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### AGAINST ALL ODDS: TRANSITION OF EXTREMELY LOW BIRTHWEIGHT (ELBW) INFANTS FROM ADOLESCENCE TO YOUNG ADULTHOOD (YA)

*S SAIGAL[1], B STOSKOPF[1], J PINELLI[1,2], L HOULT[1], M BOYLE[3], D STREINER[4], N PANETH[5] [1]MCMASTER UNIVERSITY, PEDIATRICS, HAMILTON (CANADA), [2]MCMASTER UNIVERSITY, SCHOOL OF NURSING, HAMILTON (CANADA), [3]MCMASTER UNIVERSITY, PSYCHIATRY & BEAHVIOURAL NEUROSCIENCES, HAMILTON (CANADA), [4]UNIVERSITY OF TORONTO, PSYCHIATRY,TORONTO, [5]MICHIGAN STATE UNIVERSITY, EPIDEMIOLOGY, EAST LANSING (USA)*

**Background:** Traditionally, educational attainment, getting a job, living independently and getting married / parenthood have been considered as 'markers' of successful transition to adulthood.

**Objective:** To describe and compare the achievement and age of attainment of the above markers of adulthood between ELBW and NEW YA. Design/Methods: Prospective longitudinal study. Participants: Population-based cohort of 166 ELBW survivors, 501-1000g BW (1977–82 births) and 145 sociodemographically matched NBW reference group. Information was obtained through well-validated questionnaires. Results: At YA 149/166 (90%) ELBW and 133/145 (92%) NBW completed the assessments at a mean age of 23.3 (SD 1.2) years. Data presented are inclusive of YA with neurosensory impairments (ELBW 27%; NBW 2%). In terms of educational attainment, there were no statistically significant differences between the groups:24% of ELBW and 25% of NBW completed high school education; 5% of ELBW and 14% of NBW had completed university education. One-third of both groups are still pursuing post-secondary education (32% vs 33%). Approximately half of both cohorts had permanent employment (ELBW 47%; NBW 52%). There were no differences in job status or in mean annual income. There were no differences in the proportion who had left the parental home (ELBW 42%; NBW 53k%; NS); however, 2.7% of ELBW vs none of NBW were living in group homes. A similar proportion were married/cohabiting (21% vs 23%), or were parents (11% vs 14%). The age of attainment of the above markers was similar for both cohorts. Conclusions: It appears that against all odds, a significant majority of ELBW have overcome their earlier difficulties to become functional YAs in terms of educational attainment, employment and independent living. Our findings support the concept of 'resilience'.

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### COMPARISON OF GROWTH OF ELBW SURVIVORS AND NBW FROM BIRTH TO YOUNG ADULTHOOD

*S SAIGAL[1], J PINELLI[1,2], B STOSKOPF[1], L HOULT[1], M BOYLE[3], D STREINER[4], N PANETH[5] [1]MCMASTER UNIVERSITY, PEDIATRICS, HAMILTON (CANADA), [2]MCMASTER UNIVERSITY, SCHOOL OF NURSING, HAMILTON (CANADA), [3]MCMASTER UNIVERSITY, PSYCHIATRY & BEHAVIOURAL NEUROSCIENCES, HAMILTON (CANADA), [4]UNIVERSITY OF TORONTO, PSYCHIATRY, TORONTO (CANADA), [5]MICHIGAN STATE UNIVERSITY, EPIDEMIOLOGY, EAST LANSING (USA)*

**Objective:** To compare the final growth attainment of extremely low birthweight (ELBW) and normal birthweight (NBW) peers at young adulthood (YA), and to demonstrate differences in the pattern of growth from birth. Design/Methods: Longitudinal regional cohort study of a population-based cohort of 166 ELBW survivors, 501-1000g BW (1977–82), and 145 sociodemographically matched NBW reference group. Weight and length z-scores were computed at birth (Kramer 2001), and at age 3, 8, teen and YA (CDC 2000); BMI was calculated at age 3, 8, teen and YA. Gender-specific longitudinal growth measures were examined.

**Results:** At YA 147/166 (89%) ELBW survivors and 131/145 (90%) NBW were assessed at a mean age of 23.3 (SD 1.2) and 23.7 (SD 1.1) years; 23.5% ELBW were SGA (<10th percentile) and 27% had neurosensory impairments (NSI). Weight for age z-scores for ELBW showed a decline until age 3, with subsequent significant catch-up between age 8 and adolescence, particularly for females, and a further slower catch-up to YA. In terms of height for age z-scores, both sexes of ELBW were disadvantaged at every age compared to NBW. Differences between groups remained significant even after exclusion of NSI, except for YA male weight. The BMI for ELBW showed a sustained incline from 3 to YA, where both sexes are now comparable to their peers. Using the GLM model, ELBW were significantly shorter relative to the NBW peers and their expected mid-parental height.

**Conclusions:** ELBW children show growth failure during infancy followed by accelerated weight gain and crossing of BMI percentiles at adolescence - a pattern that may increase risk of insulin resistance and coronary heart disease. However, BMI (also a coronary risk factor) was slightly lower in ELBW at YA.

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### MATERNAL LPS ENHANCES EXCITOTOXIC BRAIN LESIONS IN NEWBORN RATS

*C ROUSSET[1], P GRESSENS[2], A BINET[1], C ANDRES[1], S CHALON[1], E SALIBA[1] [1]INSERM U 619 , [2]INSERM U 679, [3]INSERM U 619 CHU, [4]INSERM U 619 CHU, [5]INSERM U 619, [6]INSERM U 619 CHU (FRANCE)*

**Introduction:** Epidemiological and experimental data implicate maternal infection in the aetiology of brain white matter injury, which may lead to cerebral palsy in preterm newborns. In newborn rats, intracerebral injection of the glutamatergic analogue iboténate, induces lesions mimicking cystic periventricular leucomalacia

**Objective:** Our aim was to study the effect of a prenatal maternal treatment with LPS on excitotoxic brain lesions caused by intracerebral injection of ibotenate in rat pups.

**Methods:** Inflammation was caused by Escherichia coli lipopolysaccharide administration to four pregnant rats at days 19 and 20 of gestation (300$\mu$g/kg n=2 and 400$\mu$g/kg n=2). Two pregnant rats serving as control received a saline injection. Five neonates from each dam were injected intracerebrally with ibotenate at P4 and sacrified at P9 (LPS 300 n=10, LPS 400 n=10 and control n=10). Lesion size was estimated using Cresyl Violet staining. Brain injury was examined on 16$\mu$m coronal brain sections.

**Results:** In cortex, we observed a 38% significant increase in lesion size in LPS 300 group compared to controls ($p<0.01$) and a 61% significant increase in LPS 400 group compared to controls ($p<0.01$) (LPS 300 group: 832 $\pm$ 49.6 $\mu$m, LPS 400 group: 966.4 $\pm$ 70.4 and Controls: 601.6 $\pm$ 38.4). In white matter, we observed a 72% significant increase in lesion size in LPS 300 group compared to controls ($p<0.05$) and a 137% significant increase in LPS 400 group compared to controls ($p<0.001$) (LPS 300 group: 505.6 $\pm$ 70.4 $\mu$m, LPS 400 group: 697.6 $\pm$ 70.4 and Controls: 294.4 $\pm$ 47.9). We did not find significative difference between LPS 300 and LPS 400 in both cortex and white matter.

**Conclusions:** These results demonstrate that maternal LPS treatment combined with postnatal intracerebral injection of ibotenate enhances excitotoxic brain lesion in pups. Prenatal inflammation seems to play a predisposing role to excitotoxicity induced white matter lesions.

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### MATERNAL LPS TREATMENT INDUCES APOPTOSIS AND WHITE MATTER LESIONS IN NEWBORN RAT BRAIN

*C ROUSSET[1], S CANTAGREL[1], P GRESSENS[2], C ANDRES[1], S CHALON[1], E SALIBA[1] [1]INSERM U 619 , [2]INSERM U 619 CHU, [3]INSERM U 676, [4]INSERM U 619 CHU, [5]INSERM U 619, [6]INSERM U 619 CHU (FRANCE)*

**Introduction:** Periventricular leucomalacia is a white matter lesion characterized by hypomyelination that occurs in preterm human newborn. Maternal inflammation seems to be a major cause of this lesion.

**Objective:** Our aim was to study brain damage after maternal inflammation in newborn rats on P1 and P7.

**Methods:** Inflammation was caused by Escherichia coli lipopolysaccharide administration to pregnant rats at days 19 and 20 of gestation (LPS group, N=8). Control rats got a saline injection (N=8). Neonats were studied at P1 (7 from LPS group, 8 from control) and P7 (8 from LPS group, 7 from control). Myelination was estimated using MBP immunohistochemistry and apoptosis using Terminal transferase assay (TUNNEL) and Caspase-3 immunohistochemistry. Brain injury was examined on 16$\mu$m thickness coronal brain sections.

**Results:** At P1, a 114% increase was observed in the number of caspase-3 positive cells in the subventricular striatal zone (40 $\pm$ 5 cells per field in the LPS group vs 21 $\pm$ 6 in controls, $p<0.05$). At P7, significant increase of apoptotic cells was found in specific brain areas, i.e. (1) the periventricular striatum (TUNEL: 24 $\pm$ 3 cells per field in the LPS group vs 14 $\pm$ 2 in controls, $p<0.05$; Caspase-3: 18 $\pm$ 2 vs 8 $\pm$ 1, $p=0.001$), (2) the periventricular white matter (Caspase-3: 12 $\pm$ 3 vs 4 $\pm$ 1, $p<0.05$), (3) the germinative ventricular zone: (Caspase-3: 22 $\pm$ 4 vs 9 $\pm$ 2, $p<0.05$). At P7, we also observed a strong hypomyelination in 6 out of 8 animals from the LPS group in the external and internal capsules.

**Conclusions:** These results indicate that maternal LPS treatment induces apoptosis associated with strong white matter injury at P7. This model could be relevant for the study of the pathophysiological mechanisms involved in cerebral white matter damage in preterm human newborn.

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### ALBUMIN LAVAGE DOES NOT IMPROVE THE OUTCOME OF MECONIUM ASPIRATION SYNDROM

*B. SALVESEN[1,2], A. CASTELLHEIM[1,2], T.E. MOLLNES[2], O.D. SAUGSTAD[1] [1]DEPARTMENT OF PEDIATRIC RESEARCH RIKSHOSPITALET UNIVERSITY HOSPITAL , [2]INSTITUTE OF IMMUNOLOGY RIKSHOSPITALET UNIVERSITY HOSPITAL (NORWAY)*

Meconium aspiration syndrome (MAS) is a severe disorder with high morbidity and mortality. MAS occur in about 5–12% of all deliveries with meconium stained amniotic fluid (MSAF). Still current therapies are supportive only. Meconium contains desquamated cells from skin and alimentary tract, lanugo hairs, fatty material, amniotic fluid and intestinal secretions. The free fatty acids and bile acids may affect pulmonary capillary permeability, pulmonary vascular resistance and surfactant function. Albumin may bind lipid and bile acids. We have previously in a piglet model shown a significant reduction in oxygenation index (OI) when meconium was mixed with albumin before instillation (1) and also a significant improvement in lung compliance when albumin was instilled endotracheally after instillation of meconium (2). Meconium is also a potent activator of the complement system in vitro and in vivo. (3) We here investigate whether rescue therapy with albumin improves ventilation and oxygenation in experimental MAS and influences proinflammatory cytokines and TCC.

**Methods:** Anaesthesia was induced with Halothane and maintained by intravenous Fentanyl and Midazolam. Hypoxia was induced by supplying 8% oxygen in nitrogen until base excess reached -15mmol/l. MAS was then induced by instillation of meconium into the lungs of newborn pigs in a well-known model of MAS. Albumin 15ml/kg was instilled 5 minutes after instillation of meconium . Endotracheal suction was performed 15 minutes after instillation of meconium and every hour. Control animals received only meconium or saline under otherwise identical conditions. The observation period was 6 hours. Hemo- and lung dynamics were recorded. Systemic complementactivation (TCC) and cytokines were measured in plasma samples by immunoassays.

**Results:** There were no statistic significant differences in Oxygenation index (OI) and VI between the two groups. OI in the meconium albumin group was 9,7 and in the meconium group 4,21 after one hour of reoxygenation and 12,24 and 5,04 after 6 hours. There were no significant differences between cytokines and TCC in the groups.

**Conclusion:** We intended that Albumin should cleanse the airways and bind free fatty acids in the meconium. Albumin itself may alter surfactant function and albumin lavage will shed surfactant from the lungs. Albumin instillation/lavage did not improve lung dynamics. Ref: 1 Tølløfsrud et al. Pediatr Res 2002;52:545–553. 2 Lindenskov et al..Ped research, in press. 3 Castellheim et al. Pediatr Res 2004; 55:310–318.

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### IMMUNOLOGICAL AND VIROLOGICAL EFFECTS OF BOVINE LACTOFERRIN IN HIV-1 VERTICALLY INFECTED CHILDREN

*F SALVINI[1], L GEMMELLARO[1], C BETTIGA[1], A RUSCITTO[1], GV ZUCCOTTI[2], M GIOVANNINI[1] [1]PAEDIATRIC DEPARTMENT UNIVERSITY OF MILAN-SAN PAOLO HOSPITAL-MILAN-ITALY , [2]PAEDIATRIC DEPARTMENT-LEGNANO HOSPITAL-MILAN-ITALY (ITALY)*

**Background:** Lactoferrin (LF) is a mammalian iron-binding glycoprotein with antiviral effects, possibly inhibiting HIV-1 replication. The aim of the present study is to evaluate the effect of bovine LF on immunological and virological status of HIV-1 vertically infected children

**Methods:** Twenty-two HIV-vertically-infected children (9 girls, 13 boys; age 3–18 years) monitored from birth were enrolled. Children did not change antiretroviral regimens during the previous 12 months or longer (8/22 naïve-group 1; 11/22 NRTI/NNRTI-group 2; 3/22 HAART). Bovine LF was orally administered (3 g/day) for 6 mo. CD4 + T lymphocytes and viral load (VL) were assessed quarterly from 6 mo before (T-6) starting (T0) LF administration up to 6 mo after (T6) and 2 months after the end of supplementation (T8).

**Results:** None of the patients showed any new HIV-1 related symptom at follow-up. Statistically significant variations both in VL values ($p<0.0001$), and in CD4+ T-lymphocytes % values ($p=0.005$) were registered during the supplementation period. Viral load declined from an average (SD) of 4.54 log10 (0.65) to 4.28 log10 (0.60) at T6, while CD4+ median values increased from 21.5% at T0 to 24.5% at T6. No significant variations in virological and immunological parameters were observed during the pre-treatment period (respectively $p=0{,}923$ for VL and $p=0{,}130$ for CD4+ %). Mean VL value two months after treatment interruption (T8) did not differ significantly neither from basal (T-0; $p=0.079$) neither from the mean VL at the end of lactoferrin administration (T-6; $p=0.274$); CD4+ % values at T8 remained significantly higher than to the basal level ($p=0.029$). The median VL % variation was not significantly different in group 1 and group 2 (-42% and -49% respectively; $p=0.70$). The median % variation of CD4+ T-lymphocyte count was significantly different between the two groups ($p=0.023$; + 13% group 1; + 27% group 2).

**Conclusions:** Lactoferrin, expecially when associated with antiretroviral therapy, seems to have a positive effect on plasma viral load and on the immune system modulation in HIV-1 vertically-infected children. LF could integrate well in the treatment of HIV infection in paediatric age. Further studies on a larger scale and longer follow-up period are warranted in order to define ways and times of LF administration and to obtain the best effect.