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APGAR SCORES PREDICT SHORT-TERM OUTCOME IN INFANTS BORN AT 25 WEEKS GESTATION

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Background: Several scoring systems have been developed for assessing the condition of the newborn infant at birth and for predicting mortality and morbidity. Apgar scores are generally used for evaluation of preterm infants although their predictive value has been debated.

Aim: To investigate whether Apgar scores and the clinical risk index for babies (CRIB) can predict short-term outcome in extremely preterm infants cared for with an active management strategy. **Method:** Prospectively recorded data in a regional perinatal database were investigated for the time-period 1995–2001 (n= 108000 births). Short-term outcome variables included mortality and severe intracranial pathology (IVH grade 3–4 or cystic PVL). Ninety-two liveborn infants, and five stillborn infants, with gestational age 25+0 to 25+6 weeks were identified in the register. Ten infants died within the first week of life, and 10 died later. Among the non-survivors were three infants with congenital malformations. Seventy-two infants were alive at a postnatal age of 180 days, 6 of these infants had IVH grade 3–4 or PVL. Four of the surviving infants were excluded from further analysis due to inappropriate Apgar scores.

Results: Apgar scores at 1, 5 and 10 minutes were significantly correlated with survival without severe intracranial pathology (p=0.016, 0.003, and 0.003, respectively). The strongest model for predicting survival without severe intracranial pathology was created from 5-minute Apgar scores and the CRIB-score (p=0.000). Survival without severe intracranial pathology was higher in single versus multiple births (p=0.030), but was not associated with infant gender (p=0.407), or mode of delivery (p=0.479).

Conclusion: Apgar scores, already at 1 minute after birth, are highly predictive of outcome in extremely preterm infants with gestational age 25 weeks. The accuracy of the prediction of outcome increases when the Apgar scores are combined with CRIB-scores.

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GROWTH, MOTOR SKILLS AND INTELLECTUAL DEVELOPMENT BETWEEN 9 AND 15 YEARS OF AGE IN VERY LOW BIRTHWEIGHT CHILDREN AND CONTROLS

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Background: Few follow up studies of Very Low Birthweight (VLBW) children are conducted longitudinally. We have performed repeated follow up examinations of a cohort of VLBW children and their controls. At 9 years of age the VLBW children lagged behind in anthropometric measurements, but also in academic achievements. The aim of this study was to investigate whether the differences noted at 9 years persisted at 15 years of age.

Methods: This is a population based study including all surviving VLBW children (n=86) born during a 15 month period in 1987 to 1988 within the Southeast region of Sweden and normal birth weight controls (n=86). The following assessments and tests were performed: anthropometric measurements, state of puberty, motor skills (Bruininks-Oseretsky test), intellectual ability (Raven's matrices at 9 years, Wechsler Intelligence Scale for Children; WISC-III at 15 years of age), reading ability and word decoding skills.

Results: Three children with cerebral palsy (CP) were not included in the follow up study. Two children with CP participated. 62 VLBW children and 56 controls could be examined up to 15 years. *Growth:* There were no differences between VLBW- and control-groups at 15 years of age in stages of puberty. VLBW boys and girls were significantly shorter and lighter, whereas VLBW girls had smaller head circumference compared with controls at both ages. *Motor skills:* There were no significant difference between female VLBW and controls in total score of motor skills, whereas male VLBW children showed impaired motor skills compared to male controls. *Academic achievement tests:* There were significant differences for most tests at both 9 and 15 years of age. VLBW children improved their reading skills as much as the controls between these investigations. However, the differences between VLBW children and controls in the WISC test seemed to increase between 9 and 15 years of age, both in composite and subscales.

Conclusion: VLBW children differed significantly from controls in growth both at 9 and 15 years of age. Differences in intellectual ability seemed to increase with time.

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SURFACTANT LUNG LAVAGE AND INHALED NITRIC OXIDE IN THE TREATMENT OF MECONIUM ASPIRATION SYNDROME 2- INFLUENCE ON DURATION OF MECHANICAL VENTILATION, INHALATION OF NITRIC OXIDE, HOSPITALIZATION, AND COMPLICATIONS

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The most severe clinical problem which coexist with the meconium aspiration syndrome /MAS/ is persistent pulmonary hypertension /PPHN/. **The aim of our study** was to evaluate the efficacy of treatment of MAS for selected clinical parameters. The designed therapeutic approach consisted of surfactant lung lavage /SLL/ and surfactant instillation together with Nitric Oxide inhalation /iNO/. The study population was randomized into two groups: group A /n=7/ treated with SLL, surfactant instillation and iNO, and group B /n=6/ treated with surfactant instillation and iNO. Criteria for inclusion: maturity > 35 weeks of gestation, time after delivery < 24hours, presence of fluid containing meconium below vocal cords, respiratory insufficiency demanding mechanical ventilation /Fi0240%/, radiological changes, and echocardiographic features of pulmonary hypertension. **Method:** SLL was performed with natural surfactant solution (Survanta, Ross Abbott Laboratories) in concentration of 5mg of phospholipids/1 ml 0,9% NaCl, a dose of 15ml of solution per 1 kg. A dose of 100 mg of Surfactant per 1 kg was applied. The initial NO dose was 20 ppm. The parameters analyzed: duration of IMV, duration of iNO, duration of hospitalization, air leaks and deaths.

Results: (mean value ±b SD). Duration of IMV: GROUP A- 6,6±b 2,5days vs. GROUP B- 7,3±b 1,7days (NS). Duration of iNO: GROUP A- 2,9 ±b1,5days vs. GROUP B- 3,5 ±b1,3days (NS). Duration of hospitalization: GROUP A- 16,4 ±b5,4 days vs. GROUP B- 19, ±b2,9 days (NS). Air leaks: GROUP A- 0 vs. GROUP B- 2 (NS). Deaths: GROUP A- 0; GROUP B- 2 (NS).

Conclusions: The associated treatment of SLL with natural surfactant solution together with iNO in the therapy of severe meconium aspiration syndrome with persistent pulmonary hypertension does not have a significant influence on the reduction of duration of IMV, iNO and the hospitalization time and on the reduction of occurrence of complications and deaths.

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SURFACTANT LUNG LAVAGE AND INHALED NITRIC OXIDE IN THE TREATMENT OF MECONIUM ASPIRATION SYNDROME 1- INFLUENCE ON OXYGENATION

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The aim of study was to evaluate the efficacy of treatment of severe meconium aspiration syndrome /MAS/ complicated with persistent pulmonary hypertension /PPHN/ in the improvement of oxygenation. The designed therapeutic approach consisted of surfactant lung lavage /SLL/ and surfactant instillation together with Nitric Oxide inhalation /iNO/. The study population was randomized into two groups: group A /n=7/ treated with SLL, surfactant instillation and iNO, and group B /n=6/ treated with surfactant instillation and iNO. Criteria for inclusion: maturity >35 weeks of gestation, time after delivery <24 hours, presence of fluid containing meconium below vocal cords, respiratory insufficiency demanding mechanical ventilation /Fi0240%/, radiological changes, and echocardiographic features of pulmonary hypertension. **Method:** SLL was performed with natural surfactant solution (Survanta) in concentration of 5mg of phospholipids/1 ml 0,9% NaCl, a dose of 15ml of solution per 1 kg. A dose of 100 mg of Surfactant per 1 kg was applied. The initial NO dose was 20 ppm. The parameters analyzed: Pa02, MAP, Fi02, IO, aADO2 at 0h, 1h, 2h, 4h, 24h, 48h of treatment.

Results: (Mean value ± SD). PaO2 0h- Group A- 48,4± 14,9mmHg vs. Group B- 45,0± 14,3mmHg (NS); 1h- Group A- 114,3± 49,8 mmHg vs. Group B- 46,7± 14,9mmHg (p<0,05). MAP 0h- Group A- 14,3± 4,1 vs. Group B- 13,8± 8,2 (NS); 24h- Group A- 4,0± 3,5 vs. Group B- 8,0± 3,7 (p<0,05). FiO2 0h- Group A- 95,7± 11,3% vs. Group B- 95,0± 12,2% (NS); 2h- Group A- 67,1± 19,9% vs. Group B 96,6± 8,1% (p<0,05); 4h- Group A- 57,1± 16,5% vs. Group B- 89,1± 5,6% (p<0,05). IO 0h- Group A- 29,8± 12,4 vs. Group B- 32,3± 24,9 (NS); 1h- Group A- 11,2± 12,4 vs. Group B- 28,8± 12,0 (p<0,05); 2h- Group A- 10,0± 5,5 vs. Group B- 26,7± 19,0 (p<0,05); 4h- Group A - 6,3± 6,4 vs. Group B- 22,1± 18,4 (p<0,05); 24h- Group A - 2,7± 2,2 vs. Group B - 10,4± 8,0 (p<0,05). a/ADO2 0h- Group A- 575,6± 91,0mmHg vs. Group B- 589,5±95,8mmHg (NS); 2h- Group A- 364,2±128,8mmHg vs. Group B- 581,18± 71,1mmHg (p<0,05); 4h- Group A- 306,3±122,8mmHg vs. Group B-506,2±112,6mmHg (p<0,05).

Conclusions: The associated treatment of SLL together with iNO allows a significant improvement of oxygenation and reduction of parameters of mechanical ventilation.

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INCREASED S100B URINARY MEASUREMENTS AT BIRTH MAY PREDICT NEONATAL DEATH IN PRETERM NEWBORNS

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Background: To date no effective biochemical/biophysical tools exist to predict, among preterm infants, the cases at higher risk for perinatal death. The present study is aimed at investigating whether the measurement of S100B protein in urine may represent a useful tool to early identify patients at risk of postnatal death.

Methods: A retrospective case-control study was performed to measure S100B protein in urine fluid of preterm infants (n= 165) admitted to three tertiary NICUs (from January 1, 1999 to May 31, 2003), of whom a subgroup (n= 11) suffered spontaneous early neonatal death within the first week of age. Routine laboratory variables, neurological patterns and urine concentrations of S100B protein were determined at four time-points (at first urination, and after 24, 48, 96 hour). Ultrasound imaging were assessed within the first 72 hours from birth.

Results: S100B levels, in infants who died within the first week of age, were already higher at first urination and progressively increased from 24 to 96 hour time-points than controls (p<0.001, for all). Multiple logistic regression analysis showed a significant correlation between S100B protein urine concentrations and the occurrence of neonatal death. An S100B concentration cut-off of 12.7 MoM at first urination had a sensitivity of 100 percent and a specificity of 98.3 percent for predicting an abnormal neonatal follow-up. The positive predictive value was of 78.57%, the negative predictive value was of 100%.

Conclusion: Measurement of S100B protein urine levels in newborns, could be aid to identify newborns at higher risk for developing neonatal death.

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A META-ANALYSIS OF THE USE OF ANTIBIOTICS FOR PRETERM LABOUR WITH INTACT MEMBRANES (PTL), OR PRETERM PRE-LABOUR RUPTURE OF MEMBRANES (PPROM) IN PREGANCIES ≤34 WEEKS

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Background: Chorioamnionitis (chorio) has a profound effect on neonatal outcomes, but previous meta-analyses examining therapy with antibiotics in preterm labour or PPROM, included infants near to term. We assessed the influence of prophylactic antibiotic therapy on infants ≤ 34 weeks GA, who are more susceptible to the complications of prematurity.

Methods: Two independent reviewers conducted literature searches (including a hand search of proceedings). Eligible papers were randomized controlled trials administering oral or intravenous antibiotics for > 24 hours to pregnant mothers ≤ 34wks GA. Following agreement on eligibility of 22 papers, data was extracted. Prior sub-group analysis was specified for preterm labour (PTL) with intact membranes; or Preterm Pre-labour Rupture of Membranes (PPROM). If possible data is shown by sub-group. Data for obstetric & Neonatal (NN) outcomes was analyzed using Revman 4.2 software. The data is presented as: Number of studies where outcomes were extractable (N St), number of subjects randomised to treatment (N Rx), number of subjects randomized to control (N C); & summarised as weighted mean differences (WMD) or Odds Ratio (OR) with 95% CI, * shows significance p<0.05.

Results: Relevant primary outcomes are grouped by presentation:

i) Obstetric Outcomes: Latency [days]

	N St	N Rx	N C	WMD
PPROM	4	192	197	0.3(0.2,0.5)*
PTL	4	181	167	5.6(0.3,10.9)*

ii) Infection Outcomes:

	N St	N Rx	N C	OR
Chorio PPROM	9	629	690	0.6(0.4,0.7)*
Chorio PTL	6	368	358	0.3(0.1,0.5)*
NN Infection PPROM	11	737	762	0.6(0.4,0.8)*
NN Infection PTL	9	502	487	0.5/0.3,0.7)*

	N St	N Rx	N C	OR
NN NEC PPROM	10	698	719	1.1(0.8,1.7)
NN NEC PTL	5	321	320	0.4(0.1,1)

iii) NICU: Stay [days]

	N St	N Rx	N C	WMD
PPROM	4	151	158	-5.0(-9.6,-0.4)*
PTL	3	114	111	-3.0(-3.6,-2.5)*

iv) Perinatal-neonatal Complicatons:

	N St	N Rx	N C	OR
All Perinatal Death	17	1135	1143	0.9(0.7,1.3)
All RDS	17	1077	1098	0.8(0.7,0.9)*
All BPD (O2 28 d)	3	411	427	0.6(0.4,0.9)*
Any IVH PPROM	9	635	660	0.8(0.6,1)
Any IVH PTL	4	278	282	0.5(0.2,1.6)

Conclusion: Treatment prolongs latency in both groups, and reduces maternal and infant infections. A decrease in NN length of stay was seen. Prior Cochrane reviews suggested trends to positive impacts for neonatal outcomes, when antibiotics are used in PROM in up to 36 weeks GA. These findings are confirmed in this higher risk (≤ 34 week GA) group. Prior reviews show no benefit of antibiotics in PTL up to 36 week, in contrast we find in ≤34 weeks some benefits. For preterm infants ≤34 weeks, we conclude that there are significant advantages to be gained from the use of prophylactic antibiotics for both PTL and PPROM.

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RISKS FOR PERSISTENT PATENT DUCTUS ARTERIOSUS (PDA) AFTER TREATMENT WITH INDOMETHACIN

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Aims: The study investigates the influence of gestational age (GA), Apgar, pH-value, blood pressure and indicators for infection on the success of indomethacin in closing a PDA

Methods: All 118 preterm infants treated with indomethacin between 1997–2002 sorted in following therapeutic outcome groups: Success: A haemodynamic sig. PDA was closed by (maybe multiple) treatments with indomethacin or became haemodynamic not sig. At the end of the observation period the PDA was closed. Non-success: A haemodynamic sig. PDA was not closed by (maybe multiple) application of indomethacin. At the end of the observation period the PDA was haemodynamic significant. A logistic model was created to analyse GA, Apgar 10min, minimal pH-value of the day indomethacin was started, elevated CRP as indicator for infection, maximal CRP-value, microbiol growth, endotracheal colonisation with Ureaplasma urealyticum (Uu) and blood pressure. To account for the age dependency of blood pressure a new variable (MAD-deviation) was calculated: The MAD deviation is the difference of mean arterial pressure from the reference value which corresponds to the weeks of GA.

Results:85 (72%) of the 118 preterm infants were treated successfully, 22 (19%) of the 33 treatment failures received surgical ligation, 5 died with PDA, 6 were transferred with PDA (3 because of NEC). Higher GA (p=0,0001) and higher MAD-deviation (p=0,04) increase the chance of a successful medical treatment (Odds Ratio (OR) 2,27/ 1,22). (Mean-Success 27,8±2,3 weeks/ 10,3±6,6mmHg; Mean non-success 25,2±1,8 weeks/ 6,4±3,6mmHg). In non-success group the blood pressure amplitude was significant lower than in the success-group (16±4,8 mmHg vs. 20±6,3 mmHg; p=0,0001).The chance of successful medical treatment will decrease if there is an endotracheal colonisation with Uu (p=0,028/OR= 0,165). Surprisingly pos. microbiological cultures are associated with a higher success rate of indomethacin treatment (OR=7,2/p=0,011). No association with treatment outcome were found for pH, Apgar and CRP.

Conclusion: Gestational age remains the main determining factor for success of indomethacin. The low mean arterial pressure in treatment failures might be indicative of a higher shunt volume. Chronic inflammation with Uu might cause prostaglandin activation which impedes the closure of the PDA. Taking these risk factors for treatment failure in account, might help in the decision whether to ligate the PDA surgically or try repeated courses of indomethacin.

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MATURITY-DEPENDENT OLIGODENDROCYTE APOPTOSIS CAUSED BY HYPEROXIA

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Background: In the developing human brain, periventricular leukomalacia (PVL) is the predominant white matter injury underlying the development of cerebral palsy. PVL has its peak incidence in the premature infant during a well-defined period in human brain development (23–32 weeks, postconceptional age) characterized by extensive oligodendrocyte migration and maturation. We hypothesized that the dramatic rise of oxygen tissue tension associated with mammalian birth may be harmful to immature oligodendrocytes. We therefore investigated the effects of hyperoxia on cultured rat premature, immature and mature oligodendroglia cells.

Methods: Flow cytometry was used to assess apoptosis via annexin-V, anti-active caspase-3 antibody, and propidium iodide staining, while cell viability was measured by metabolism of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium (MTT).

Results: Apoptosis was detected at various stages (early: annexin-V, effector: caspase-3) after 24–48 h incubation with hyperoxia (80% O2) in preoligodendrocytes, immature oligodendrocytes (OLN-93) but not in mature oligodendrocytes. These results were confirmed in MTT assays.

Conclusion: Hyperoxia directly initiates the apoptotic cascade in immature oligodendrocytes and pre-oligodendroglia cells. This mechanism may contribute to the white matter damage observed in PVL.

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USEFULNESS OF AN EARLY BREASTFEEDING ASSESSMENT SCORE TO PREDICT EXCLUSIVE BREASTFEEDING FAILURE

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Background: A comprehensive breastfeeding assessment score (BAS) has been recently proposed to identify infants at risk for early cessation of breastfeeding. International guidelines for the infant feeding recommend exclusive breastfeeding during the first 4–6 months of age. This observational study assessed whether BAS evaluated at hospital discharge may be a useful tool to predict stopping exclusive breastfeeding within the first month of life.

Methods: A total of 175 mothers who delivered vaginally at the same hospital healthy full-term infants, and exclusively breastfed in the maternity ward, entered in the study. Mothers practiced 24 hours rooming in, breastfed on demand and started breastfeeding within the first hour of delivery. BAS was evaluated at hospital discharge. BAS includes maternal age (y) (<21, 21–24, >24), previous breastfeeding experience (failure, none, successful), latching difficulty (every feeding, half the feeding, <3 feeding), and breastfeeding interval (hours) (>6, 3–6, <3). Stopping exclusive breastfeeding during the first month of delivery was the outcome measure. Statistical analysis was based on the Mann-Whitney U test or the Chi-square test. Significance was posed at the level of P<0.05.

Results: Mean (SD; median) length of hospital stay was 2.2 (0.2; 2.2) days. At 1 month of delivery 86.9% of babies were still exclusively breastfed; 6.3% were complementary breastfed and 6.9% formula fed. Mean (SD; median) BAS was 9 (1; 9) in mothers exclusively breastfeeding and 8 (1; 8.5) in mothers no more exclusively breastfeeding at 1 month of delivery (P=0.021). No difference in BAS occurred between mothers who switched to complementary breastfeeding or stopped breastfeeding (P=0.88). Mothers without previous successful breastfeeding experience (P=0.001) or exhibiting higher latching difficulty (P=0.001) were at risk for stopping exclusive breastfeeding. No significant association of stopping breastfeeding within 1 month was found with maternal age ((P=0.885) or breastfeeding interval (P=0.219).

Conclusion:BAS index may be an early and useful measure to predict exclusive breastfeeding failure. Supported by AISTMAR

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COST-BENEFIT ANALYSIS OF PREVENTION OF NEONATAL ANEMIA WITH RECOMBINANT HUMAN ERYTHROPOIETIN IN PREMATURE INFANTS

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Background: Premature infants frequently develop anemia. This results from blood sampling and also from a relatively poor erythropoietic response to anemia. As a result, these infants often receive multiple transfusions with the risk of disease transmission. The aim of this study was to determine the efficacy and cost effectiveness of recombinant human erythropoietin (r-HuEPO) in reducing erythrocyte transfusion needs in preterm infants.

Methods: 93 premature infants of gestational age less than 34 weeks and birth weight less than 1500g were admitted in our unit from March 1998 to June 1999 and received r-HuEPO 750 U/kg per week intravenously or subcutaneously from day 5–15 to day 40–55. They also received oral iron 3–6 mg/kg per day from day 10. These infants were compared to 81 iron supplemented premature infants born during 1997 before the protocol r-HuEPO was introduced in 1998.

Results: Gestational age (30.2 vs 30.5), birth weight (BW) (1220 vs 1229g), hemoglobin upon admission (15.6 vs 15.6 g/dl), and phlebotomy losses (20.9 vs 20.2 ml/kg) were similar in both groups. The mean number of transfusions per infant was 0.8 compared with 1.9 transfusions per control infant (p <0.0001). Volume of erythrocytes transfused was 17.5 mL/kg in r-HuEPO-treated infants and 45.8 mL/kg in control infants (p <0.0001). The number of infants without transfusion was significantly higher in the r-HuEPO-treated group (64.8 vs 27.2% ; p <0.0001). The cost per patient for transfusion and r-HuEPO was 188 euros for r-HuEPO recipient and 281 euros for control infant. Blood pressure, neutrophil count, platelet count and complications of prematurity were not significantly different in both groups of infants. Of infants with gestational > 32 weeks (18 vs 17 infants) or weight >1200g at birth (46 vs 57 infants), mean number of transfusions was not significant.

Conclusion: R-HuEPO is cost-effective in the prevention of anemia of prematurity for children born before 32 weeks or with BW <12000 g. This treatment doesn't exclude other procedures to prevent transfusion requirements.

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GENETIC POLYMORPHISMS AS DETERMINANTS OF INTRAVENTRICULAR HAEMORRHAGE, PERIVENTRICULAR LEUKOMALACIA AND HYDROCEPHALUS IN VERY-LOW-BIRTH-WEIGHT-INFANTS

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Background: Genetic polymorphisms might influence the development and severity of brain diseases of very-low-birth-weight-(VLBW)-infants, like intraventricular haemorrhage (IVH), periventricular leukomalacia (PVL) and hydrocephalus.

Methods: Genetic association study. 1136 infants were studied: 150 VLBW-infants with IVH and/or PVL, 696 VLBW-infants without IVH or PVL and 290 healthy term born infants. Subgroups of VLBW-infants who were compared to VLBW-infants with normal brain-ultrasound-studies included VLBW-infants with IVH grade IV or PVL (n=54), VLBW-infants with IVH grade I-III (n=96) and VLBW-infants who subsequently developed hydrocephalus requiring ventriculoperitoneal shunting (n=27). Polymorphisms which were determined: factor-V-Leiden, prothrombin-G20210A, factor-VII-del/ins, toll-like-receptor4–896G, toll-like-receptor-2-Arg753Gln, NOD2–3020insC, interleukin-6-G(-174)C, plasminogen-activator-inhibitor-4G/5G, stromelysin1–6A/5A, CD14–159T, interleukin-4-C582T and lymphotoxin-alpha-A252G.

Results: Two polymorphisms were more frequent in VLBW-infants with abnormal ultrasound-studies. The homozygous lymphotoxin-alpha-A252G-polymorphism was more frequently found in VLBW-infants with hydrocephalus (33%) than in VLBW-infants without hydrocephalus (12.7%, OR 3.4, 95%CI 1.5–8, p=0.002) and in healthy infants born at term (10.1%). The heterozygous or homozygous prothrombin-G20210A-polymorphism was more frequently found in VLBW-infants with IVH grade IV or PVL (9.1%) compared to VLBW-infants without IVH (2.9%, OR 3.3, 95%CI 1.2–9.3, p=0.03) and healthy infants born at term (2.2%).

Conclusion: Although the majority of polymorphisms selected by our group was previously reported to be associated with intracranial haemorrhage or infarction in adults or VLBW-infants, we detected significant associations only for two polymorphisms. Our study underlines the importance of large cohorts in candidate gene association studies for severe diseases of VLBW-infants.