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### SURFACTANT PROTEINS IN PREMATURITY IN RELATION TO PERINATAL COMPLICATIONS

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**Background:** The outcome of premature infants is mainly determined by lung function in the first days of life. The pulmonary surfactant (SF) system plays a major role in maintaining lung function and is strongly impaired in the premature lung. We aimed to investigate surfactant protein (SP) levels in tracheal aspirates (TA) of preterm infants and their relation to perinatal complications.

**Methods:** 45 intubated and mechanically ventilated preterm infants (median 27, range 23–31 weeks gestational age; GA), all suffering from respiratory distress syndrome (RDS), were prospectively included in the study. TA were obtained in the first 12 hours of life before SF treatment following a standardized study protocol, SP-A, B, C and D concentrations were determined by means of ELISA techniques and normalized to the phospholipid (PL) concentration of each sample. Clinical variables were monitored. 12 pulmonary healthy infants (0–4 months of age), intubated before elective surgery, served as control group. Mann-Whitney U test was performed for statistical analysis.

**Results:** Levels of SP-C (0.53; 0.11–5.82 % (w/w) SP-C/PL) and SP-D (0.0011; 0.0002–0.0207 % (w/w) SP-D/PL) were significantly reduced in preterm infants <32 weeks GA compared to controls (1.80; 0.38–6.06 % SP-C/PL, $p<0.01$; 0.0118; 0.0029–0.0233 % SP-D/PL, $p<0.005$; median and range each). In contrast, SP-B concentrations were significantly elevated in preterms (0.41; 0.14–1.74 % (w/w) SP-B/PL) compared to controls (0.20; 0.15–0.45 % (w/w) SP-B/PL, $p<0.005$), whereas SP-A was not significantly different between the groups. SP-C concentrations were significantly elevated in the group of preterms delivered by c-section with contractions (0.62; 0.47–0.86 vs 0.46; 0.11–2.18 % (w/w) SPC/PL; $p<0.04$). Furthermore, SP-B and -D levels were significantly increased in preterm infants when clinically relevant haemorrhage was apparent under birth ($p<0.002$).

**Conclusion:** This is the first report describing levels of all four SP in tracheal aspirates in a well defined group of preterm infants. It was shown that SP are differentially regulated in preterm infants and are depending on perinatal complications.

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### SONOGRAPHIC DIAGNOSIS OF CEREBRAL ATROPHY AT DISCHARGE IS RELATED TO UNFAVOURABLE NEURODEVELOPMENTAL OUTCOME AT THREE YEARS OF AGE

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**Background:** In contrast to IVH and PVL, it is not yet clear, if minor abnormalities on neonatal cranial ultrasound - periventricular flares, ventricularmegaly, widened interhemispherics fissure or extracerebral space as signs of cerebral atrophy – are related to adverse outcome. Aim of the present study was to correlate these ultrasound findings to neurodevelopmental outcome at three years of age.

**Methods:** In 1997 all preterm infants born in our unit with a gestational age less than 32 weeks or birth weight below 1500g were prospectively enrolled in the study. Standard cranial ultrasound examinations were performed at predefined intervals between the first day of life and discharge. Ultrasound scans were analysed by 3 independent examiners for the presence of IVH, parenchymal hemorrhage, PVL, periventricular flares, and signs of cerebral atrophy (ventricularmegaly, widened interhemispheric fissure, enlarged extracerebral spaces). At the age of three years Bayley Scales of Infant Development II were performed.

**Results:** Eighty-seven preterm infants were enrolled (birth weight 430-2500g (median 1200g), gestational age 24–34 weeks (median 29 weeks)). Eighty-one infants survived (93%). In 11 infants IVH I, in 7 infants IVH II, in one IVH III, and in 3 infants IVH III plus parenchymal hemorrhage were diagnosed. All infants with IVH III plus parenchymal hemorrhage died. Forty-two infants exhibited periventricular flares, in 16 infants these were only detectable within the first two weeks of life, in 26 infants the flares persisted longer than two weeks. At discharge, 36 preterm infants had signs of cerebral atrophy. Neurodevelopmental outcome at three years of age was assessed by Bayley Scales in 64 infants (79% of all survivors). Infants with IVH II had significant lower MDI and PDI-scores than children without hemorrhage. Infants who presented with signs of cerebral atrophy at discharge had significant lower MDI (atrophy 95.7 / no atrophy 103.1; $p=0.043$)-, PDI- (atrophy 98.8 / no atrophy 106.9; $p=0.04$) and Behaviour Rating Scale (atrophy 50.5 / no atrophy 69.5; $p=0.022$) -scores than infants without signs of cerebral atrophy. Periventricular flares and IVH I had no impact on the neurodevelopmental outcome.

**Conclusion:** Our data suggest that in addition to IVH and PVL the sonographic diagnosis of a cerebral atrophy at discharge is related to an unfavourable neurodevelopmental outcome at three years of age.

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### ANTENATAL BETAMETHASONE DECREASES CORD PLASMA ADIPONECTIN IN PRETERM INFANTS

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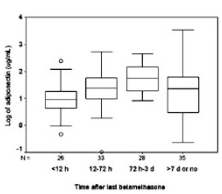
**Background:** Adiponectin is an adipocyte-derived hormone with profound metabolic effects that include increased insulin sensitivity and decreased atherogenesis. Glucocorticoids downregulate adiponectin *in vitro*. Despite the wide use of antenatal steroids, their *in vivo* effect on adiponectin in preterm infants has not been studied. Our aim was to study whether cord blood adiponectin concentration is related to the time from the last dose of betamethasone.

**Methods:** We measured adiponectin in cord plasma of 122 preterm infants with GA <32 (mean 28.7, SD 2.5) weeks and BW (mean 1195, SD 410) g. Infants were divided into four groups according to time after the last betamethasone dose (figure).

**Results:** Adiponectin concentration was adjusted for gestational age, birth weight SDS, number of betamethasone doses and gender. Infants with at least 7 d after last betamethasone ($n=25$), or no betamethasone ($n=10$), served as a reference group. Compared with this group, adiponectin concentrations were reduced in infants with less than 12 h after betamethasone ($p=0.002$), similar in those with 12 to 72 h after last betamethasone ($p=1.0$), and increased in those with 72 h to 7 d after last betamethasone ($p=0.0002$).

**Conclusion:** Our data show a transient decrease in cord plasma adiponectin concentration after antenatal betamethasone. This indicates that therapeutic doses of glucocorticoids modulate adiponectin *in vivo*. The finding is significant because it is possible that a part of the adverse metabolic effects of perinatal glucocorticoids may be mediated by decrease in adiponectin concentration.

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### TREATMENT OF PATENT DUCTUS ARTERIOSUS WITH IBUPROFEN IN VERY LOW BIRTH WEIGHT INFANTS

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**Background:** Since studies have shown equal efficiency and less side effects of Ibuprofen compared to Indomethacin, Ibuprofen became the preferential substance for the treatment of ductus arteriosus in preterm infants at many centres. We present our experiences since we have changed from Indomethacin to Ibuprofen in December 2002.

**Methods:** From December 2002 to March 2004 99 preterm infants <1500g were admitted to our centre. All infants, mechanically ventilated on day 3 of life, with echocardiographically confirmed patent ductus arteriosus (regardless of ductal diameter or shunt velocity) received Ibuprofen in three intravenous doses (10; 5; 5 mg/kg) in 24 hours intervals. Forty-one infants were treated, starting on day 3 - 14 of life. The birth weight ranged from 355 - 1230g (810g), gestational age 23 – 29 weeks (median 26 weeks). Eleven of 54 (20%) infants with birth weight 1000 - 1500g (VLBW) and 30 of 55 (55%) infants <1000g (ELBW) were treated with Ibuprofen.

**Results:** In the group of VLBW infants the ductus closed in 6 of 11 patients (55%) after the first course of Ibuprofen. Two infants (18%) received a second cycle of Ibuprofen, one patient (9%) needed surgery. In 8 of 30 (27%) ELBW infants ductal closure was achieved after the first cycle of Ibuprofen. Eleven infants (37%) were treated with a second cycle and 11 (37%) needed surgical ductus ligation. Anuria was not observed. Three infants exhibited oliguria during the first 24 hours after the start of treatment. An increase in creatinine serum levels of > 0.3 mg/dl from baseline was occurred in 5 infants. Two infants developed NEC 4 and 6 days after the start of treatment with Ibuprofen, respectively. Oxygen demand did not change significantly during ibuprofen treatment.

**Conclusion:** Ibuprofen treatment was well tolerated in very low birth weight infants. However, the number of infants who needed surgery was high in the group of infants with birth weight <1000g (20% of all ELBW infants).

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### ADIPONECTIN IN CORD PLASMA CORRELATES WITH GESTATIONAL AGE

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**Background:** Adiponectin is an adipocte-derived hormone that improves insulin sensitivity. Adiponectin is present in cord blood of term infants, but it has not been studied in preterm infants. The effects of gestational age and fetal growth pattern on adiponectin concentration at birth are unknown.

**Methods:** 197 newborn infants were studied. Of them 122 were born at 22–32 wk gestation (bw 455 - 2010g), and 75 at 36 - 42 wk gestation (bw 2140 - 4630g). At birth a blood sample was drawn from umbilical vein. Plasma was separated and the concentration of adiponectin was determined with ELISA (R&D Systems).

**Results:** In the preterm infants the concentration of adiponectin ranged from 0.08 to 31.4 imol/L and in term infants it was 4.4 - 54.8 imol/L. Significant correlations existed between adiponectin and gestational age in both preterm ($p<0.0001$) and term ($p<0.0001$) infants. In preterm infants birthweight standard deviation score correlated with adiponectin ($p=0.0001$), whereas in term infants no such relationship was found ($p=0.2$). No association was found between adiponectin and ponderal index in preterm or term infants.

**Conclusion:** At birth a strong correlation exists between the concentration adiponectin and gestational age. Adiponectin may play physiological roles in fetal development and in postnatal adaptation.

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### FACTOR V MUTATION ENHANCES THROMBIN FORMATION IN HEALTHY NEWBORN INFANTS

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**Background:** At birth, coagulation system is activated resulting in thrombin formation in the newborn. In sick newborns, the coagulopathy may lead to bleeding or thrombotic complications. Known genetic prothrombotic defects are risk factors for thrombosis in adults but their potential influence on perinatal coagulopathy remains unknown. Accordingly, we prospectively studied the influence of genetic thrombophilia on thrombin formation during the first two weeks of life.

**Methods:** Newborns from 10 pregnant women, with thrombophilia (Factor V Leiden (FVL, n=7), anticardiolipin antibodies (n=2), or lupus anticoagulant (n=1)), treated with low-molecular-weight heparin to improve pregnancy outcome, were enrolled to the study. All pregnancies ended in term vaginal delivery and the infants were born healthy. Blood samples were collected from the umbilical cord, and on postnatal days 1 and 14. Newborns were screened for FVL mutation and 4 heterozygotes were found. No infant tested positive for anticardiolipin antibodies or lupus anticoagulant. Thrombin formation was assessed by measuring prothrombin fragment F1+2. For samples on day 1, a previous cohort of 32 newborns (mean gestational age 33.6 weeks) treated in our neonatal intensive care unit (NICU) was used as an additional control.

**Results:** As expected, enhanced thrombin formation (F1+21.1 nM) was detected in cord blood and on day 1 in all newborns. On day 1, in the 4 newborns with FVL, F1+2 was significantly more elevated (median F1+2=8.9 nM) than in those negative for FVL ($n=6$, median F1+2=1.8 nM, $p=0.02$), or in the 32 newborns in NICU (unknown FVL status) (median F1+2=2.3 nM, $p=0.007$). A significant difference between FVL positive and negative newborns was observed in the pattern of resolution of the thrombin surge; FVL positive infants showed an increase from umbilical sample to day 1 (day 1 minus umbilical cord, median ΔF1+2 = 3.7 nM), whereas F1+2 decreased in FVL negative infants (median ΔF1+2 = -0.7 nM, $p=0.02$). By the day 14 F1+2 levels were similar and low in both FVL positive and negative infants.

**Conclusions:** Factor V mutation enhanced thrombin formation in healthy newborns during the first days of life. After two weeks enhanced thrombin formation was normalized.