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Obstructed hemivagina with ipsilateral renal anomaly, OHVIRA syndrome with urogenital sinus: Neonatal presentation of an extremely rare complex variant

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INTRODUCTION: Herlyn-Werner-Wunderlich syndrome, also known as OHVIRA, is described by the classic triad of uterine didelphys, obstructed hemivagina and ipsilateral renal agenesis. Usually undiagnosed in childhood, the syndrome may manifest around the age of menarche with vague pelvic pain or may be detected during evaluation for infertility.

METHODS: We report the case of a late preterm neonate who developed recurrent resistant *E. coli* urinary tract infections (UTI) despite being on antibiotic prophylaxis. We discuss the findings of pelvic sonography, magnetic resonance imaging (MRI) of pelvis and intra-operative fluoroscopy that helped to identify the complex structural urogenital anomaly and review the literature.

RESULTS: The neonatal screening of a late preterm birth with the background of antenatally diagnosed left hydronephrosis and absent right kidney, revealed clitoromegaly and a translucent vulval prominence. The abdominal sonography and MRI revealed uterus didelphys, obstructed left hemivagina with left hydronephrosis and crossed fused ectopia of right dysplastic kidney and poorly visualized ureters and urinary bladder. Recurrent UTI ensued and repeat sonography revealed a heterogeneous cystic structure in the pelvis due to hematometra and hematocolpos in addition to the other urogenital anomalies. Cystoscopy and intra-operative fluoroscopy confirmed the presence of a urogenital sinus with a common urogenital opening.

CONCLUSION: The spectrum of OHVIRA syndrome complicated with urogenital sinus or other developmental malformations is extremely rare. MRI plays an essential role to overcome the diagnostic and management challenges.

Keywords: OHVIRA syndrome, crossed fused ectopia, urogenital sinus, neonatal onset, UTI, MRI

Evaluation of ultrasound-guided central line insertion in preterm neonates: A prospective study

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INTRODUCTION: Among preterm neonates, PICC is the standard line insertion procedure used, however it places neonates at risk of hypothermia and discomfort. Newer techniques such as Ultrasound-guided central line insertion technique might be less invasive with less morbidity. We evaluate the ease of use, success and morbidity rate of Ultrasound-guided catheterization of internal jugular vein (US-IJV) in preterm neonates by comparing it to standard techniques of blind PICC.

METHODS: This is a prospective randomized quasi-experimental study of neonates admitted to Saint George University Hospital between October 2013 and June 2014. Neonates were assigned into 2 groups; the control group underwent peripheral blind Epicutaneo-cava-catheter (ECC) insertion (PICC); while the intervention group had an ultrasound-guided percutaneous insertion of the ECC in the internal jugular vein (US-IJV). Success in first attempt, malpositioning of the catheter, incidence of per and postoperative complications, duration of catheterization and number of attempts until successful insertion were compared between the two groups.

RESULTS: A total of 50 eligible neonates were enrolled in the study. The US-IJV insertion showed higher rates of successful first attempt (P -value <0.001), successful insertion (P -value = 0.001), less procedure duration (P -value <0.001) and less number of trials (P -value <0.001) compared to PICC with no difference in complications (P -value = 1.000).

CONCLUSION: Our results show that US-IJV insertion technique is faster than PICC with higher success rate among preterm neonates.

Keywords: Ultrasound, central line, preterm neonates, internal jugular vein, PICC

tCAN Syndrome (tight cord around the neck syndrome)

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INTRODUCTION: Cord compression due to Nuchal cord, can cause obstruction of blood flow in thin walled umbilical vein, while blood continues to be pumped out through the thicker walled umbilical artery causing blood loss, acidemia and respiratory distress, dusky face, and petechiae which is akin to adult non-lethal strangulation.

METHODS: Literature searched on nuchal cords to compile into a possible syndrome called tCAN syndrome (Tight Cord Around Neck Syndrome). We defined tCAN syndrome as “A cluster of Cardio-Respiratory and Neurological signs and symptoms associated with unique physical features that occur secondary to tight cord around the neck”. Based on this definition, literature was searched systematically and found the data to group them into one syndrome.

RESULTS: Literature search revealed, tight nuchal cord babies have physical features, including facial duskiness, skin abrasion of neck, facial suffusion, petechiae, subconjunctival hemorrhage, pallor of body, cardio-respiratory disturbances and neurological signs such as hypotonia as a result of tight nuchal cord. Possible grading based on severity of tightness of nuchal cord include: Grade1- conjunctival hemorrhage and petechiae, Grade2- duskiness of face, facial suffusion and pallor, Grade3 - pressure on airway and suffocation (chest compression), respiratory distress and with or without pneumothorax/pneumomediastinum, and Grade4- stupor and hypotonia.

CONCLUSION: Tight Nuchal Cord is similar in pathophysiology to non-lethal adult strangulation. Fundoscopy, EEG and otoscope may play a role. Brain pathology and possible hyoid bone fractures in tight Nuchal cords babies and long-term neurodevelopmental problems needs exploring. Adult terminology “Compressional Asphyxia” may be applied to tCAN babies.

Keywords: Nuchal cord, non-lethal strangulation, tight nuchal cord syndrome

Changing patterns of surfactant use in very low birth weight (VLBW) infants over two decades in L'viv Regional Clinical Hospital, Ukraine

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INTRODUCTION: Surfactant therapy became available in Ukraine in 1996 simultaneously with the development of regionalization and implementation of modern neonatal care. Since that time international recommendations for surfactant use have changed several times. The aim of the study was to evaluate changes in surfactant use and compare relative clinical outcomes.

METHODS: This was a retrospective study of outborn VLBW babies admitted to the Neonatal Intensive Care Unit at L'viv Regional Clinical Hospital in 2013-2014, compared with similar cohorts from 2011-2012, 2008-2010, 2000-2002, and 1997-1999. Data collected included gestational age, birth weight, antenatal steroid use, numbers receiving surfactant, timing of first dose, dose given, duration of mechanical ventilation, oxygen supplementation, oxygen dependency at 36 weeks, length of hospital stay and mortality.

RESULTS: There were 310 admissions from 1997-1999, 269 from 2000-2002, 602 from 2008-2010, 401 from 2011-2012, and 437 from 2013-2014. Infant's age on admission decreased ($P < 0.001$) and use of antenatal steroids and surfactant increased from 8.71% and 3.23% (1997-1999) to 61.33% and 38.05% (2013-2014) respectively ($P < 0.001$). A median (IQR) time of surfactant administration decreased from 10 (4-24) hours to 5 (2-8) hours. Newborns admitted in 2008-2014 were significantly smaller and of lower gestational age. Overall mortality was 27% (1997-1999) compared with 24% (2008-2010) and 27% (2013-2014) ($p > 0.05$). BPD rate increased from 2.9% (1997-1999) to 16.67% (2013-2004) ($P < 0.001$). Regional neonatal and infant mortality have significantly decreased since 1997.

CONCLUSION: Modern standards of surfactant therapy have not been completely implemented in our clinical settings leaving an important opportunity for improvement.

Keywords: Surfactant therapy, very low birth weight infants, clinical outcomes

Retinopathy of prematurity in relationship to serum apelin concentration

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INTRODUCTION: Retinopathy of prematurity (ROP) is a disorder affecting the retina of the premature infants. The survival rate of premature infants has increased due to the advances in care taken and therefore the incidence of long term ocular problems has increased. The aim of the study was to evaluate the role of serum apelin as a diagnostic tool in retinopathy of prematurity disease.

METHODS: A prospective case-control study was conducted on patient group: 35 preterm neonates below 37 week and had ROP. Control group: 35 preterm neonates without retinopathy for comparing. History, examinations and fundus examination were done. The first fundus examination was done at 4-6 weeks postnatal age. Blood samples were obtained twice; at birth and after 4-6 weeks for testing the serum level of apelin.

RESULTS: No statistically significant difference between groups regarding apelin at birth but there is a statistically significant difference between groups regarding apelin at time of diagnosis. The best cut off value of apelin at birth and after 4-6 weeks are 2.18 ng/mL and 2.7 ng/mL, respectively.

CONCLUSION: Serum apelin at time of diagnosis of the disease (4-6 weeks) was significantly lower than those in the control groups, while the basal serum apelin levels were similar in both groups at birth.

Keywords: Preterm, retinopathy, apelin

Antenatal and perinatal risk factors for high grade intraventricular hemorrhage: A 10 – year retrospective review of very low birthweight infants in Singapore General Hospital

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INTRODUCTION: Identification of risk factors for high grade IVH (Grade 3 and 4) is very important in the survival of premature infants.

METHODS: Out of 573 VLBW preterm infants, 50(8.7%) infants with low grade IVH (Grade 1 and 2), 38(6.6%) infants with high grade IVH (grade 3 or 4), 485(84.6%) infants has no IVH, were identified from January 2002 to Dec 2012. Maternal and neonatal factors, labor and delivery characteristics, as well as results of cranial ultrasound examinations were collected.

RESULTS: The following variables increase the risk of having high grade IVH using the One-way ANOVA for the continuous variables and the Chi-square/Fischer exact test: Male gender (P -value <0.024), maternal pyrexia, low Apgar score, low birthweight, low gestational age, high FiO₂, high MAP, hypotension requiring inotropes, HMD, pulmonary hemorrhage, PDA, hypoglycemia requiring increase in total fluid intake and air leak ($P < 0.001$). Antenatal steroid decreases the risk of IVH with a P -value 0.02. Multivariate logistic regression showed that the following factors are associated with greater risk of high grade IVH occurrence compared to a combined low grade IVH and No IVH : Male (adjusted OR 1.73; 95% CI: 1.73 - 1.03; P -value 0.04), High FiO₂ (adjusted OR 1.02; 95% CI: 1.01-1.03 P -Value 0.0001), pulmonary haemorrhage (adjusted OR 2.98; 95% CI: 1.09-7.78; P -Value <0.028) and hypoglycaemia requiring increase in total fluid intake (adjusted OR 2.34; 95% CI : 1.36-4.02; P -Value <0.002).

CONCLUSION: Prevention and timely treatment of described factors crucial in prevention of higher grade IVH are very important.

Keywords: IVH, high grade IVH, antenatal and perinatal risk factors in Singapore, Antenatal and perinatal risk factors

Non-invasive inhaled nitric oxide for persistent pulmonary hypertension of the newborn: A single center experience

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INTRODUCTION: Nitric oxide is a potent, selective pulmonary vasodilator that has been proven to decrease pulmonary vascular resistance and has been part of the treatment arsenal for persistent pulmonary hypertension of the newborn (PPHN). In 2009, the approach to the administration of inhaled nitric oxide (iNO) at Winnie Palmer Hospital for Women and Babies changed to emphasize avoiding invasive ventilation while maintaining optimal ventilation to perfusion ratio, avoiding hyperventilation and alkalosis agents, and avoiding hyperoxemia and hyperoxia exposure. Our aim is to describe the outcomes of babies whose primary treatment for PPHN was noninvasive (NIV) iNO.

METHODS: A retrospective chart review of inborn infants from October 1, 2009 through October 1, 2014 was conducted. Inclusion criteria: >34 weeks gestational age, echocardiographic evidence of PPHN within the first week of life, and NIV iNO as the primary treatment.

RESULTS: Twenty-four babies met criteria; of them 21 solely treated non-invasively and 3 required invasive support. Supplemental oxygen need was $\geq 50\%$ for 21 babies pre-iNO treatment and dropped to $<30\%$ for all babies post-iNO. Average exposure to supplemental oxygen was 6.3 days. Mean duration of iNO administration was 3 days. Average length of stay was 14 days. All babies survived.

CONCLUSION: Our review revealed a low incidence of escalation to invasive ventilation. Non-invasive iNO was found to be an effective and well-tolerated frontline approach for treating PPHN in near-term and term infants with an intact respiratory drive. Further studies could provide the necessary evidence on clinical outcomes as well as cost effectiveness to guide best practice.

Keywords: Persistent pulmonary hypertension of the newborn, inhaled nitric oxide, non-invasive

Oral administration of *Bifidobacterium bifidum* stimulates intestinal sIgA secretion in low birth weight infants

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INTRODUCTION: Low birth weight (LBW) infants have many risks such as IVH, PVL, CLD, NEC, and sepsis after birth. Previous reports described the decline in the incidence of late-onset sepsis following oral *Bifidobacterium bifidum* OLB6378 (OLB6378) administration. This strain stimulated the production of IgA in murine Peyer's patch *in vitro*. Therefore, we evaluated the stimulation of IgA production by oral administration of either viable or heat-treated OLB6378 in LBW infants.

METHODS: LBW infants (within 48 h after birth) were randomly divided into three groups; L group ($n=30$, given viable OLB6378; approximately 2.5×10^9 cells/day), H group ($n=30$, given heat-treated OLB6378; approximately 2.5×10^9 cells/day), and N group ($n=27$, no OLB6378 administered). Twice daily oral administration of OLB6378 to infants was employed throughout this study. The feces were collected at 0, 1, 2 and 6 months of age, and fecal IgA concentration was measured using a commercial ELISA kit.

RESULTS: Birth weight of neonates and gestation period did not differ between the groups. The fecal IgA concentration was significantly larger in the H group than in the L and N groups at 1 month of age. This finding was also seen at 2 months of age, but became less apparent at 6 months of age.

CONCLUSION: Oral administration of OLB6378 stimulated intestinal IgA secretion in infants. This stimulation was especially remarkable in that the heat-treated OLB6378 group showed significantly more stimulation than the viable OLB6378 group.

Keywords: *Bifidobacterium bifidum*, IgA, low birth weight infants

Epigenetic changes are detected only 7 days after preterm birth - preliminary results of the EpiPrem Study

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INTRODUCTION: Once preterm babies are born, they have to undergo numerous medical interventions to survive. The EpiPrem Study investigates the effects of preterm birth and these medical interventions on the epigenome.

METHODS: Recruitment for the EpiPrem Study started in 2014; as part of the study, whole blood spots are obtained from preterm babies (<32 weeks) at birth (D0), the next day (D1) and at 7 days of age (D7). Genomic DNA is isolated, bisulfite converted and analyzed using the Illumina 450K Human Methylation Array to investigate the methylation state at over 450,000 sites throughout the genome.

RESULTS: On preliminary analysis of DNA from 5 preterm infants, we found 2001 differentially methylated probes (DMPs) between D0 and D7 with $P < 0.05$ when applying a moderated t -statistic with adjustment for multiple testing. There were no DMPs detected after one day of life. Details of the D7 methylation changes and how the DMPs relate to probes and gene locations previously reported to be relevant for human gestation, parturition, prematurity and diseases related to preterm birth are presented.

CONCLUSION: The epigenome of preterm babies changes within a few days after birth. Cell type heterogeneity may contribute to our results and its potential effects are being explored. Our study is ongoing and, of course, much larger proband numbers will be needed and DMPs will need to be verified. Our long term vision is identification of early biomarkers for outcome and development of tools allowing identification and thus minimization of adverse epigenetic effects of neonatal therapies.

Keywords: Epigenetics, preterm birth

Implementation of 5S methodology for quality improvement in a neonatal intensive care unit

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INTRODUCTION: The Stollery Children's Hospital Neonatal Intensive Care Unit (NICU) at the Royal Alexandra Hospital is the referral center for high-risk deliveries, for northern and central Alberta as well as the Northwest Territories. Approximately 1200 patients are admitted yearly to this 69-bed NICU.

The Alberta Health Services (AHS) Human Factors Team has specialized training in studying how health care teams work. They design processes and/or equipment to facilitate the provision of high quality care with the goal of improving patient safety and process efficiency.

5S methodology is used in the creation and maintenance of a clean, organized, and efficient work space.

METHODS: The Human Factors Team evaluated the clean preparation areas of the NICU, including physical space and processes. Based on their recommendations, a plan for revision of the designated work spaces was created. Minimal construction and supplies were required. An interdisciplinary team of front-line staff was recruited to assist with the plan's execution. All team members received training in 5S methodology, followed closely by a Kaizen event¹ during which the work was completed. The total time for the project was six hours. Audits of the work spaces are completed weekly.

RESULTS: The clean preparation areas have distinct areas for medication and feed preparation, designated "parking spots" for frequently used items, and specific quotas for stocked supplies. Regular audits demonstrate compliance at 88%.

CONCLUSION: Implementation of 5S methodology in the NICU has improved nursing work flow in preparation areas, and reduced the risk of infection and cross contamination, thus positively impacting patient safety.

Keywords: NICU, human factors, 5S, process efficiency, patient safety

¹A Kaizen event is defined as a plan which is executed from the brainstorming stage through to completion within a small period of time. It is based on Plan-Do-Check-Act (PDCA) cycles.

Regional lung ventilation pattern in preschool children with bronchopulmonary dysplasia is modified by bronchodilator response regardless of history of wheezing

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INTRODUCTION: Regional lung ventilation in children with bronchopulmonary dysplasia has not been precisely described. Aim of this study was to assess whether bronchodilator response (BDR) modifies regional lung function in a cohort of preschool VLBW children.

METHODS: Electrical impedance segmentography (EIS) was measured in a group of VLBW children at the age of four ($n=45$; gestational age = $28,3 \pm 2,3$ weeks; 51% boys) with history of BPD ($n=28$, gestational age = $27,1 \pm 1,9$ weeks; 60,1% boys) and without BPD ($n=17$, gestational age = $30,1 \pm 1,4$ weeks; 35% boys) before and 15 minutes after salbutamol inhalation (400ug, pMDI and spacer). BPD was defined as oxygen demand at the age of 28 days. Impedance was measured during spontaneous tidal breathing in upright position using Angelie EIS System (EMS Biomedical, Austria). Results were expressed as the difference of mean segmental impedance amplitude and ventilation inhomogeneity index (*II*) in four lung segments (upper left [UL], upper right [UR], lower left [LL], lower right [LR]).

RESULTS: Significant increase in mean impedance amplitude in both upper segments (520 ± 264 vs. 678 ± 388 ; +30,3%; $p=0,002$; UR: 605 ± 348 vs. 806 ± 497 ; +33%; $p=0,002$) and lower left segment (593 ± 294 vs. 687 ± 318 ; +16%) was observed after salbutamol in children with BPD. There was no change in non-BPD children. There was no relationship between BDR and history of wheezing, frequent respiratory tract infections or daycare attendance. There was no correlation between BDR and length of mechanical ventilation in the NICU.

CONCLUSION: Breath amplitude and regional ventilation inhomogeneity in gravity non-dependent lung regions increase after salbutamol in children with BPD, but not in children without BPD.

Keywords: Electrical impedance segmentography, preterm, bronchopulmonary dysplasia, follow-up

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Comparison of the effects of two natural surfactants on cerebral, renal and mesenteric tissue oxygenation in extremely preterm infants

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INTRODUCTION: Although surfactant improves systemic oxygenation, there is very limited data about its' effects on cerebral tissue oxygenation. The aim of this prospective study was to compare the effects of two natural surfactants on cerebral, renal and mesenteric oxygenation in preterm infants with respiratory distress syndrome (RDS).

METHODS: This study was performed in extremely preterm infants (≤ 28 weeks of gestation and/or ≤ 1000 g) who were admitted to NICU with RDS and given surfactant as early rescue treatment. Infants were randomized into two groups (poractant of 200 mg vs. beractant of 100 mg per kg). Near-infrared spectroscopy was used for determination of tissue oxygenation. It was recorded for the first 24 hours of life.

RESULTS: Two groups were similar in terms of demographic features. The oxygenation of the cerebral, renal and mesenteric tissues showed an increase just after surfactant administration. Although the oxygenation of the cerebral renal and mesenteric tissues were higher at 1 hour of surfactant on beractant group, this was not statistically significant ($p > 0.05$). The oxygenation of the cranial and renal tissues were also higher at 4, 6, and 24 hours on beractant group, this was not statistically significant ($p > 0.05$).

CONCLUSION: Although both surfactants improved oxygenation just after administration in cerebral, renal and mesenteric tissues, there were no significant differences between two surfactant groups in terms of tissue oxygenation at 1, 4, 6 and 24 hours. This is the first study showing the effects of different surfactants on cerebral, renal and mesenteric tissue oxygenation.

Gastric aspirate, a novel source to estimate respiratory epithelia gene expression in the newborn

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INTRODUCTION: Two of the most common respiratory disorders in the human newborn, respiratory distress syndrome and transient tachypnea, have been associated to changes in gene expression of aquaporin-5 (AQP5) and β subunit of the epithelial sodium channel (β -ENaC). The aim of this observational, proof-of-concept, cross-sectional study was to determine gene expression of AQP5 and of β -ENaC in exfoliated respiratory epithelial cells contained in the gastric aspirate, and to compare the values with those found in scraped nasal epithelial cells, which have been validated as a surrogate of distal lung epithelia.

METHODS: We recruited term neonates born after uneventful pregnancies either by vaginal or elective abdominal delivery. Recorded maternal data: age, gestational age, presence of gestational diabetes and blood group. Newborn data: birth weight, gender, method of delivery, relative gene expression of AQP5 and β -ENaC, presence of sample contamination with blood and/or meconium and rate of adverse effects. Protocol approved by institutional review boards.

RESULTS: In this sample of term neonates, AQP5 mean expression detected in gastric aspirate was significantly better than the levels in nasal mucosa, while no difference was observed for the mean expression levels of β -ENaC.

CONCLUSION: It is feasible to identify and quantitate the expression of AQP5 and of β -ENaC in the gastric aspirate, obtained shortly after birth from term newborns, the rate of gene expression observed in gastric aspirate samples is better than that found in scraped nasal epithelial cells. Our data confirms previous observations in regard to greater β -ENaC activity in those babies delivered vaginally.

Keywords: Aquaporin 5, epithelial sodium channels, infant, newborn, gastric lavage/utilization

Structured neonatal physiotherapy intervention and its effect on neuromotor development of preterm infants at follow up

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INTRODUCTION: Moderate to late preterm infants contribute to more than 80% of total preterm births in United States. Literature has provided substantial evidence that these infants being metabolically and physiologically unstable are at risk of developing adverse short term and long term outcomes. Thus the aim of the present study was to provide developmental care interventions during the crucial Neonatal Intensive Care Unit (NICU) period to promote optimum development.

METHODS: Study was approved by institutional ethical committee (IEC), Manipal University. Based on inclusion criteria, twenty six infants born between 32^{0/7} weeks and 36^{6/7} weeks were recruited. Written informed consent was taken from parents. Allocation to control and experimental group was done through block randomization. Control group continued to receive standard care whereas experimental group underwent treatment based on American Physical Therapy recommendations (joint range of motion exercise, joint compressions, self-calming activities, visual stimulation using black and white cards, massage, vestibular stimulation, positioning, swaddling, music therapy) for a period of 15 sessions during their NICU stay. Infants were reassessed for their developmental status at 3 month follow up using Bayley Scale of Infant & Toddler Development- III edition (BSID-III).

RESULTS: A total of 26 infants (13 intervention; 13 control) were analyzed for cognitive, language and motor domains of BSID-III. Raw scores were converted into scaled scores and independent t test was used to find the difference between control and intervention group. Cognitive scaled scores (0.004) and motor scaled scores (0.02) showed statistically significant difference, however language domain (0.06) results were found to be insignificant.

CONCLUSION: Present study suggests physical therapy intervention provided during NICU stay can support better development of moderate to late preterm infants and even the effects are carried over at 3 month follow up.

Keywords: Neonatal physiotherapy, development, Bayley scale, preterm, follow up