

34

INSULIN-LIKE GROWTH FACTOR I DEFICIENCY IS ASSOCIATED WITH CHRONIC LUNG DISEASE OF PREMATURITY.

R.J. Bolt, M.M. van Weissenbruch, H.A. Delemarre-van de Waal, H.N. Lefeber VUmec, Pediatrics, Amsterdam, Netherlands

Objective: Insulin-like growth factor I (IGF-I) is necessary for normal growth and development in infants. Recent research suggested that IGF-I deficiency is associated with the development of oxygen-induced retinopathy of prematurity (1). We hypothesized that low IGF-I levels might be a risk factor for oxygen-induced pulmonary damage in preterm infants, which leads to chronic lung disease (CLD) of prematurity.

Methods: We measured growth hormone (GH) secretory patterns and levels of IGF-I and IGF binding protein 3 (IGFBP-3) in 34 preterm infants (gestational age(GA): 25–32 weeks, weights 526–1985 grams) at risk to develop chronic lung disease. Measurements were performed in clinically stable infants, requiring respiratory support. Between the 4th and 12th day of life, 6 h (with hourly intervals) and 24 h (with 6 h intervals) blood samples were taken for the determination of GH. In addition, IGF-I and IGFBP-3 levels were measured in the first blood sample. Results were adjusted for GA and birth weight SD score (BWSDS).

Results: No significant differences in GH concentration were found between the different time points studied either in the 6 h or 24 h profiles; GH concentration between infants who developed CLD vs no CLD was not different (mean GH respectively 77 ± 11 vs 79 ± 8 mg/L, $p=0.86$, adjusted $p=0.56$). IGF-I levels were significantly lower in CLD vs no CLD infants even adjusted for GA and BWSDS (respectively 1.3 ± 0.1 vs 1.9 ± 0.2 nmol/L, $p=0.02$, adjusted $p=0.04$). IGFBP-3 levels were not different between both groups (CLD 0.60 ± 0.04 mg/L vs no CLD 0.71 ± 0.05 mg/L, $p=0.11$, adjusted $p=0.94$).

Conclusion: Our results support the hypothesis that IGF-I deficiency may increase the risk to develop CLD. Since GH levels do not differ between infants who develop CLD and those who do not, differences in IGF-I levels may be explained by a relative GH resistance. Alternatively, levels of IGF-I may be lower due to a decreased production in preterm infants. With respect to the relationship between IGF-I and the development of serious sequelae associated with prematurity (1) our findings are comparable with observations by others. We therefore suggest that IGF-I may play an important role in the development of chronic lung disease of prematurity. **Reference:** Hellstrom A, Carlsson B, Niklasson A, et al. IGF-I is critical for normal vascularisation of the human retina. *J Clin Endocrinol Metab* 2002;87:3413–3416.

37

EARLY NASAL CONTINUOUS POSITIVE AIRWAY PRESSURE (NCPAP) IN COMBINATION WITH EARLY CURATIVE SURFACTANT THERAPY IN PRETERM INFANTS LESS THAN 28 WEEKS GA

F. Boubred, L. Fayol, F. Arnaud, S. Hassid, C. Grosse, F. Garraix, G. Sarhan, V. Millet, U. Simeoni Faculté de Médecine, Université de la Méditerranée - Assistance Publique Hôpitaux de Marseille - Hôpital la Timone, Département de Néonatalogie, Marseille, France

Background: Benefit and tolerance of early nCPAP, applied in the delivery room, in combination with surfactant therapy are still discussed in the management of respiratory distress syndrome (RDS) in extremely low birth weight infants (ELBW). **Objective:** To assess the feasibility and safety of early nCPAP in combination with early curative surfactant therapy (nCPAP + surfactant) in less than 28 weeks gestational age (GA) preterm infants and its eventual effects on neonatal morbidity. **Design/Methods:** Outcomes of two groups of preterm infants with GA <28 wks (commonly managed by nCPAP in the delivery room (DR)), admitted in our NICU from January 1999 to December 2002 were compared before (period I: 1999,2000; n = 92) and after (period II: 2001,02 ; n = 119) the adoption of early nCPAP + surfactant policy, for the treatment of RDS. Such strategy was proposed electively to preterm infants unaffected by hemodynamic failure, apnea or metabolic acidosis (pH <7.20).

Results: (mean +/-SD) GA and birth weight (BW) during period II were lower in comparison with period I: 26.5 ± 1.3 vs 27 ± 1 wks ($p<0.05$) and 895 ± 197 vs 940 ± 239 , respectively. Administration of antenatal steroids (complete course) was not different between the two periods, 51% (period I) vs 58% (period II). 80% and 78% of preterm infants within periods I and II received surfactant therapy respectively. The number of infants managed with early nCPAP + surfactant for RDS was higher during period II, 7 vs 28% ($p<0.005$). GA and BW of such patients (n = 30) were 26.6 ± 1.3 wks and 876 ± 182 g. The number of preterm infants receiving MV, within the first week of life, was lower during period II: 61% vs 75% ($p<0.05$). No infant managed with nCPAP had pneumothorax. The incidence of bronchopulmonary dysplasia (need for oxygen at 28 days) and [death or chronic lung disease (need for oxygen at 36 wks PCA)] were not significantly different: 50 vs 55% and 31.5 vs 37% respectively. Rate of severe cerebral damage (intraventricular haemorrhage grade III/IV or cystic periventricular leukomalacia) and mortality was 9.8% and 7.5% during period I and II, respectively. The mortality rate was 16.3% during period I and 10% during period II.

Conclusion: Early nCPAP, in the delivery room, in combination with early curative surfactant therapy in ELBW infants appears feasible. Neonatal short term morbidity and mortality are not affected by such strategy. Controlled prospective studies are needed to assess the benefit of such strategy

35

POSTNATAL SERUM INSULIN-LIKE GROWTH FACTOR I DEFICIENCY IS ASSOCIATED WITH CHRONIC LUNG DISEASE OF PREMATURITY

R.J. Bolt, M.M. Weissenbruch, van, H.N. Lefeber, H.A. Delemarre-van de Waal VU University Medical Center, Pediatrics, Amsterdam, Netherlands

Objective: Insulin-like growth factor I (IGF-I) is necessary for normal growth and development in infants. Recent research suggested that deficiency of IGF-I is associated with the development of oxygen-induced retinopathy of prematurity (1). We hypothesized that low IGF-I levels in might be a risk factor for oxygen-induced pulmonary damage in preterm infants, which causes chronic lung disease (CLD) of prematurity.

Methods: We measured growth hormone (GH) secretory patterns and levels of IGF-I and IGF binding protein 3 (IGFBP-3) in 34 preterm infants (gestational ages: 25–32 weeks, weights 526–1985 grams) at risk of developing chronic lung disease. Measurements were performed in clinically stable infants, requiring respiratory support. Between the 4th and 12th day of life, 6 h (with hourly intervals) and 24 h (with 6 h intervals) growth hormone samples were taken. In addition, IGF-I and IGFBP-3 levels were measured in the first blood sample. Results were adjusted for gestational age and birth weight SD score.

Results: No significant differences in GH concentration were found between the different time points studied in the 6 h or 24 h profiles or in infants who developed CLD vs no CLD (mean GH respectively 77 ± 11 vs 79 ± 8 mg/L, $p=0.86$, adjusted $p=0.56$). IGF-I levels were significantly lower in CLD vs no CLD even adjusted for gestational age and birth weight SD score (respectively 1.3 ± 0.1 vs 1.9 ± 0.2 nmol/L, $p=0.02$, adjusted $p=0.04$). IGFBP-3 levels were not significantly different between both groups (CLD 0.60 ± 0.04 mg/L vs no CLD 0.71 ± 0.05 mg/L, $p=0.11$, adjusted $p=0.94$).

Conclusion: Our results support the hypothesis that IGF-I deficiency may increase the risk of development of CLD. Since GH levels do not differ between infants who did develop CLD and those who did, differences in IGF-I levels may be explained by relative growth hormone resistance. Alternatively, levels may be lower by a decreased production of IGF-I in preterm infants. Our findings are comparable to those find by others with respect to the relationship between IGF-I and the development of retinopathy of prematurity. IGF-I may play an important role in the development of serious sequelae associated with prematurity, which requires further investigation. **Reference:** Hellstrom A, Carlsson B, Niklasson A, et al. IGF-I is critical for normal vascularisation of the human retina. *J Clin Endocrinol Metab* 2002;87:3413–3416.

38

OPINIONS IN SCOTTISH NEONATAL UNITS ABOUT ENTERAL FEEDING OF PRE-TERM INFANTS

E.M. Boyle¹, G. Menon¹, R. Elton², N. McIntosh¹ ¹Royal Infirmary of Edinburgh, Neonatal Unit, Edinburgh, United Kingdom; ²University of Edinburgh, Department of Public Health Sciences, Edinburgh, United Kingdom

Background: Enteral feeding of preterm and low birth weight infants is a contentious issue. There is uncertainty about the optimum approach. Concerns relate to the competing, serious potential risks of necrotising enterocolitis and catheter-related infection associated with different feeding methods. Evidence on which clinicians can base clinical practice is weak. Research studies have been small and results conflicting. Large randomised trials are needed. To ensure that trial interventions are relevant and acceptable to clinicians and that results are generalisable, it is important to be informed about ranges of opinion influencing current practice.

Aim: To document current opinion and reported practice of neonatologists in Scotland with respect to enteral feeding of preterm and low birth weight infants.

Methods: Senior clinicians from 15 Scottish neonatal units participated in a survey of opinions and policies about feeding of preterm (≤ 32 weeks) and low birth weight (≤ 1500 g) babies. A single researcher using face-to-face interviews and semi-structured questionnaires conducted the survey.

Results: 8(53%) units have written guidelines for initiation of feeds, 5(33%) for the rate of increase and 3(20%) for the discontinuation of feeds. All aim to introduce maternal breast milk on day 1 or 2 of life. None delay milk introduction for >48 hours in the absence of specific contraindications. If breast milk is unavailable, 1(7%) unit uses donor milk, 6(40%) use preterm formula, 5(33%) term formula and 3(20%) hydrolysed protein formula. Preferred volumes for initiating feeds are variable, ranging from 0.5ml every 6–12 hours to 1ml/hour. Criteria for discontinuing feeds based on gastric aspirates are inconsistent between units. Gastric residual volumes considered "large" vary from $\geq 25\%$ of the hourly feed volume to ≥ 2 hourly feed volumes. Decisions to withhold feeds are made by a variety of staff in most units. One clinician indicated that consultants in that unit usually make such decisions, another that decisions are most often made by nurses.

Conclusion: There is wide variation in opinion among neonatologists in Scotland and variable use of feeding guidelines. This probably reflects clinical uncertainty and is likely to lead to similar disparity in practice. Such differences may influence important outcomes such as necrotising enterocolitis and line- or parental nutrition-related complications. There is an urgent need for large, well-designed studies to define optimum feeding strategies.

36

EFFECTS OF INTRAUTERINE GROWTH RESTRICTION (IUGR) AND POSTNATAL CATCH-UP GROWTH ON ARTERIAL BLOOD PRESSURE (BP), GLUCOSE TOLERANCE (GT) AND RENAL FUNCTION IN ADULT RATS

F. Boubred¹, C. Buffat², M. Pegorier-Lelièvre³, M. Tsimaratos², C. Oliver², U. Simeoni¹ ¹Faculté de Médecine, Université de la Méditerranée - Assistance Publique Hôpitaux de Marseille - Hôpital la Timone, Département de Néonatalogie, Marseille, France; ²Faculté de Médecine, Université de la Méditerranée - Assistance Publique Hôpitaux de Marseille - Hôpital la Timone, UPRESS EA 2193 Recherche en diabétologie, Marseille, France; ³INSERM U356, Centre de Recherche biomédicales des Cordeliers, Paris, France

Background: Epidemiological and experimental studies have demonstrated a relationship between low birth weight and increased risk of hypertension and metabolic diseases in adulthood. Rapid postnatal catch-up growth, favoured by high caloric and protein intakes, may constitute an additional risk factor.

Aim: to investigate the effects of early postnatal overfeeding (OF) after IUGR on arterial systolic blood pressure (SBP), GT, and renal function in adult rats. **Methods:** 4 groups of animals were investigated from birth to 16 weeks: group I, controls: offspring of dams fed normal diet (NP, casein 22%); group II: offspring of dams fed isocaloric low-protein diet (LP, casein 9%); group III, same conditions as group I, postnatal OF; group IV: same conditions as group II, postnatal OF. OF was obtained by reduction of litter size down to 3 pups from day 3. SBP was measured at 4 and 8 weeks, and glomerular number was determined in newborn pups. Renal function (creatinine clearance (CrCl), fractional excretion of sodium (FeNa), proteinuria (PROT)) and glycaemia were assessed at 16 weeks of age. Data were analyzed by Kruskal-Wallis and Mann-Whitney tests.

Results: (mean +/- SEM). Offspring of dams fed LP diet had a 20% birth weight reduction ($p<0.001$). Group III pups had the higher growth rate during suckling period ($p<0.05$). Although smaller at birth, group IV rats caught up the weight of control offspring within the first postnatal month. Catch-up growth was associated with an elevated SBP at 4 weeks of age (110 ± 3 ; 117 ± 2 ; 116 ± 3 ; 127 ± 2 mmHg in groups I, II, III, IV respectively; $p<0.05$). During adulthood, SBP was significantly elevated in groups II, III, IV in comparison with group I (144 ± 3 ; 146 ± 1.6 ; 144.5 ± 3 ; 130 ± 3 mmHg, respectively; $p<0.05$). Despite a 38% reduction of glomerular number in pups exposed in utero to LP diet ($p<0.05$), CrCl and FeNa were not different between the groups. However, PROT was higher in rats that were exposed both in utero to LP diet and OF (10.9 ± 1.4 ; 13.7 ± 1.2 ; 19.2 ± 1.5 ; 30.2 ± 1.7 mg/Kg/day in groups I, II, III, IV respectively; $p<0.05$). Group III rats had a higher glycaemia in comparison with groups I and II rats (1.43 ; 1.74 ; 2.09 ; 1.84 g/l in groups I, II, III, IV respectively).

Conclusion: Early catch-up growth in IUGR rats enhances alteration of SBP, glucose tolerance and renal function in adulthood. Single nephron hyperfiltration rate may occur in such condition, and may cause BP, and renal function alterations.

39

IS THERE EVIDENCE OF OXIDATIVE STRESS IN MATERNAL AND FETAL CIRCULATION IN PREECLAMPSIA?

K. Braekke¹, N.K. Harsen², A.C. Staff² ¹Ullevål University Hospital, Pediatric, Oslo, Norway; ²Ullevål University Hospital, Obstetrics and Gynecology, Oslo, Norway

Background: Preeclampsia (PE) is a pregnancy-induced syndrome associated with increased maternal and fetal morbidity and mortality. The major fetal consequences of PE are intrauterine growth restriction and premature delivery. It is hypothesized that placental oxidative stress results in shedding of circulating factors into the maternal circulation, leading to endothelial dysfunction and inflammation in the maternal circulation. This mediates the maternal characteristics of PE: hypertension and proteinuria. There are conflicting reports as to what extent fetal circulation is involved. Oxidative stress is a condition where prooxidants dominate over antioxidants. Several studies have associated PE with augmented oxidative stress. 8-isoprostane is a stable marker of oxidative stress; it is formed by free radicals attack on arachidonic acid in cell membranes phospholipids. The aim of this study was to compare the level of oxidative stress in both maternal and fetal circulation in PE and uneventful pregnancies.

Methods: Maternal venous blood samples were obtained before cesarean section from 25 PE and 39 uneventful pregnancies. Umbilical cord blood samples were obtained separately from umbilical vein (16 PE, 34 controls) and arteries (15 PE, 21 controls). Total 8-isoprostane concentrations were measured with GC-MS, and antioxidants evaluated as FRAP (ferrous reducing ability of plasma) and vitamin E.

Results: The median level of total 8-isoprostane in plasma was significantly higher in maternal circulation in PE compared to controls (404 pg/ml vs 207 pg/ml, $p=0.003$). Median FRAP concentration was 26% higher in the PE group, vitamin E levels did not differ between the groups. The median level of 8-isoprostane in the umbilical vein was high, but there was no difference between PE and controls (955 pg/ml vs 801 pg/ml, $p=0.52$). No difference in umbilical artery 8-isoprostane concentrations was found between the groups (233 pg/ml vs 276 pg/ml, $p=0.65$). In the umbilical vein, both median FRAP and vitamin E concentrations was higher in the PE group. In the umbilical arteries, median FRAP concentration was higher in the PE group, but no difference was found in median vitamin E levels.

Conclusion: This study confirms increased oxidative stress in maternal circulation in PE. In the fetal circulation, we found no difference between PE and control group, but the concentration of 8-isoprostane delivered to the baby from the placenta was high, whereas blood from the baby had a much lower 8-isoprostane concentration.