Of Recombinant Factor VIIa For Massive Post Partum Hemorrhage.**

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MATERIALS METHODS: All patients with PPH were admitted to the Surgical Intensive Care Unit of Civil Hospital, Karachi, Pakistan for evaluation and management. From March 2005 to September 2006, 18 patients who fulfilled the criteria of massive PPH and who received rFVIIA to regulate bleeding (study group) were compared with 18 who patients who fulfilled the criteria of massive PPH, but did not receive rFVIIa (control group). Physcian discretion, drug availability and drug cost influenced administration of rFVIIa during this time period. Main outcome measures were the amount of blood and blood products transfused, preservation of fertility, correction of disseminated intravascular coagulation, and maternal mortality risk.

RESULTS: Fourteen of 18 patients (78%) who received rFVIIa, survived, as compared to 8 of 18 women (44%) who also had massive PPH, but did not receive rFVIIa and died. Fertility was preserved in 13 of 18 (72%) study patients compared to 8 of 18 (55%) patients in the control group. The mean number of transfusions in study was 10, compared to16 in the control group . The mean prothrombin times and activated partial thromboplastin times were significantly reduced in the study group following rFVIIa administration (32 sec to 12 sec; 52 to 29 sec, (p value .006 and .005 respectively). The mean ICU stay in the study group was 3.6 days, compared to 6.2 days in control group. No thromboembolic event or myocardial infarction was observed in the entire study population.

CONCLUSION: Activated recombinant factor VII can be a life saving drug in patients with massive PPH. Limitations of the drug include cost and availability. This case series represents the largest published experience with rFVIIa in a single institution. Additional studies are needed to evaluate the safety and efficacy of this promising, potentially life saving, measure in the setting of massive PPH.

Title: **Acute hepatitis E infection in pregnancy is associated with high maternal and perinatal mortality rates .Authors**: Nazli Hossain, MBBS FCPS1, Nargis Soomro, MBBS FRCOG2, Tahir Shamsi, MBBS FRCP3 and Michael Paidas, MD1. 1)Yale Women and Children's Center for Blood Disorders; 2) Dow University of Health Sciences Karachi Pakistan. 3) Bismillah Taqee Institute of Health Sciences& Blood Disorder

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Materials &Methods: From January 2006- September 2006, patients suspected of having liver dysfunction in pregnancy underwent screening for Hepatitis E in addition to laboratory evaluation for preeclampsia syndromes, intrahepatic cholestasis, acute fatty liver of pregnancy (AFLP), hepatitis B and hepatitis C. Liver and renal function testing, as well as coagulation profiles were obtained in all patients.

Results : Thirty five women were identified with liver dysfunction based upon transaminitis. Fourteen (40%) of the women presented in the second trimester, and 22(60%) presented in the third trimester. Eight (22%) women were registered for antenatal care, where as 27(77%) were unregistered. Out of 35 women , 11(31%) were primigravid, 8(22%) were in their second pregnancy and 17(48%%) were multigravid. Twenty two of the 35 (62%) women had isolated acute hepatitis E; 5(14%) had HELLP syndrome; 2 (5%)had cholestasis and 2(5%) had AFLP. In women with hepatitis E, the mean value of bilirubin and SGPT were 12 mg/dl and 675 u/l respectively. Coagulation profile of the group was abnormal 20(57%)women, and in 18 of 22 (82%) with hepatitis E. Fulminant hepatic failure was seen in 5 (14%)patients, all of whom had hepatitis E. Seven women (20%) underwent cesarean section; 26(74%) delivered vaginally, and 2 women remained undelivered in the postmortem state. There were 6 maternal deaths in the study population; 4 (67%) were due to hepatitis E, and one each from HELLP and AFLP. The overall perinatal mortality of the group was 40%. Hepatitis E was associated with a 36% (8/22) preterm delivery rate, and 27% (6/22)rate of fetal demise.

Conclusion In this series, Hepatitis E was the most common cause of liver dysfunction, fulminant hepatic failure and maternal death. Patients with liver dysfunction should be screen for **hepatitisE**.

Factors Influencing Decision Making For Invasive Prenatal Genetic Testing

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Objective: To determine which factors influence a patient's decision for invasive prenatal diagnosis when there is a personal or family history of a testable genetic condition

Methods: Genetic counseling records were reviewed from a single Maternal-Fetal Medicine referral center from 2000-2002. Pregnant women with a personal or family history of mental retardation, congenital anomalies or genetic disease were identified. Data collected included diagnosis, inheritance pattern, availability of genetic testing, severity of the condition, maternal age, and the patient's relation to the affected individual. Patients who accepted and declined testing were compared using logistic regression analysis controlling for advanced maternal age.

Results: 2304 Records were reviewed. 455 patients met the inclusion criteria. 51 women had an indication for invasive testing other than maternal age. 19 (39%) opted to have invasive testing (chorionic villous sampling or amniocentesis) to determine fetal disease status. Of the factors studied, a previously affected child was the only predictor for invasive testing (p value less than 0.0001). Patients with this history were 4.2 times more likely to opt for invasive testing than patients with another affected relative (CI 1.6-10.9). History of disease affecting the parent, grandparent, sibling or a distant relative did not significantly influence the decision. Similarly, disease severity was not a significant factor.

Conclusion: Among gravidas with a family history of a testable inheritable condition, only a previously affected child influenced the decision to undergo invasive prenatal diagnosis.

Response of lung fetal type II epithelial cells to injury induced by mechanical distension

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Background :
A central component in the pathogenesis of BPD is the release of inflammatory mediators triggered by barotrauma secondary to mechanical ventilation. Although alveolar type II epithelial cells are essential to restore a normal alveolar epithelium after lung injury, type II cells are also exposed to barotrauma and may enhance the inflammatory cascade by releasing cytokines. Therefore, understanding the molecular and cellular mechanisms by which overdistension of alveolar type II cells contributes to the pathogenesis of BPD is critical to design therapeutic strategies.

Objective :
We hypothesized that overdistension of fetal type II epithelial cells induces cell death and stimulates cell proliferation. We also speculated that this injurious stimulus promotes lung inflammation by creating an imbalance between pro- and anti-inflammatory cytokines.

Methods :
Fetal rat pulmonary epithelial cells on E19 (term=E22) were isolated and cultured on silastic membranes precoated with fibronectin. E19 monolayers were then exposed to 5% or 20% elongation at 40 cycles/min for 6h and 24 h. Unstretched samples were used as controls. Type II cell cytotoxicity was assessed by LDH release. Apoptosis was analyzed by TUNEL assay. Cell proliferation was studied by DNA incorporation of the thymidine analog 5-bromo-2'-deoxyuridine (BrdU). Cytokines release into the supernatant was analyzed by ELISA.

Results :
5% stretch at 40 cycles/min for 24 h increased LDH release into the supernatant by 10%, apoptosis by 60% and cell proliferation by 50%. In contrast, 20% elongation increased LDH release by 19%, apoptosis by 10-fold and type II cell proliferation by 3-fold when compared to unstretched samples. Mechanical stretch also significantly increased the release of pro-inflammatory cytokines TNFα, IL-6 and IL-1β into the supernatant in an elongation- and time-dependent fashion. In contrast, the anti-inflammatory cytokine IL-10 initially increased after 6h of 20% stretch, but it did not change after 24 h, when compared to control samples.

Conclusions :
Overdistension of fetal type II epithelial cells induces cell death via necrosis and apoptosis. Mechanical stretch also stimulates cell proliferation; this may represent a compensatory mechanism to restore cell population after lung injury. IL-10 response to mechanical strain decreases overtime. These results may provide a unique opportunity for intervention to reduce lung injury secondary to mechanical ventilation.

Syncytiotrophoblasts of preeclamptic placentas overexpress corticotropin-releasing hormone mRNA

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OBJECTIVE: Corticotropin-releasing hormone (CRH) peptide is largely localized to the syncytiotrophoblasts of human placenta. CRH rises exponentially during the last trimester of normal gestations. However, preeclampsia is associated with an exaggerated rise of CRH peptide in maternal and umbilical blood. We aimed to examine the pattern of CRH gene expression in preeclamptic placentas.

STUDY DESIGN: Third trimester fresh frozen placentas from normotensive controls and preeclamptic cases were examined by in-situ hybridization using ^{35}S-labelled riboprobes for CRH, human placental lactogen (hPL), and beta-actin. Counterstaining was performed with hematoxylin and eosin. Probe hybridization and trophoblast mass were quantified with ImageJ. Trophoblast cellular content was used to normalize the mRNA concentration. Statistical analysis was performed using the Chi-square test.

RESULTS: In normal placentas, CRH mRNA hybridization paralleled its peptide distribution with higher concentrations in areas of syncytiotroblastic nuclei aggregation, also known as syncytial knots. In preeclamptic placentas, CRH mRNA density was significantly higher due to enhanced overall hybridization as well as excessive syncytial knots. In contrast, the mRNA contents of actin and hPL were similar in normotensive and preeclamptic gestational age-matched placentas.

CONCLUSIONS: The expression of CRH, a stress-responsive hormone, is up regulated in the syncytiotrophoblasts of preeclamptic placentas. Increased syncytial knots are also associated with forms of placental stress, such as preeclampsia and fetal growth restriction. This suggests that the increase in both CRH and syncytial knots may be triggered by a common stressor affecting the preeclamptic placenta. Whether CRH overexpression is part of the cause or the consequence of preeclampsia remains to be determined.

Parent Physician Communication in the Neonatal Intensive Care Unit: A Qualitative Study

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Background: Evidence suggests that communication between Neonatologists and the parents of their patients is a major factor in those parents' satisfaction with their child's medical care. Studies have shown, however, that parents often feel this communication is inadequate and among the weakest of their physician's skills.

Objectives: To identify the determinants of successful communication from both the physician and parental standpoint.

Study Design: In order to capture the experience of communicating with physicians beyond what the authors could hypothesize a priori, a qualitative methodology was chosen. In this study, data were gathered from extensive, nondirective interviews conducted in July – September 2007 with the mothers of ill neonates and the attending neonatologist with whom they most extensively communicated. Twelve interviews were conducted in total. Interviews transcripts were analyzed for themes with the assistance of QSR Nivo7 software and, consistent with grounded theory methodology, the general theory of this paper was constructed as themes of the interviews emerged. Interviews were conducted until no new themes emerged from analysis.

Results: In describing patient communication in their own words, physicians tended initially focus on the medical history of the neonate and information they conveyed to the parent. Mothers tended to initially focus on their evaluation of and personal response to the experience of having a child in the NICU. During the course of these interviews, both parents and physicians brought out similar themes about the creation of a working relationship between physician and parent. Two distinct sets of themes were most often shared: first of the creation of an empathetic connection, second the definition of this relationship by deliberate professional distancing.

Conclusions: Conceptualizing the communication between physician and parent as information exchange leads to a metric of successful communication more meaningful to physicians rather than parents. Reconceptualizing this process as the creation of professional relationship out of the balance of two opposing forces, that of creating empathetic closeness and maintaining professional distance, may come closer to describing how medical communication occurs for parents. Exploring the success or failure of communication from this standpoint could lead to better training of physicians in the art of medical communication and better metrics of parental satisfaction.

Maternal Obesity: Population Trends, Inflammatory Profiles and Immune Dysregulation

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Background: Large population-based studies suggest increased risks of antenatal, intrapartum, and neonatal complications secondary to obesity in pregnancy. Obesity during pregnancy is associated with a pro-inflammatory state as well as immune dysregulation; factors known to influence neonatal outcome. The potential associations between serum levels of cytokines and the weight status of the gravida are largely unknown.

Objective: 1) To examine time trends of obesity prevalence in pregnant women, and 2) to evaluate the hypothesis that obesity in pregnancy is associated with increased levels of pro-inflammatory and immunomodulatory cytokines/growth factors.

Methods: Population-based information was obtained from the Maine State Birth Records Database and evaluated for prevalence and degree of obesity (defined as early second trimester BMI >=30) from 1981-2005. A pilot study was performed using maternal serum collected in the early second trimester examining several biomarkers associated with the inflammatory process by ELISA. Values were compared relative to maternal body mass index (BMI) among four weight categories: normal (BMI 20-26.5), overweight (BMI 26.6-31), obese (BMI 31.1-41), and morbidly obese (BMI >41) (n=80; 20 from each weight group). Statistical analyses were performed by Kruskal-Wallis ANOVA.

Results: Among 219,173 pregnant women, mean second trimester weight increased linearly from 139 pounds in 1981 to 161 pounds in 2005, at a rate of approximately one pound per year (**Table 1**). To account for maternal age-related trends with median primiparous ages increasing over the studied time period, 27 year old mothers were examined for the 25 year period and the median weight gain was also 25 pounds in 25 years. Macrophage Chemotactic Protein (MCP)-1, Leptin, and C-reactive protein (CRP) were statistically significantly different between the groups. Comparisons of groups revealed that MCP-1 ($p=0.002$); Leptin ($p<0.001$) and CRP were significantly increased with morbid obesity ($p<0.001$) (**Table 2**). Interleukin (IL)-2 tended to exhibit a U-shaped relationship with body weight and the distribution of transforming growth factor (TGF)-β-1 levels tended to widen with decreasing body mass.

Conclusions: Median maternal weight has increased significantly over time. Maternal obesity is associated with upregulation of several pro-inflammatory factors which might be transmitted to the fetus and influence neonatal outcome. These findings provide the basis for future research regarding the complex interactions between maternal obesity and complications of pregnancy in the mother and infant.

Table 1: Trends in Maternal Weights in 25 years

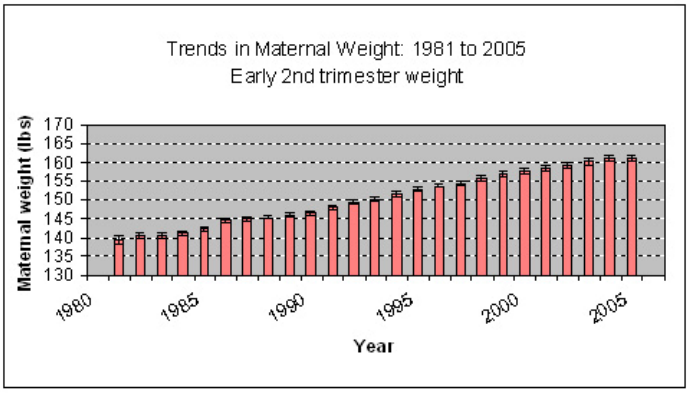

Table 2: Markers of Inflammation by BMI category

Markers	Normal BMI n=20	Over Wt. BMI n=19	Obese BMI n=21	Morbidly Obese BMI n=20	p-value
MCP	323 (265 - 381)	329 (242-346)	315 (208-361)	387 (359-430)	0.002
TNF	3.8 (1.6-8.3)	3.6 (1.9-5.7)	4.5 (2.7-6.9)	4.47 (1.36-11.3)	0.77
TGF	12.4 (8.9-15.9)	11.1 (9.2-13.3)	10.5 (8.9-12.1)	10.6 (8.40-11.3)	0.45
Leptin	12.4 (8.4-16.7)	25.5 (21.4-33.1)	30.4 (24.2-35.7)	49.6 (38.6-54.9)	<0.001
HGF	1.40 (1.2-1.8)	1.44 (1.1-1.7)	1.62 (1.3-2.1)	1.47 (1.07-1.59)	0.38
IL-2	1.45 (0.0-3.8)	0.95 (0.0-4.0)	0.00 (0.0-2.0)	1.70 (0.00-3.98)	0.46
hsCRP	0.28 (0.17-0.39)	0.71 (0.31-0.92)	0.75 (0.54-1.3)	1.44 (0.94-1.71)	<0.001

All values are medians (interquartile ranges). Statistical analysis performed using Kruskal-Wallis ANOVA test.

Do Increasing C-Section Rates Lower the Risks of Shoulder Dystocia or Brachial Plexus Injury?

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OBJECTIVE: To determine if rising cesarean section rates are protective against shoulder dystocias and/or neonatal brachial plexus injuries.

STUDY DESIGN: ICD-9 and CPT code data were reviewed from all births at Brigham & Women's and Massachusetts General Hospitals from 1997-2004. Total births, c-sections (C/S), forcep deliveries (Frcp), total operative vaginal deliveries (OpV), infants weighing >4,500gms delivered vaginally (Mac), shoulder dystocias (SD) and neonatal brachial plexus injuries (Erb) were recorded. The rates for these data were calculated and the trends were assessed using a nonparametric test of trend.

RESULTS: There were 100,149 births (range: 10,652-13,417 per year) with an average c-section rate of 24.3% during the study interval. The results and clinical trends are summarized in Table 1. A statistically significant increasing trend was observed for the rate of c-section overall. Statistically significant decreasing trends included forcep delivery and total operative vaginal delivery. The rates of shoulder dystocia, brachial plexus injuries and macrosomic vaginal delivery were unchanged.

CONCLUSION: Our data suggest a rise in cesarean section rates is not protective against shoulder dystocias or neonatal brachial plexus injuries even though the rate of macrosomic infants delivered vaginally was unchanged concomitant with a drop in the rates of forceps deliveries and overall operative vaginal deliveries. These finding are consistent with the observation that both shoulder dystocias and neonatal brachial plexus injuries have proven to be difficult to predict and prevent.

Table 1: Annual Rates (%) of Clinical Events

	C/S	Frcp	OpV	Mac	SD	Erb
1997	21.5	3.6	8.4	1.9	1.1	0.12
1998	20.8	3.2	8.2	2.3	1.1	0.2
1999	22.5	3.1	8.0	2.4	1.0	0.12
2000	22.4	2.2	7.6	1.9	1.3	0.14
2001	24.2	1.7	6.7	2.0	1.0	0.16
2002	25.4	1.8	7.6	3.4	1.5	0.11
2003	28.0	1.7	7.3	3.8	1.2	0.19
2004	29.2	1.9	7.2	3.4	1.0	0.09
p=	0.01*	0.02*	0.03*	0.08	0.41	0.41

Effects of Methadone on Admission Intrapartum Fetal Heart Rate Patterns.

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Objective: To compare characteristics of admission intrapartum fetal heart rate patterns in women on methadone maintenance to women not on methadone. **Methods:** In this institutionally-approved retrospective case-controlled study, we identified all women on methadone delivering a singleton vertex fetus ≥ 37 weeks from 10/1/99—6/30/04. Exclusion criteria were fever >37.9, positive toxicology screen, IUGR, oligohydramnios, preeclampsia, diabetes, or fetal anomaly. Each subject was matched to the next 2 non-methadone dependent women for gestational age (± 1 week), membrane status on admission, and labor onset (spontaneous or not in labor). One examiner, blinded to methadone status, analyzed the first 2 hours of fetal heart rate tracing according to the 1997 NIH guidelines. Continuous variables were compared by the unpaired t-test, dichotomous variables by the chi-square. **Results:** 18 cases and 36 controls were included. Methadone users were younger (24.7 ± 5.8 vs 31.4 ± 5.9, p=.0002), more likely to smoke (72% vs 5.6%, p=.0002), and their newborns were smaller (3210 ± 350g vs 3430 ± 420g, p=.05) than control infants. Fetal heart rate tracing characteristics were similar statistically regardless of methadone exposure (table). **Conclusion:** Admission intrapartum fetal heart rate characteristics are similar in methadone dependent and non-dependent women.

Characteristics	Methadone	Control
Baseline	129 ± 10	133 ± 12
# accelerations/10 minutes	1.1 ± 1.3	0.8 ± 1.3
≥ 1 acceleration/10 minutes	42.3%	38.4%
Decreased variability (<5 bpm)	27.6%	24.7%
Increased variability (> 25 bpm)	1.9%	1.2%
Decelerations: Any	36.8%	39.7%
Early	1.4%	3.2%
Variable	34.7%	34.4%
Late	0.7%	1.6%

Heterogeneity in the Epidemiology of Extremely Low Gestational Birth

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Objective: We describe the obstetrical antecedents of delivery between 23 and 27 weeks in a multi-center, prospectively collected cohort. We hypothesize that the contribution of specific antenatal complications to the incidence of preterm delivery will change with advancing gestational age.

Methods: Women at 14 tertiary centers underwent a standardized interview regarding medical and pregnancy history in addition to a standardized chart review. Each delivery was classified by antenatal complication: preterm labor, preterm premature rupture of fetal membranes (pPROM), preeclampsia, placental abruption, cervical incompetence, and fetal distress/intrauterine growth restriction. These indications were then examined for variation with gestational age and fetal number. Comparisons were made using T-test and one way ANOVA.

Results: 1,249 mothers were enrolled between 3/2002 & 8/2004. The median age was 28 years and the median gravidity/parity was 2/0. 19% of pregnancies were multiples. 13% of patients used fertility assistance. The incidence (%) of each complication was: preterm labor (42), pPROM (22), preeclampsia (15), placental abruption (11), cervical insufficiency (5), and fetal indication/IUGR (4). Among singletons, the incidence of preterm labor significantly decreased, while the incidence of preeclampsia significantly increased with advancing gestational age. The incidence of the other causes of delivery did not vary. Among the multiples, none of the complications varied by gestational age. A significantly lower incidence of preeclampsia occurred among the multiples compared with the singletons (3 vs.18 percent). The rate of complete steroid administration varied significantly by the complication and was highest for pPROM.

Conclusions: We describe the first prospectively collected, gestational age-defined, multi-center cohort of deliveries in the extremely low gestational age range. The incidence of preterm labor significantly decreased and the incidence of preeclampsia significantly increased with gestational age among singletons. Compared with singletons, a significantly higher proportion of multiples was delivered for preterm labor and a significantly lower proportion was delivered for preeclampsia. The incidence of complication varies significantly with advancing gestational age. Inferences about the epidemiology of antenatal complications leading to extremely low gestational age delivery will need to be specific regarding the parameters used to assemble the cohort under study. We suggest there is sufficient gestational age specific heterogeneity to make epidemiological inference sensitive to the parameters of cohort collection – an underappreciated characteristic in extremely low gestational age birth research.

Title: Dose-Response Relationship Between Parenteral Nutrition Exposure And Direct Hyperbilirubinemia In Infants <1500 Grams At Birth

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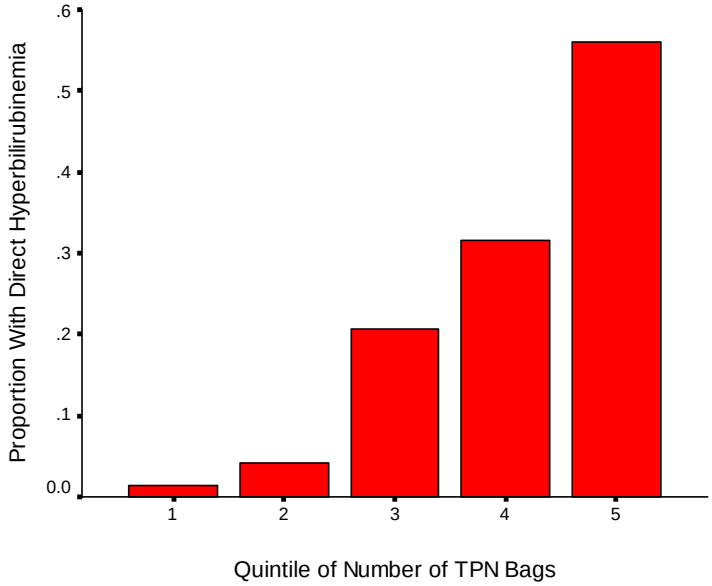
Background: A variety of clinical factors have been associated with development of conjugated hyperbilirubinemia (CH) in very low birth weight (VLBW, <1500 g at birth) infants.

Objective: To identify potentially modifiable risk factors for the development of CH in VLBW infants.

Design/Methods: We examined clinical databases and medical records for all VLBW infants born 2000-2005, admitted ≤2 days (d) of age, and treated for ≥7 d at a single center. Data were collected regarding infant characteristics, medical course, and nutritional therapy. Univariate and multivariate analyses were used to identify factors associated with CH (conjugated bilirubin ≥2 mg/dl).

Results: Inclusion criteria were met by 348 infants, of whom 78 developed CH with mean±SD peak conjugated bilirubin 5.5±3.4 mg/dl. Annual incidence varied from 15%-35%. Infants with vs without CH had significantly ($p<.05$) lower birth weights (925±242 vs 1137±264 g), more exposure to parenteral nutrition (PN) (42±22 vs 21±12 d) and mechanical ventilator (17±26 vs 6±10 d), and more intraventricular hemorrhage grade 3/4 (9% vs 3%) and necrotizing enterocolitis in the 1st 21 d of life (6% vs 1%). There was no detected difference in incidence of SGA or fungal or bacterial infection in the 1st 21 d of life. In mulitvariate analysis, only number of d PN was associated with CH. Odds of CH increased 5% per day PN exposure, and increased five-fold with >20 d PN exposure (Figure). ROC curve area using PN d as the sole predictor of CH was 0.82. For infants with CH, peak bilirubin correlated with d PN exposure ($p<.001$).

Conclusions: This cohort showed a direct relationship between PN exposure and incidence and severity of CH that outweighed all other tested risk factors. Further research is needed to identify PN components associated with CH and reduce PN-related compromise in liver function.



The Patient With Asymptomatic Shortened Cervix At 23 – 28 Weeks: Is Delivery Imminent?

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Objective: To compare the incidence of preterm delivery within 2 weeks in patients with premature cervical shortening (cervical length less than 1.5 cm) on routine ultrasound and symptoms of preterm labor versus asymptomatic patients with the incidental finding of a shortened cervix less than 1.5 cm.

Study Design: A retrospective cohort study was performed. The cohort included patients from 23 to 28 weeks' gestation with shortened cervix (cervical length less than 1.5 cm) on routine ultrasound. Two groups were defined: patients with no evidence of preterm labor were compared to patients with symptoms of preterm labor (abdominal tightness, contractions, and vaginal spotting). The incidence of delivery within 2 weeks was determined for both groups. The groups were compared with the Fisher exact test.

Results: A total of 88 patients with cervical length (CL) < 1.5 cm were identified from an ultrasound database. 52 patients had CL < 1.5 cm and no symptoms. Of these, 2 (3.8%) delivered within 2 weeks. 36 patients had a CL < 1.5 cm and symptoms of preterm labor. Of these, 11 (30.6%) delivered within 2 weeks, a statistically significant increase (p=.01).

Conclusion: Premature cervical shortening (CL<1.5 cm) at 23 to 28 weeks, in the absence of symptoms of preterm labor, is often not associated with preterm delivery within 2 weeks. Following those patients clinically may prevent prolonged hospitalization and allow steroid administration close to the date of delivery.

Maternal and Neonatal Factors Associated With Post-Partum Hypothermia In Infants <1500 Grams At Birth

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Background: Hypothermia in the minutes following birth increases risk for morbidity in VLBW (≤1500 g) infants. **Objective:** To identify maternal and infant factors predisposing VLBW infants to post-partum hypothermia (PPH). **Methods:** Medical records were reviewed in a single-center retrospective study of VLBW infants born 2004-5 and their mothers. Infants were excluded if they expired at delivery or had congenital anomalies. Data were collected regarding mother and infant characteristics, delivery and resuscitation, clinical and environmental factors pertinent to temperature (T) control, and outcomes. Univariate and multivariate hierarchical analyses were used to identify clinical factors associated with PPH (initial T<36 ^{o}C). **Results:** Records were reviewed for 125 infants from 106 mothers. Delivery room (DR) T was set at 24 ^{o}C for vaginal DRs, 19 ^{o}C for cesarean sections (CS). Initial T was measured later for infants receiving vs not receiving surfactant (Surf) (51±29 vs 32±24 min). Overall, 45% of infants had initial T<36 ^{o}C. Mothers of infants with PPH had significantly (p<.05) more preeclampsia (39% vs 16%) and less exposure to any antenatal steroids (ANS) (72% vs 93%). Infants with PPH had significantly more frequent CS, lower birth weights, lower 5 min Apgar score, and less DR Surf administration. Infants with vs without PPH were similar regarding maternal T, chorioamnionitis, delivery <1 hour after maternal admission, and nonreassuring fetal heart tracing. In hierarchical logistic regression, increasing birth weight and administration of ANS and DR Surf reduced odds of PPH, while maternal preeclampsia and CS increased it (Table). **Conclusions:** PPH was common in this cohort. Lower DR T may account for the observed increase in PPH with CS. The protective effect of Surf may reflect later measurement of initial T. ANS and preeclampsia may directly influence infant thermoregulation or serve as markers of obstretric stability. These results support calls for minimum DR T and standardized timing of serial postpartum T measurements.

	OR	**95% CI**	**P**
Preeclampsia	2.8	1.1, 7.4	.037
Antenatal steroid exposure	0.3	0.09, 0.98	.047
Cesarean delivery	4.6	1.6, 13.2	.005
Birth weight, per 50 g	0.86	0.79,0.93	<.001
Surfactant in DR	0.2	0.1, 0.5	.001

TACE ACTIVITY DURING MURINE LUNG DEVELOPMENT

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Background: Fibroblast-Type II epithelial cell communication in fetal lung development involves the ErbB receptor family (EGFR, ErbB2, ErbB3, ErbB4). The ErbB receptor ligand neuregulin (NRG) is secreted by fetal lung fibroblasts and activates ErbB3 and ErbB4 on Type II cells to stimulate surfactant synthesis. NRG is synthesized as a membrane-bound pro-protein whose release into the extracellular space requires cleavage by TACE, a membrane metalloprotease. ErbB and other receptors activate TACE via protein kinase C-stimulated Ca++ activity.

Objective: We hypothesized that TACE activity is involved in fibroblast-Type II cell communication promoting surfactant synthesis.

Design/Methods: We studied developmental expression of TACE in fetal mouse lung (gestational d16-d18) using immunohistochemistry (cell-specific expression), immunoblotting (inactive and active peptides) and DSPC assays (its effect on surfactant synthesis). We also measured TACE activity in fibroblasts via cleavage of a fluorochrome-labeled peptide substrate.

Results: TACE is abundant in d16 lung mesenchyme and epithelia. Thereafter mesenchyme expression strongly localizes to areas underlying developing respiratory bronchioles and alveolar ducts; epithelial expression localizes to distal epithelium, consistent with developmental concentration of TACE at sites of fibroblast-Type II cell communication. Immunoblots from cultured fetal lung fibroblasts identified inactive 120kDa and active 75kDa TACE species. In females the ratio of active to inactive TACE at d16 was 2.7 and decreased to 2.0 then 1.5 at d17 and d18. In contrast, ratios in males increased from 1.5 at d16 and d17 to 3.5 at d18. A different antibody directed against the enzyme active site also recognized 70kDa and 55Kda active peptides. In females the ratio of 55kDa/120Kda decreased from 4 at d16 to 2.7 at d17 and 2.4 at d18. Again males increased from 2.5 on d16 to 5 on d17 and 6 on d18. In d17 cells PMA stimulated TACE enzymatic activity by 30%. This was dose-dependently decreased by the TACE inhibitor IC-3 to 60% of the uninhibited condition. Media from PMA-treated d17 fibroblasts induced Type II cell DSPC synthesis dose-dependently, reaching 300±27% of control by 100ng/ml PMA.

Conclusions: These data support the role of TACE in the pathway of fibroblast-Type II cell communication. Funded by NIH HL37930; Peabody Foundation. IC-3 was a gift of Amgen (Seattle, WA).

Obstetricians' Responses to the Threat or Reality of Medical Malpractice

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Background: Professional discussions about medical malpractice tend to focus on monetary issues and litigation prevention, however survey data suggest that affective issues may be a central concern for physicians. More than 95% of physicians who are sued experience emotional distress, and up to 39% demonstrate symptoms of major depression.

Objective: To investigate obstetricians' affective, cognitive, and behavioral responses to the threat and the reality of medical malpractice litigation. We hypothesize that physicians are most affected by the emotional impact of professional liability.

Methods: Fifteen structured interviews were conducted with practicing obstetricians in the Boston area to elicit information on the participants' attitudes towards practicing in the current malpractice environment. Each physician completed a questionnaire about demographics and claim history. Interpretive Phenomenological Analysis was used to explore participants' responses to the interview and elicit relevant themes.

Results: Respondents overwhelmingly pointed to emotional factors as being their primary concern related to medical malpractice litigation. When asked whether the most difficult aspect of the malpractice situation is the financial element, the emotional threat of being sued, or another aspect; only 3 of the 15 physicians chose the financial component. Ten of the 11 physicians who had been named in a claim described an emotional aspect such as a feeling of failure or the "vile accusations" as the worst part of being sued. Many respondents pointed to the implications of the malpractice situation on patient care and job satisfaction.

Conclusions: Professional discussions and policy debate regarding medical malpractice should consider affective – as well as financial – aspects of this issue.

Claim History of Present Sample and ACOG 2003 Sample

	ACOG	Present Sample (n=15)
Named in Claim (%)	76.30	73.30 (11/15)
Named in Residency (%)	29.60	40.006 (6/15)
Number of Claims (mean)	2.64	1.73 (range 0-4)
Age (mean)		43.07 (Range 30-61)
Years in Practice (mean)		13.33 (Range 1-35)
Female		46 (7/15)

Duration of Lactation and Incidence of Myocardial Infarction In Middle-To-Late Adulthood

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Background: Lactation is associated with favorable maternal glucose and lipid metabolism and lower blood pressures. Women who have breastfed have a lower risk of type 2 diabetes. We hypothesized that lactation may also be associated with a lower risk of coronary heart disease.

Methods: We conducted a prospective observational cohort study of 88,908 parous women participating in the Nurses' Health Study from 1986 to 2002. Our primary outcome was incident myocardial infarction or death from coronary disease.

Results: During the study period, 2555 cases of coronary heart disease were diagnosed during 1,386,803 person-years of follow-up. Compared with parous women who had never breastfed, women who had breastfed for a lifetime total of ≥2 years had 36% lower risk of coronary heart disease (95% CI 22-48%, p for trend <0.0001), controlling for age, parity and stillbirth history. When additional adjustment was made for early-adult adiposity, parental history, smoking, diet, exercise, and use of aspirin, alcohol, postmenopausal hormones and multivitamins, women who had breastfed for a lifetime total of ≥2 years had a 24% lower risk of coronary heart disease (95% CI 6-38%, p for trend = 0.02) than women who had never breastfed. Women who had breastfed for a lifetime total of >1 year had a 13% (95% CI 2-23%) lower covariate-adjusted risk of coronary heart disease than women who had never breastfed.

Conclusions: In a large, prospective cohort, longer duration of breastfeeding was associated with a reduced risk of coronary heart disease. Whether this relationship is causal requires further investigation.

In Utero Androgen Exposure Affects Hoxb-5 Protein Levels and Spatial Localization in Developing Murine Lung

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Background: Androgen exposure beginning in early lung development stimulates lung branching and cell proliferation but delays alveolar epithelial maturation contributing to the increased risk of respiratory morbidity in male newborns. In the human prostate dihydrotestosterone (DHT) cooperates with Hox genes to regulate branching morphogenesis and promote cell proliferation in prostate cancer. We and others have shown the importance of Hoxb-5 and Hoxa-5 to lung airway branching morphogenesis and lung maturation but an interaction between androgen and Hox gene control of lung development has not been investigated. **Objective:** We hypothesized that DHT treatment beginning early in lung development differentially regulates Hoxb-5 and Hoxa-5 protein expression coordinate with the known roles of these Hox genes in lung morphogenesis. **Design/Methods:** Timed pregnant mice were implanted with DHT pellets (2mg/day) on d11 of gestation (term=19 days). Animals were sacrificed on d18 of gestation, fetuses sexed and fetal lungs processed for either immunostaining or Western blot experiments. Coronal lung cryosections were immunostained for Hoxb-5 and Hoxa-5 using alkaline phosphastase detection methods. Western blot with densitometry was performed on whole lung lysates using the same Hoxb-5 or Hoxa-5 antibodies followed by re-probing of each membrane with GAPDH as an internal control. **Results:** Immunohistochemistry showed that DHT exposed Gd18 fetal lungs had less developed terminal saccular morphology, increased intensity of mesenchymal nuclear staining for Hoxb-5 protein and loss of the central < peripheral gradient of restricted Hoxb-5 expression around developing bronchioles and alveolar sacs. Conversely, Hoxa-5 protein localization did not change, although cuboidal epithelium appeared more intensely positive for Hoxa-5. Western blot with densitometry analysis showed that DHT treatment increased Hoxb-5 protein levels by 3 fold as compared to control in Gd18 female fetal mouse lungs but did not alter Hoxa-5 protein levels. **Conclusions:** We conclude that androgen effects on fetal lung structural development and maturation may be in part mediated through modified protein levels and cellular localization of Hoxb-5 protein. Supported by HL-44784, HL37930, Peabody Foundation.

A Prospective Study Of Insulin Resistance, Glucose Intolerance And Infant Birth Weight

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Objective: We sought to investigate the relationship between early glucose intolerance, third trimester glucose intolerance and infant birth weight.

Study design: Fasting serum samples from 439 women in the Massachusetts General Hospital Obstetrical Maternal Study were collected from 16-18 weeks gestation and analyzed for HOMA. GLT was collected as part of routine care. We hypothesized that both early insulin resistance and later glucose intolerance would affect infant birth weight and risk of macrosomia-related c-section. We used linear regression to predict infant birth weight as a function of pre-pregnant BMI, gestational weight gain, maternal age, HOMA and GLT. Using logistic regression, we modeled risk of c-section and macrosomia as a function of those variables.

Results: 73 women delivered macrosomic infants. 52 women underwent a c-section for macrosomia or failure to progress. Neither HOMA nor GLT were predictive of infant birth weight. Significant predictors of infant birth weight were gestational weight gain ($p<0.001$), pre-pregnancy BMI ($p<0.001$) and maternal age ($p=0.02$). Pre-pregnant BMI and gestational weight gain were significantly associated with risk of macrosomia. Pre-pregnant BMI and GLT were also significantly associated with risk of c-section for macrosomia or failure to progress.

Conclusion: These data suggest that maternal BMI and gestational weight gain should be emphasized when attempting to modify risk of fetal macrosomia and associated adverse outcomes.