# An Experience of Rapid HIV Testing During Labor and Delivery

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BACKGROUND: A large CDC study of Ora-Quick HIV testing during labor has demonstrated 100% sensitivity and 99.9% specificity of the test. "Last minute prophylaxis" still decreases perinatal transmission of HIV from natural rate of 25% to about 11%.

OBJECTIVES: To determine population characteristics of women with unknown HIV status at delivery, to analyze our experience of perinatal rapid HIV testing by Ora-Quick and to assess the compliance with prenatal HIV screening at our institution.

DESIGN/METHODS: We determined HIV sero-status of all women who delivered at Lincoln Medical and Mental Health Center (LMMHC) from 01/01/05 to 12/31/05. We compared Ora-Quick results to the results of confirmatory EIA and Western Blot.

RESULTS: 2496 women were admitted at LMMHC for labor and delivery during the study period. HIV sero-status was documented prior to admission in 2260 (90.54%) women and the remaining 236 women had rapid HIV testing by Ora-Quick at the time of admission. Being single mother, primiparity and age < 20 were associated with unknown HIV status at delivery. Average time from test to results was 4 hours for Ora-Quick, 13 hours for EIA and 96 hours for Western Blot.

CONCLUSIONS: Ora-Quick has high sensitivity and specificity when compared with conventional HIV tests and with immediate availability of results perinatal HIV prophylaxis can be administered in a timely manner to prevent transmission of HIV to the newborn.

# Outcome of Infants 21-28 Weeks Gestation Born at an Inner City Hospital over an Eight Year Period

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BACKGROUND: Improving rates of survival as well as high rates of disability among infants at the threshold of viability has been reported from many tertiary networks in the United States and Europe over the past decade.

OBJECTIVES: We reviewed the outcome of all live births 21-28 weeks gestation (GA) and < 1250 gm birth weight (BW) over an eight year period at Lincoln Medical and Mental Health Center. We compared our survival rates with other outcome data, ascertained the causes of mortality in this population and assessed short-term neonatal and neuro-developmental morbidities among < 25 weeks gestation or < 800 grams birth weight (ELGA) survivors.

DESIGN/METHODS: NICU admission logbook and monthly morbidity-mortality reports were used to tabulate outcome by BW and by GA. Medical records and autopsy findings were used to assign a main cause of death. Over the past two years (2003-04) medical records of every ELGA infant were also reviewed to assess significant morbidities.

RESULTS: From January 1, 1997 to December 31, 2004 there were 23,046 total live births at our institution. 339 (1.47%) of these were 21-28 weeks GA or < 1250 gms BW. During the same interval 71 fetuses of the same GA were stillborn. 80 of 339 (23.6%) died. Of these 80 deaths 26 (32.5%) were extremely immature at 21-22 weeks GA. Other causes of death were respiratory distress syndrome (15%), infection (15%), pulmonary hemorrhage (10%) and lethal malformations (6.3%). Survival outcomes in each weight group except < 500 gms were similar to that from Pediatrix Medical Group (2001-02) and US Vital Statistics (2002), the latest available published data. Mortality and major morbidity outcome was analyzed separately amongst the ELGA infants over the last two years (2003-04). 27 of the 34 (79%) ELGA infants survived to discharge. The incidence of serious neuro-morbidity, severe CLD or ROP requiring treatment was 52%. 5 of 27 survivors (18.5%) had more than one major morbidity, while 13 of 27 (48%) had none.

CONCLUSIONS: Despite inconsistent prenatal care, survival rates in this high-risk urban population compared well with other published data. In the ELGA subset (2003-04) survival of 79% is better than 39% form UK-Ireland (EPICURE Study 1995), 44% from Belgium (EPIBEL Study 1999-2000) and 63% from Canada (CNN Study 1996-2000). These were large population studies and their cohorts were from before 2000. Our cohort is more recent and our numbers too small to be conclusive. Major morbidity free survival in the above three studies was 15% (UK-Ireland), 13% (Belgium) and 14% (Canada) compared to 38% (13/34) in our group. The increasing survival of infants at the threshold of viability at huge economic costs and high morbidity is an ethical dilemma that needs to be addressed by society.

# Neonatal sepsis Interacts with Gestational Age and Prolonged Exposure to Oxygen in the Etiology of Retinopathy of Prematurity

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## ABSTRACT

The interactions between known risk factors for any retinopathy of prematurity (ROP) remain to be clarified. The aim of this study was to assess the interrelationships between three risk factors of ROP, i.e., low gestational age (<26 weeks), prolonged oxygen exposure (defined as supplemental oxygen requirement at 28 postnatal days), and neonatal sepsis. From an institutional cohort of 1,518 very preterm newborns with a gestational age <30 weeks or a birth weight <1501g, we selected infants with a gestational age less than 30 weeks who were examined for ROP (N=577). Of these, 271 (47%) newborns were diagnosed with ROP. In multivariable analyses, low gestational age (Odds Ratio 2.7, 95%CI 1.6-4.7), prolonged oxygen exposure (1.8, 1.1-2.4), and any neonatal sepsis (2.1, 1.3-3.1) conveyed risk information beyond that conveyed by confounders. We found more than additive joint effects of sepsis and low gestational age (11, 6-22), and for sepsis and prolonged oxygen exposure (9, 5-16). Moreover, we observed a more than multiplicative joint effect of prolonged oxygen exposure and low gestational age (14, 8-26). We conclude that ROP should be considered a complex disorder with a "multi-hit" etiology. Future research should attempt to identify genetic factors and antenatal adverse exposures that might be involved in the etiology of ROP.

**Title: Pigment Epithelium Derived Factor (PEDF) in a Mouse Model of BPD**

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**Background:** The lung pathology in bronchopulmonary dysplasia (BPD) is characterized by impaired development of the alveolar unit (alveolar epithelium and the underlying capillary bed). Vascular remodeling is an important component of the injury/repair process of the alveolar unit in BPD. Vascular endothelial growth factor (VEGF), an angiogenic growth factor, is important in vascular development. Studies suggest that VEGF activity and vascular remodeling participate mechanistically in the alveolarization process. PEDF, an angiostatic cytokine, inhibits VEGF, creating a necessary control of angiogenesis. Matrix metalloprotease-9 (MMP-9) is involved in hyperoxic lung injury, where it can degrade extracellular matrix. MMP-9 also regulates proangiogenic and angiostatic molecules.

**Objective:** PEDF is an important mediator of injury to the components of alveolar unit in oxygen mediated injury in developing lung leading to impaired vascular development in BPD**.**

**Design/Methods:** Eight -day-old WT (CD1) and MMP-9 (-/-) mice were exposed to hyperoxia or room air for five days. Western blot analyses for PEDF, VEGF and MMP-9 were done in lung lysates. 5 micron lung sections from paraffin embedded lungs were examined by immunohistochemistry for PEDF and co-stained for PECAM to show the endothelial localization of PEDF.

**Results:** PEDF was higher in the lungs of WT and MMP-9 (-/-) oxygen-exposed mice compared to room air-exposed WT and MMP-9 (-/-) mice. The increase with hyperoxia was significantly less in MMP-9 (-/-) (1.9 fold increase) than WT (7.2 fold increase vs WT (room air); N=3, $P < 0.0001$). VEGF in the lungs from oxygen-exposed WT mice was significantly reduced compared to room air-exposed (N=3; $P = 0.014$). This reduction was not seen in MMP-9 (-/-) mice after hyperoxia compared to room air-exposed MMP-9 (-/-) ( $P = 0.07$). In addition, MMP-9 expression was increased after hyperoxia in WT mice ($P = <0.05$). Immunohistochemistry for PEDF revealed expression was strongly increased in the enlarged alveolar regions after exposure to hyperoxia.

**Conclusions:** PEDF, an angiostatic cytokine, is upregulated in developing lung following hyperoxic exposure in association with decreased VEGF and abnormal alveolar unit development. Increased MMP-9 may increase PEDF activity. Altered PEDF and VEGF may contribute to the arrested alveolarization seen in BPD by inhibiting normal vascular remodeling in the developing alveolar unit. (Support by NIH HL37930).

# Methadone versus buprenorphine for the treatment of opiate dependence: a cohort study.

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**Background:** Treatment for opiate dependence has changed dramatically in the last few years with the introduction of community-based treatment with buprenorphine, an opiate agonist/antagonist. The goal of this study is to compare the maternal and infant outcomes of a cohort of opiate dependent women treated with methadone versus buprenorphine for opiate dependence during pregnancy.

**Methods:** Mothers treated for opiate dependence during pregnancy and delivered at a single institution were prospectively identified by maternal and neonatal databases. Methadone was administered within a structured treatment program that included daily visits to the treatment center and mandatory counseling. Buprenorphine was administered by community providers (occasionally the obstetric provider) with recommended substance abuse counseling. Data were compared with Student's t-test, Wilcoxon Rank sum test, or Fisher's exact test as indicated with $p<0.05$ considered significant.

**Results:** Women treated with buprenorphine started opiate agonist therapy sooner, had slightly longer gestational lengths, and larger infants compared to those treated with methadone. Treatment for neonatal abstinence syndrome and length of stay was reduced in infants of mothers that received buprenorphine.

| | n | Methadone | n | Buprenorphine | p |
|---|---|---|---|---|---|
| **Maternal age (years)** | 120 | 24.9± 4.3 | 66 | 25.2± 4.2 | 0.59 |
| **Nulliparity (%)** | 120 | 34 (28.3) | 66 | 20 (30.3) | 0.87 |
| **Smoker (%)** | 120 | 103 (85.8) | 66 | 59 (89.4) | 0.51 |
| **Gestational age at initial visit** | 116 | 10 (8, 15) | 63 | 10 (8, 15) | 0.91 |
| **Gestational age at start of opiate agonist therapy** | **103** | **10 (0, 21)** | **58** | **0 (0, 14.5)** | **0.01** |
| **Gestational age at delivery** | **120** | **38.6 (36.8, 39)** | **66** | **39.7 (38.2, 40.1)** | **0.001** |
| **Preterm (%)** | 120 | 22 (18.3) | 66 | 8 (12.1) | 0.30 |
| **Birthweight (gm)** | **122** | **2896±588** | **67** | **3207±593** | **0.0006** |
| **Birthweight z-score** | **122** | **-0.63±0.94** | **67** | **-0.31±1.03** | **0.03** |
| **Neonatal hospital stay** | **108** | **6.5±3.5** | **55** | **4.9±1.7** | **0.002** |

**Conclusions:** The improved perinatal outcome with buprenorphine may reflect the stabilization of disease prior to pregnancy or a more motivated patient population. A randomized trial is required to further explore these findings. Long term outcomes of buprenorphine exposed infants are needed.

# ULTRASOUND-BASED, THREE DIMENSIONAL SOLID MODELING OF THE CERVIX IN PATIENTS WITH CERCLAGE

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OBJECTIVE To develop a method of demonstrating ultrasound-based, 3D anatomic relationships during pregnancy and apply that method to images of patients with cerclage.

STUDY DESIGN A cross-sectional study of subjects with and without cerclage was performed. Three-dimensional ultrasound volumes of the cervix were obtained using a transvaginal transducer (Philips iU22 system, 3D9-3v transducer). Commercially available 3D mechanical design software (SolidWorks, Concord MA) was used to construct 3D solid models of ultrasound data. Ultrasound data was transferred to the design software using a three-step protocol. First, ultrasound quantification software (QLAB, Philips Ultrasound) was used to export ultrasound data as a series of 30 two-dimensional (2D) images spaced 1.2 mm apart. Second, the 2D images were imported into an image-processing program (Analyze 7, AnalyzeDirect) and converted into a standard 3D format (Analyze 7.5). Third, representative images were transferred to mechanical design software to construct the anatomic models.

RESULTS Ten subjects were studied: abdominal cerclage (n=2), prophylactic cerclage (n=4) and no cerclage (n=4). The gestational age range was 20 – 24 weeks. Ten images in two planes were used to construct the amniotic cavity, uterine wall and cervix. The cerclage path was determined by defining a 3D curve using a series of six points. The error between the model-based cerclage path and the ultrasound-based cerclage path was less than 1.5 mm.

CONCLUSION Solid modeling tools aid interpretation of 3D cervical sonography and improve conceptual understanding of cerclage placement during pregnancy.

**Title: Adult Rat Bone Marrow Stem Cells Promote Fetal Type II Cell Surfactant Synthesis**

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**Rationale:** Bronchopulmonary dysplasia is a chronic complication of immature lungs due to injury-induced delay of lung development. Pluripotent bone marrow stem cells (BMSC) can engraft in injured lungs, differentiate into type II cells (T2C), and repair injured tissue. The mechanisms of BMSC interactions with lung cells are still unknown.

**Objective:** To study 1) effects of BMSC on fibroblast (F) and T2C proliferation and surfactant synthesis and 2) changes in activity of BMSC exposed to lung cells.

**Methods**: Rat BMSC were isolated by differential adherence and co-cultured with primary fetal d19 and d21 rat F and T2C. Effects on surfactant synthesis (choline incorporation into disaturated phosphatidylcholine (DSPC)) and on F and T2C proliferation (thymidine incorporation) were measured. We also determined the effect of F and T2C on BMSC proliferation.

**Results:** Culturing BMSC with T2C in a mixed culture system increased DSPC synthesis to 150±7% (mean±SEM), but did not change cell proliferation, similar to co-culturing of BMSC and F. Co-cultures of BMSC and d21 T2C on Transwell® inserts increased DSPC synthesis in T2C to 150±38% (mean±SEM). T2C proliferation was decreased to 65±7% (mean±SEM), but F proliferation was unchanged. BMSC proliferation increased to 200±15% (mean±SEM) when co-cultured with T2C, and to 250±20% (mean±SEM) when co-cultured with F.

**Conclusions:** BMSC can stimulate maturation and inhibit proliferation of T2C at a time in gestation when T2C must mature and synthesize surfactant to prepare for birth. Fetal lung cells promote BMSC proliferation. We speculate that BMSC, T2C, and F form an interactive loop to promote differentiation which is part of the mechanisms by which intratracheal BMSC prevent lung injury in rats exposed to prolonged hyperoxia.

**ErbB Signaling in Hypoxia- and Hyperoxia-induced Lung Epithelial Cell Injury**

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**Background:** Hypoxia causes cell injury or cell death secondary to ATP depletion following the switch to anerobic metabolism. Oxygen therapy is widely used to treat disease processes that cause hypoxia. However, prolonged exposure to hyperoxia leads to the generation of excessive reactive oxygen species that cause acute lung injury and contribute to the development of bronchopulmonary dysplasia. ErbB receptors (ErbB1, ErbB2, ErbB3, and ErbB4) have key roles in fetal lung development and repair to maintain the homeostatic integrity of lung structure and function. Little is known about ErbB receptor regulation in hypoxia- and hyperoxia-induced lung injury and repair.

**Objective:** We hypothesize that exposure to hypoxia influences the development of hyperoxia-induced lung injury. ErbB signaling is important in regulating repair from hypoxia and hyperoxia-induced lung injury.

**Design/Methods:** Mouse lung epithelial (MLE)12 cells were treated with 10%$O_2$ for 1 hour, followed by 21% or 95%$O_2$ treatment for 48 hours. Control cells were either exposed to 21%$O_2$ or 95%$O_2$ only. $^3$H thymidine or $^3$H choline were added in the last 24 hours to measure cell proliferation and choline incorporation, respectively. Cell viability was assessed by MTS assay. Effects on ErbB receptor expression were studied by Western blot.

**Results:** Exposure to 95%$O_2$ significantly reduced MLE12 cell viability (by 50%), proliferation (by 37%), and choline incorporation (by 33%) compared to room air controls. This was accompanied by an overall ErbB receptor down-regulation (by 25-77%), most prominently of ErbB4. An initial exposure (pre-conditioning) to 10% $O_2$ followed by 95%$O_2$ significantly improved cell viability (by 25%) and ErbB4 protein expression (by 25%) compared to hyperoxia alone, but cell proliferation was inhibited even further. Hypoxia pre-treatment did not affect choline incorporation compared to cells exposed to 95%$O_2$ alone. After 48 hours of recovery in room air, cells pre-treated wtih 10%$O_2$ showed a recovery of cell proliferation and ErbB4 receptor expression.

**Conclusions:** Hyperoxia causes lung epithelial cell damage, impaired surfactant phospholipid synthesis, and downregulation of ErbB receptor expression. Pre-conditioning with short term hypoxia improved cell viability and increased ErbB4 expression, suggesting that hypoxia may stimulate signaling pathways involved in ErbB4 upregulation that protect against hyperoxic cell injury. (NIH HL 04437, HL37930, DFG 378/3-1)

**The Lasting Effects of Neonatal Brain Hemorrhage**

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**Background:** VLBW children are at increased risk of neurodevelopmental disabilities and poor academic achievement. Participants in the indomethacin trial had decreased rates of severe IVH. **Objective:** To compare cognitive, language, behavioural and educational outcomes of VLBW children to term controls at 12 years, and to evaluate the impact of neonatal insults, indomethacin and environmental risk factors on intellectual function. **Design/Methods:** 375 children (85% of survivors) born in 1989-1992 with birth weight <1250g and 111 term controls were evaluated at 12 years of age. Neuropsychometric testing, neurological exam, and questionnaires on educational needs were completed. **Results:** VLBW children obtained scores 6-14 points lower than term controls on all psychometric tests after adjustment for socio-demographic factors. 22-24% of VLBW children scored in the abnormal ranges on the CELF (basic language) vs 2-4% of controls. Preterm children required more school services (47% vs 16%), and support in reading (29% vs 9%), writing (22% vs 4%), and mathematics (31% vs 6%) compared to controls. There were no differences in behaviour problems. On multiple linear regression, severe neonatal brain injury (grade 3 and 4 IVH, PVL, ventriculomegaly grade 2 and above) was the strongest predictor of poor intelligence (β coefficient -22.1; CI -28.1, -16.2). Antenatal steroids, higher maternal education, and 2-parent family were associated with better cognition, whereas minority status incurred a disadvantage. Indomethacin did not affect intellectual function. **Conclusions:** VLBW children, especially those with severe brain injury, have serious deficits in their neuropsychological profile and greater special education needs compared to term controls.

**TITLE:** The post-treatment GBS culture – Useful data or misinformation?

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**INSTITUTION:** Tufts-New England Medical Center, Division of Maternal-Fetal Medicine

**ABSTRACT:**

*Objective:*

To determine whether a vaginal-rectal culture obtained after antibiotic therapy has begun accurately detects pre-existing colonization with group B streptococcus (GBS).

*Rationale:*

Women in preterm labor transferred to tertiary institutions often receive GBS prophylaxis en-route, and are subsequently cultured for GBS colonization upon arrival at the tertiary facility. If their labor is arrested the result of this culture may dictate whether the patient receives GBS prophylaxis during a subsequent labor episode. Previous studies have demonstrated that antepartum antibiotics decrease the rate of colonization in GBS-positive women, but do not eliminate infection in all subjects. It is unclear whether a post-treatment culture can be reliably used to guide management during a subsequent episode of labor.

*Methods:*

In a prospective cohort study, women presenting in labor and known to be colonized with GBS based on routine screening, were recruited between March and December 2007. Two GBS cultures were obtained. The first GBS culture was performed prior to administration of antibiotic prophylaxis with intravenous penicillin. The second GBS culture was performed two hours following the first dose of antibiotics. Comparison of the two results in each patient was made to determine whether two hours exposure to antibiotics affects the result of a GBS culture.

*Results:*

A total of 80 patients were recruited. Complete results were obtained for 63 (79%) patients. Of these, 48 (76%) were still GBS positive on initial culture. Persistence of GBS on culture 2 hours after antibiotic exposure was seen in 32/48 (67%). Conversion from GBS positive to GBS negative status was seen in 16/48 (33%) (95% confidence interval 22 – 47%).

*Conclusion:*

A vaginal-rectal culture for GBS performed after antibiotic prophylaxis has commenced may not accurately reflect a patient's GBS colonization status.

**Maternal Obesity Is Associated With Low Neonatal Apgar Scores**

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**Background:** The Apgar score is a measure to evaluate a newborn's condition at birth and the need for resuscitation. As such, it is also a measure of fetal well-being. Low Apgar scores are associated with neonatal mortality and neurological disability. Maternal obesity during pregnancy, a growing epidemic, is well established to increase obstetric complications, and is now emerging as a risk factor for neonatal morbidities and mortality. The role of maternal obesity as a risk factor for low Apgar scores is unclear.

**Objective:** To determine in a population-based birth registry the role of maternal obesity as a risk factor for low neonatal Apgar scores while adjusting for maternal, pregnancy and neonatal confounders.

**Methods:** Data were obtained from the Maine State Birth Records Database from the years 1998-2005. We restricted our analyses to 60,000 white women (97% of the registry population) and singletons only. Maternal, pregnancy, and neonatal factors that may be associated with low Apgar scores, including maternal body mass index (BMI) were evaluated using univariable and multivariable logistic regression. BMI groups were defined as <25 (normal), 25-29 (overweight), 30-39 (obese) and >=40 (morbidly obese). Apgar scores were grouped as <4 (very low), 4-6 (low) and 7-10 (normal).

**Results**: Compared to newborns of women with a normal BMI, those whose mother had a BMI of >=25 were not at increased risk of very low Apgar scores. However, we found an increased risk for a low Apgar score among newborns of mothers with a BMI of >=25. In a multivariable model adjusting for maternal age, prematurity, cesarean section, gestational diabetes mellitus and pregnancy-induced hypertension, only the risk increase among morbidly obese mothers' newborns achieved formal statistical significance (odds ratio 1.6, 95% CI 1.2-2.2), p<0.0001).

**Conclusions:** Above and beyond being a risk factor for adverse events in pregnancy, extreme maternal obesity appears to be associated with an increased risk for low, but not for very low Apgar scores. Further studies are needed to clarify the relationships between maternal obesity, complications of pregnancy, and neonatal outcome.

# Short Term Outcomes of Complex Congenital Heart Disease: The Role of Birth Weight and Gestational Age

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**OBJECTIVE:** To evaluate short-term outcomes and survival of low birth weight (LBW), very low birth weight (VLBW), and preterm infants with four of the most common types congenital heart disease (CHD) at one institution. **STUDY DESIGN:** We performed a retrospective cohort study of all neonates at our institution diagnosed with CHD from Dec 1998 through Dec 2006. Maternal ultrasound, neonatal, and pediatric cardiology records were reviewed to determine type of CHD, survival to discharge, length of stay (LOS), and neonatal morbidities. Outcomes of LBW and VLBW neonates were compared to those infants with BW ≥2500 gm, and neonates born <37 weeks were compared with term infants using Student t-test and Chi square. **RESULTS**: We evaluated 129 neonates with four types of CHD:hypoplastic left heart syndrome, A-V canal, transposition of the great arteries, and Tetrology of Fallot. Survival rates, LOS, and neonatal morbitidites are shown in the table. When compared to term neonates with CHD, those who delivered prior to 37 weeks had a higher mortality rate (32% vs.14%, P=.04), longer hospital stay (31.6 vs. 22.7 days, P=.01), and higher rateof IVH ( 8% vs. 0%, P=.04).

**CONCLUSION**: Survival among VLBW neonates with CHD was low in our study population, while survival rates were much higher (84%) for both LBW and normal BW in cases of common complex CHD. In addition, preterm infants had a lower survival rate and longer hospital stay. This information may be helpful in counseling parents who face early delivery of a child with CHD.

**Neonatal Outcomes**

| Birth Weight | VLBW | LBW | ≥2500 gm | P-value |
|---|---|---|---|---|
| **Survival n(%)** | 1 (25) | 21 (84) | 84 (84) | .01 |
| **LOS (days)** | 9.3±15.3 | 39.7±33.9 | 16.3±21 | .0001 |
| **BPD n(%)** | 0 (0) | 4 (16) | 1 (1) | .01 |
| **NEC n(%)** | 0 (0) | 2 (8) | 5 (5) | .75 |
| **IVH n(%)** | 0 (0) | 2 (8) | 0 (0) | .01 |
| **Seizures n(%)** | 0 (0) | 1 (4) | 4 (4) | .92 |

Use of Ibuprofen Lysine for Treatment of Symptomatic Patent Ductus Arteriosus in Infants <1500 gms.

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Ibuprofen lysine is currently approved by the FDA for the treatment of patent ductus arteriosus in the neonate. Until recently, indomethacin had been the only drug available for medical closure of patent ductus arteriosus (PDA) and is widely use in neonatal intensive care units (NICUs).

**Objective:** To evaluate the rate of PDA ligations of infants treated with ibuprofen compared to those treated with indomethacin for symptomatic PDA.

**Methods:** The infants studied were all <1500 gms birthweight (gestational age 23 & 4/7- 30 & 4/7) who were diagnosed as having an echocardiographically confirmed, hemodynamically significant PDA. Infants treated with ibuprofen treated received the standard regimen (10 mg/kg first dose followed by 5mg/kg at 24 hour intervals) were compared to a historical cohort (2004-2006) who received a standard dosing regimen of indomethacin (0.2 mg/kg given at 12 hour intervals). Primary outcome of PDA ligation were compared between the two groups and other collected data included urine output, plasma creatinine, need for additional pharmacological treatment and clinical complications.

**Results:** The 28 infants who received ibuprofen for closure of PDA had a median birthweight of 802 gms (range 550-1380 gms) and a mean gestational age of 27 & 1/7 (range 23 & 4/7 – 30 & 4/7). PDA ligation was performed in 5/28 infants (18%) in the ibuprofen group compared to 38/127 (30%) in the indomethacin group (relative risk 0.60; 95% confidence interval, 0.26 to 1.38; p= 0.25). In the ibuprofen group, there was also no difference in the rate of PDA ligation rate in infants less than 800 gms (3/16) compared to infants greater than 800 gms (6/18), (relative risk 0.72; 95% confidence interval, 0.39 to 1.33; p= 0.45).

**Conclusion:** Similar to previous published reports, the use of ibuprofen for treatment of symptomatic patent ductus arteriosus is as efficacious as indomethacin in infants < 1500 gms. There was no difference in the rate of PDA ligation in infants less than 800 gms compared to those greater than 800 gms.

# FAILED LABOR INDUCTION: IMPACT OF BODY MASS INDEX ON THE CESAREAN DELIVERY RATE

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**OBJECTIVE:** To evaluate the influence of prepregnancy body mass index (BMI) on the cesarean delivery (CD) rate in term patients undergoing labor induction (IOL).
**STUDY DESIGN**: This is a retrospective cohort study of term patients undergoing IOL from 5/01 to 4/07 with BMI categories defined as: underweight (< 18.5), normal weight (18.5-24.9), overweight (25-29.9), obesity class 1 (30-34.9), class 2 (35-39.9) and class 3 (≥40.0). Maternal and obstetric characteristics were examined as predictors of CD using multivariate logistic regression analysis. Multiple gestation, fetal anomaly, malpresentation, prematurity (<37 weeks 0 days), planned CD and attempted vaginal birth after cesarean section were excluded.
**RESULTS:** The risk of CD by BMI category, stratified by parity, using normal BMI as reference for 3727 women is tabulated below. Other factors associated with an increased risk of CD included weight gain (kg) during pregnancy (OR 1.03; 95% CI 1.01-1.04), maternal age >30 (OR 1.76; 95% CI 1.45-2.13), nulliparity (OR 2.78; 95% CI 2.09-3.68), bishop score ≤5 (OR 2.20; 95% CI 1.82-2.65) and neonatal birth weight ≥4 kg (OR 2.12; 95% CI 1.63-2.76).
**CONCLUSION:** The rate of CD increases with increasing prepregnancy BMI in nulliparous women undergoing IOL at term. This increase was noted only in obesity class 2 and 3 multiparous patients. Maternal weight gain and age, nulliparity, unfavorable bishop score and neonatal birth weight were independently associated with an increased risk of CD.

| | Parous (n=2046) AOR (95% CI) | Nulliparous (n=1681) AOR (95% CI) |
|---|---|---|
| Underweight | 0.77 (0.32, 1.83) | 0.75 (0.40, 1.40) |
| Overweight | 1.25 (0.88, 1.77) | 1.77 (1.32, 2.35) |
| Class 1 | 1.33 (0.84, 2.09) | 2.75 (1.94, 3.90) |
| Class 2 | 2.30 (1.32, 4.14) | 1.85 (1.11, 3.09) |
| Class 3 | 3.79 (2.03, 7.05) | 3.21 (1.75, 5.86) |

**APGAR SCORES AND NICU ADMISSION WITH NUCHAL CORD, TIGHT NUCHAL CORD, AND TRUE KNOT IN PATIENTS DELIVERING AT TERM.**

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OBJECTIVE: To evaluate the relationships between nuchal cord, tight nuchal cord, and true knot, with Apgar scores and NICU admissions, in term deliveries.

STUDY DESIGN: The perinatal database at our institution was queried for all term (>= 37 weeks gestation) deliveries occurring between 02/02 and 07/07. Data regarding gestational age at delivery, birth weight, Apgar scores, nuchal cord, true knot and NICU admission were collected from the perinatal database. For vaginal deliveries with a nuchal cord, comparison of loose versus tight nuchal cord was performed. Whether the nuchal cord was cut or reduced prior to delivery was used to infer whether the nuchal cord was tight or loose. Comparisons were made using the Chi square test.

RESULTS: A total of 14,944 term deliveries, with mean gestational age 39.5 weeks, and mean birth weight 3416 g, had data available for analysis. Of these, 4176 (27.9%) involved a nuchal cord, and 172 (1.2%) involved a true knot. Nuchal cord was involved in 2780 (26.0% of vaginal deliveries, and 800 (28.8%) of these were tight nuchal cords. See tables.

*Tables: Apgar scores and NICU admissions for nuchal cord and true knot in term deliveries, and tight nuchal cord in vaginal term deliveries.*

| ***ALL TERM*** | **NO NUCHAL** | **NUCHAL** | **P** | ***VAGINAL*** | **LOOSE** | **TIGHT** | *P* |
|---|---|---|---|---|---|---|---|
| 1 MIN < 7 | 812 (7.5%) | 543 (13%) | <0.001 | 1 MIN < 7 | 193 (9.8%) | 181 (23%) | <0.001 |
| 5 MIN < 7 | 90 (0.8%) | 50 (1.2%) | 0.039 | 5 MIN < 7 | 16 (0.8%) | | 0.008 |
| NICU | 161 (1.5%) | 79 (1.9%) | NS | NICU | 23 (1.2%) | 23 (2.9%) | 0.001 |
| ***ALL TERM*** | **NO KNOT** | **KNOT** | **P** | | | | |
| 1 MIN < 7 | 1338 (9.1%) | 17 (9.9%) | NS | | | | |
| 5 MIN < 7 | 139 (0.9%) | 1 (0.6%) | NS | | | | |
| **NICU** | 233 (1.6%) | 7 (4.1%) | 0.010 | | | | |

CONCLUSION: Nuchal cord is associated with low Apgar scores at both 1 and 5 minutes in term infants, as is tight nuchal cord in patients delivered vaginally. Tight nuchal cord at vaginal delivery is also associated with NICU admission. A true knot is associated with NICU admission in term infants, but not with lower Apgar scores at 1 and 5 minutes.

**THE RELATIONSHIP OF NUCHAL CORD AND TRUE KNOT WITH INTRAUTERINE FETAL DEMISE (IUFD) IN PREGNANCY >= 24 WEEKS GESTATION.**

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OBJECTIVE: To Evaluate the relationships between nuchal cord and true knot, with IUFD, in deliveries at 24 weeks gestation and beyond.

STUDY DESIGN: The perinatal database at our institution was queried for all deliveries at least 24 weeks gestation, occurring between 02/02 and 07/07. Data regarding nuchal cord, true knot, fetal gender, gestational and chronic hypertension (HTN), diabetes mellitus (DM), fetal anomalies, Group B Streptococcus (GBS) carrier status, and IUFD were collected from the perinatal database. Logistic regression analysis was used to estimate adjusted odds ratios (AOR) and test significance of relationships.

RESULTS: A total of 16,948 deliveries had data available for analysis. Of these, 53 (0.3%) were IUFD. The mean gestational age was 38.8 weeks. The mean birth weight was 3280 g. For patients with IUFD, the mean gestational age was 33.9 weeks and the mean birth weight was 2060 g. See table.

*Table: Relationship of nuchal cord and true knot with IUFD, adjusted odds ratios*.

| | **NO IUFD** | **IUFD** | **AOR** | *P-VALUE* |
|---|---|---|---|---|
| **NUCHAL CORD** | **4623 (27.4%)** | **11 (20.8%)** | **0.67** | **NS** |
| **TRUE KNOT** | **198 (1.2%)** | **4 (7.5%)** | **7.35** | **<0.001** |
| HTN | 794 (4.7%) | 6 (11.53%) | 2.93 | **0.014** |
| DM | 580 (3.4%) | 0 (0%) | -- | NS |
| GBS Carrier | 3125 (18.4%) | 4 (9.4%) | 0.43 | NS |
| Fetal Anomaly | 58 (0.3%) | 4 (7.5%) | 27.8 | **<0.001** |
| Gender, Male | 8659 (51.3 %) | 33 (62.3%) | 1.55 | NS |

CONCLUSION: Nuchal cord is not associated with a higher rate of IUFD after 24 weeks gestation. True knot is associated with IUFD. This association persists after accounting for other factors, including HTN and DM, known to be associated with increased risk of IUFD.

# PERINATAL AND NEONATAL OUTCOMES OF TRIPLET GESTATIONS BASED ON PLACENTAL CHORIONICITY

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**OBJECTIVE**: To evaluate differences in perinatal and neonatal outcomes in triplet gestations based on placental chorionicity.

**STUDY DESIGN**: We analyzed all triplet sets (>20 weeks) delivering at our institutions from 1/95-4/07 (n= 137). Data was obtained via perinatal and neonatal databases, chart review, and placental pathology. We collected demographic data, gestational age of delivery, birthweight, APGARS, length of NICU stay, need for intubation, surfactant use, incidence of bronchopulmonary dysplasia, respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, and culture proven sepsis. We excluded cases of known fetal reduction and sets without data on chorionicity. Data was analyzed via t-test and Chi square.

**RESULTS:** 25 of 136 triplet sets (18.4%) contained a monochorionic pair. AOG was calculated using triplet sets. There were no significant differences in AOG (30.9 wks vs. 31.9 wks, p=NS)). Individuals within a triplet set that contained a monochorionic pair were more likely to have a lower BW (p=0.008), 5 minute APGARS < 7 (p=0.006), require ventilation (p=0.029), require surfactant (p=0.034), and have confirmed sepsis (p=0.022).

**CONCLUSION**: Individuals within a triplet set containing a monochorionic pair are more likely to have lower birthweight, 5 minute APGARS < 7, longer NICU stays, require ventilation and surfactant, and have confirmed sepsis.

# PERINATAL AND NEONATAL OUTCOMES OF TRIPLET GESTATIONS BASED ON METHOD OF CONCEPTION

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**OBJECTIVE:** To evaluate differences in perinatal and neonatal outcomes in triplet gestations based on method of conception: assisted reproductive technology (ART) vs. spontaneous (SPONT).

**STUDY DESIGN:** We analyzed all triplet sets (>20 weeks) delivering at our institutions from 1/95-4/07 (n= 137). Data was obtained via perinatal and neonatal databases, chart review, and placental pathology. ART included *in vitro* fertilization, intrauterine insemination, and ovulation induction. We collected demographic data, gestational age of delivery (AOG), birthweight, APGARS, length of NICU stays, need for intubation, need for surfactant, rates of bronchopulmonary dysplasia, respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, and culture proven sepsis. We excluded cases of known fetal reduction and sets with incomplete data. Data was analyzed via t test and Chi square.

**RESULTS:** We had 130 triplet sets available for analysis. 111/130 (85.4%) sets were conceived via ART. There were no significant differences in AOG or any outcome variables when we compared ART versus spontaneous gestations.

**CONCLUSION:** At our institutions, there were no overall differences in outcomes of triplet gestations based on method of conception.

**The utility of fetal echocardiography after a normal fetal anatomy survey performed by a perinatologist.**

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**BACKGROUND:** With a prevalence of 6-8/1000, congenital heart defect is the most common serious anomaly present at birth. Due to the significant impact these anomalies may have, prenatal diagnosis is essential. This allows determination of fetal karyotype, and counseling regarding pregnancy options, including determination of the need to deliver at a tertiary care center.

**STUDY DESIGN:** We undertook a retrospective review of records obtained from the ultrasound database of the Perinatal Diagnostic Center at Baystate Medical Center. We identified all patients with singleton pregnancies who received a detailed anatomy survey performed by a perinatologist between 16 to 20 weeks of gestation with a subsequent fetal echocardiogram, in the time period from November 2001 to July 2005. Inclusion criteria included (1) fetal anatomy surveys with adequate and normal fetal cardiac imaging of the 4-chamber view and the outflow tracts, and (2) delivery at Baystate Medical Center. These records were then compared with the hospital discharge database of newborns with a discharge diagnosis of a congenital cardiac defect. Patent foramen ovale and patent ductus arteriosus were excluded from analysis since these conditions cannot be diagnosed prenatally.

**RESULTS:** A total of 220 patients had complete data and met the criteria of satisfactory and normal cardiac views on detailed fetal ultrasound with a subsequent fetal echocardiogram performed. All 220 patients had also normal heart views on the fetal echocardiogram. At that time of discharge only one neonate was diagnosed with a heart defect. This child was diagnosed with a left ventricular outflow tract obstruction (Shone's complex).

**CONCLUSION:** Fetal echocardiography does not increase the yield for major cardiac anomalies after a normal detailed fetal anatomy survey performed by a perinatologist.

**Androgen Regulation of Key Hox Genes in Murine Lung Development**

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Androgens (DHT) delay alveolar maturation but enhance airway branching and cell proliferation. In other organs, DHT interacts with Hox transcription factors and TGFβ-SMAD pathways. Hoxb5 and Hoxa5 have dynamic spatial and cellular expression patterns in developing lung indicating distinct regulatory roles in airway branching and alveolar maturation. Hox/TGFβ/SMAD interactions in lung development have not been studied.

**Objective**: Test the hypothesis that DHT alters Hoxb5 and Hoxa5 expression patterns and modulates TGFβ-mediated SMAD protein expression in lung development.

Methods: *In vivo*: pregnant mice received DHT (2mg/day) by implants at E11 or were treated as sham. Male and female E18 fetal lungs were isolated and prepared for immunostaining or Western blots. *In vitro*: E12 mouse lungs were cultured (72 hrs) with/without DHT ($10^{-8}$M). Hoxb5, Hoxa5, SMAD2 and SMAD7 expression was analyzed by Western blot. Coronal lung sections from *in vivo* and *in vitro* experiments were immunostained for Hoxb5, Hoxa5 and PCNA.

**Results**: DHT treated lungs had densely packed terminal bronchioles and less developed terminal sacs typical of earlier lung development. Hoxb5 staining was more intense in mesenchyme with loss of normal central < peripheral expression gradient. Conversely, Hoxa5 mesenchymal staining was unchanged but cuboidal epithelium was more intensely positive. In vivo and in vitro DHT increased epithelial PCNA expression. In vivo DHT increased Hoxb5 protein levels 3 fold in female lungs but did not alter Hoxa5 levels. SMAD7 protein levels increased 40% in DHT-treated female lungs but phosphorylated and total SMAD2 were unchanged.

**Conclusion**: Androgen exposure throughout lung development differentially regulates cellular expression of Hoxb5 and Hoxa5 and modulates androgen-TGFβ interactions by increasing inhibitory SMAD 7. We speculate that androgen-TGFβ interactions in lung development are modulated by Hoxb5 alteration of inhibitory SMAD7.

# CELL FREE FETAL DNA IN MATERNAL CIRCULATION AFTER CHORIONIC VILLUS SAMPLING

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OBJECTIVE Cell free fetal DNA (cff DNA) in maternal circulation is a result of apoptosis of fetal and placental cells. The goal of this study was to determine if chorionic villus sampling (CVS) causes apoptosis as measured by levels of cff DNA before and after the procedure.

STUDY DESIGN Thirty seven pregnant women (10 5/7 to 13 2/7 weeks) were recruited prior to CVS done for a variety of indications. Using ultrasound guidance, transabdominal CVS was performed once with a 20 gauge needle. Maternal peripheral blood was collected before and within 15 minutes after CVS. Cff DNA was extracted from plasma; GAPDH amplification was used to show presence of DNA. DYS 1 was used as a marker for male fetuses, and measured by real time quantitative PCR. We analyzed all samples in triplicate. Analysis was blinded.

RESULTS Twenty six fetuses were male; eleven were female. DYS 1 amplification was undetectable in all female fetuses. Sensitivity and specificity of male fetal DNA detection using DYS 1 was 100%. In male fetuses, the mean concentration of the DYS 1 gene was 8.30 genome equivalents (GE)/mL (range, 1.16 to 122 GE/mL) before CVS and 9.68 GE/mL (range, 1.05 to 67.3 GE/mL) after CVS (P = 0.45). Results were not affected by gestational age. Post-procedure, there were no consistent trends. In some patients, cff DNA levels increased. In others, levels decreased, and some stayed the same.

CONCLUSION There was no statistically significant increase in cff DNA levels after CVS. Variability in trends between patients suggests that specific factors affect the extent of apoptosis and DNA trafficking post-procedure. These factors merit further study.

# Mechanical Stretch Releases EGFR Ligands in Fetal Type II Epithelial Cells

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Mechanical forces generated inside the fetal lung by constant distention pressure and intermittent breathing-like movements are critical for normal lung organogenesis. However, the mechanisms by which stretch promotes lung development are not well defined. We hypothesized that mechanical stretch promotes fetal type II cell differentiation via release of membrane-anchored EGFR ligands. Fetal rat lungs type II cells were isolated at E19 of gestation and cultured on silastic membranes precoated with laminin. Monolayers were incubated with several rEGFR ligands. Fetal type II cell differentiation was assessed by surfactant protein B/C (SP-B/C) mRNA and protein levels. Type II cells were also transfected by electroporation with cDNA constructs encoding alkaline phosphatase (AP)-EGFR ligand fusion proteins. Monolayers were then exposed to different mechanical stretch protocols using the Flexercell Strain Apparatus. Analysis and quantification of ligands shedding were performed by measuring AP activity in the supernatant. Incubation of E19 cells with rHB-EGF or TGF-α for 16h increased SP-B/C mRNA and protein levels. Cyclic stretch released HB-EGF and TGF-α into the supernatant. This effect was modest with 2.5% stretch (by 2-fold) and progressively increased with higher magnitudes of stretch (6-fold with 5%, 8-fold with 10% and 10-fold with 15%). Shedding of these ligands peaked within 1h of initiation of stretch in cells exposed up to 10% stretch and by 4-6h in those subjected to 15% stretch. Surprisingly, 2.5%, 5% or 10% continuous stretch did not consistently released EGFR ligands. HB-EGF and TGF-α ligands promoted type II cell differentiation. Cyclic mechanical stretch is a potent stimulus for EGFR ligands release. The magnitude of shedding varies depending on ligand, timing and stretch protocols. These studies may be relevant not only to lung development but also to mechanical ventilation-induced lung injury.

**Prenatal Sonographic Diagnosis of Hemivertebra—Associations and Outcomes.**

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**Objective:** To evaluate associated anomalies and outcomes of fetuses with prenatally-diagnosed hemivertebra. **Methods:** Fetuses with prenatally-diagnosed hemivertebra were identified by searching the prospectively maintained ultrasound databases of 4 institutions from 1997-2007. We excluded cases associated with spina bifida. Sonographic data included gestational age at diagnosis, hemivertebra location, and coexisting anomalies. Associated birth defects were tabulated by organ system and hemivertebra location. Outcomes included karyotype, gestational age, route and outcome of delivery. **Results:** Eighteen fetuses were diagnosed with hemivertebra at a mean gestational age of 21.0 ± 5.2 weeks. Thirteen (72.2%) fetuses had additional anomalies, including 7/10 (70%) with thoracic and 6/8 (75%) with lumbar hemivertebra. Additional anomalies are noted in the table. Of the fetuses with other anomalies 4 (30.7%) were syndromic (cloacal exstrophy n=3, Jarcho Levin n=1). Karyotypes were available and normal in 10 cases, each of which exhibited additional anomalies. Twelve (66.7%) offspring were liveborn at a mean gestational age of 34.4 ± 4.4 weeks, of which 7 (58.3%) delivered by cesarean section. Nine (75%) delivered preterm infants and 3 (25%) were growth restricted (<10$^{th}$ percentile). Two (16.7%) of these neonates died; both had cloacal exstrophy and large omphaloceles. The remaining pregnancies were terminated (n=3, 16.6%), had a fetal death (n=1, 5.5%), or remain undelivered (n=2, 11.1%). **Conclusions:** Most fetuses with prenatally diagnosed hemivertebra have additional anomalies, often syndromic, which impact prognosis. Affected pregnancies often experience prematurity, growth restriction, and cesarean delivery.

Table. Additional anomalies by organ system.

| Organ System | Affected Fetuses (n) |
|---|---|
| Cardiovascular | 7 |
| Genitourinary | 5 |
| Skeletal | 5 |
| Central Nervous System | 3 |
| Gastrointestinal | 3 |
| Other | 3 |

**Pregnancy following gastric bypass for morbid obesity: maternal and neonatal outcomes.**

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**Objective:** Over half of the 100,000 bariatric surgical procedures performed in the United States annually are on reproductive-aged women. Since the most common operation is Roux-en-Y gastric bypass (RYGB), we sought to compare pregnancy and neonatal outcomes after maternal RYGB to those in women without bariatric surgery.

**Methods:** Thirty-eight women with RYGB (cases) were matched for maternal age (< 35 or ≥ 35 years old) and prior cesarean to the next 2 consecutive women delivering without prior bariatric surgery (controls). We compared pregnancy and neonatal outcomes of cases and controls. Outcomes approaching or reaching statistical significance by univariate analysis were evaluated by conditional logistic regression accounting for matching variables and controlling for maternal body mass index (BMI).

**Results:** Despite RYGB, cases were significantly heavier than controls (BMI 33.4 ± 7.3 vs. 28.1 ± 6.7, p<.001) and more likely to be obese (BMI ≥ 30; n=26 vs. n=20, p<.001). Cases and controls had similar rates of preterm labor (7.9% vs. 5.3%), delivery < 37 weeks (26.3% vs. 22.4%), delivery <32 weeks (7.9% vs. 6.6%), gestational diabetes (5.3% vs. 4.0%), labor induction (19.4% vs. 18.4%), and primary cesarean (15.8% vs. 14.5%). Neonatal outcomes were similar among cases and controls, including birthweight <10% (7.7% vs. 9.0%), birthweight ≥ 4500g (0% vs. 2.6%), 5 minute Apgar <7 (2.6% vs. 0%), NICU admission (21.1% vs. 18.9%), and congenital anomalies (0% vs. 5.1%). No significant differences were found by logistic regression (table).

Table. Outcomes in gastric bypass patients and controls by conditional logistic regression.

| Outcome | Crude OR (95% CI) | Adjusted* OR (95% CI) |
|---|---|---|
| Hypertension | 3.6 (1.36, 9.92) | 2.62 (0.66, 10.50) |
| PPROM | 0.33 (0.04, 2.77) | 0.24 (0.02, 3.38) |
| Oligohydramnios | 2.00 (0.65, 6.20) | 2.39 (0.66, 8.61) |
| Gestational age ≥ 41 weeks | 0.50 (0.11, 2.36) | 0.57 (0.11, 2.97) |

*adjusted for BMI at delivery

**Conclusion:** Obstetric and neonatal outcomes in women with RYGB are similar to those of our general obstetric population.

# PLACENTAL PATHOLOGY AND NEONATAL IMPLICATIONS

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Most descriptions of placental disease have concentrated on structural abnormalities that affect the maternal circulation (uteroplacental insufficiency). Only recently has attention been focused on lesions affecting the fetal vascular supply.

We describe the neonatal complications in two newborn infants whose placentae demonstrated thrombosis in the fetal circulation. In both cases, the mothers presented with a 3 day-histories of decreased fetal movements. The first patient, a male born at 33 weeks gestation, presented with thrombocytopenia and disseminated intravascular coagulation requiring several platelets and plasma transfusions. No identifiable neurological involvement was found. His placenta demonstrated classical fetal thrombotic vasculopathy. The second patient, a female born at 27 weeks gestation, also presented with relative thrombocytopenia and a mild coagulopathy, requiring one plasma transfusion for correction. Unlike the first case, this infant had extended bilateral extended hemorrhagic venous infarctions seen on both sonogram and MR imaging. Her placenta demonstrated fetal vascular thrombosis, but did not meet all the criteria for fetal thrombotic vasculopathy.

Severe fetal placental vascular lesions place fetuses at risk for injury, especially brain injury, during the intrapartum period**.** These cases illustrate why the placenta of preterm neonates should always be examined, especially in those patients who present with thrombo-embolic events of unknown origin. A systematic review of such cases may reveal a gestational age continuum between fetal placental thrombosis and fetal thrombotic vasculopathy.

**Early Advance of Enteral Feeds May Protect Against Parenteral Nutrition-Associated Conjugated Hyperbilirubinemia In Infants <1500 Grams At Birth**

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**Background:** Infants <1500 g at birth (VLBW) exposed to parenteral nutrition (PN) may or may not develop conjugated hyperbilirubinemia (CH). **Objective:** To compare concentration of PN components, PN administration, feeding practices, and other modifiable risk factors in the 1st 28 d of life in PN-exposed VLBW infants with and without CH. **Design/Methods:** We performed a single-center case-control study comparing VLBW infants born 2000-2005 with PN-associated CH (direct bilirubin ≥2 mg/dL) to infants without CH matched for gestational age and days of PN exposure. Univariate and multivariate hierarchical regression were used to identify factors associated with development of CH. **Results:** Overall gestational age for the study cohort was 28 ± 2 wk, birth weight 1005 ± 230 g, PN exposure 28 ± 7 d. There were no significant differences between 41 cases (peak CH 4.3 ± 2 mg/dL, range 2-9.1 mg/dL) and 82 controls regarding initial illness severity scores, duration of mechanical ventilation, incidence of SGA, RDS, PDA, IVH, NEC prior to CH (or equivalent age in controls), or positive blood or urine culture prior to CH or equivalent age. The 2 groups were similar with respect to age at initiation of PN, as well as concentration and advance of PN amino acids, lipid, dextrose, trace metals, and carnitine. There was no significant difference in age at start of enteral intake or use of breast milk. However, compared to controls, infants with CH had significantly less enteral intake at 10, 14, and 21 d of age (Figure). **Conclusions:** In this single-center study, enteral intake was advanced more slowly in PN-exposed VLBW infants developing CH than in similar infants without CH. Enteral advance was not associated with illness severity or early complications of prematurity. Variation in medical practice and/or mild feeding intolerance may account for these results. Early successful advance of enteral feeds may protect against PN-associated CH in VLBW infants independently of days of PN exposure.