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PRENATAL INFLAMMATION, BRAIN DAMAGE AND TWO-YEAR NEUROLOGIC OUTCOME IN VERY PRETERM INFANTS

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Background: Intrauterine inflammation has been associated with preterm birth and with fetal inflammatory response affecting various organs including immature brain. Prenatal etiology has been defined in a majority of term infants with later neurologic sequelae but only in a minority of very preterm infants. Risk factors of cerebral white matter damage (WMD) may differ between term and preterm infants.

Objective: To examine whether prenatal inflammation serves as a risk factor of WMD and poor neurologic and neurocognitive outcome in infants born before 32 weeks of gestation with birth weight under 1000 g.

Design/Methods: A regional cohort of 61 infants born between 1998 and 2002 were enrolled in a prospective follow-up study. Medical records during hospitalization were observed. Placental pathology was examined. Sera from umbilical cord blood were analyzed for proinflammatory cytokines (IL-1 alpha, IL-1 beta, IL-6, IL-8, TNF-alpha). Serial brain ultrasound examinations and magnetic resonance imaging were performed. Neurologic and neurocognitive outcome were assessed at two years of corrected age. The study was approved by the ethics committee of Oulu University Hospital.

Results: Histologic chorioamnionitis (HCA) and high IL-6 predicted spontaneous preterm labor with high accuracy. High IL-6 and IL-8 associated with HCA. Intraventricular hemorrhage grade 2 to 3 was predicted by HCA (OR 8.1, 95%CI 1.6 - 42.5). Neither HCA or the cytokines directly associated with WMD, poor neurologic, or poor neurocognitive outcome. However, HCA and concomitant placental perfusion defect increased the risk of poor neurologic outcome (OR 15.2, 95%CI 1.3 - 181) and together with WMD additively predicted poor outcome. Several clinical factors describing cardiopulmonary instability after birth associated with WMD and with poor neurologic outcome.

Conclusions: HCA and fetal cytokine response are not risk factors of WMD in very preterm extremely low birth weight infants. Present results support the theory of a complexity of pathogenetic mechanisms leading to poor neurologic outcome.

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SUCCESSFUL TREATMENT OF PULMONARY HYPERTENSION WITH SILDENAFIL IN A NEONATE WITH SPONDYLOEPIPHYSEAL DYSPLASIA CONGENITA

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INTRODUCTION Persistent pulmonary hypertension of the newborn (PPHN) remains an important cause of mortality and morbidity in the term neonate. The severity of the illness and the outcome are related to the underlying cause. Therapies include inhaled nitric oxide (iNO), intravenous prostacyclin and sildenafil. We report the successful treatment of a neonate suffering from PPHN secondary to pulmonary hypertension caused by a skeletal dysplasia.

CASE REPORT The female infant was delivered at 37 weeks gestation with antenatal ultrasound findings a skeletal dysplasia. The diagnosis of spondyloepiphyseal dysplasia congenita was made based on the skeletal survey and clinical picture. She required significant ventilatory support and up to 100% oxygen because of PPHN. iNO resulted in a decrease in oxygen requirement to 80%. On day 36 oral sildenafil was commenced at a dose of 0.5mg/kg every 6 hours and increased over the next week to 2mg/kg every 6 hours. iNO was successfully weaned and ceased 4 days after commencing sildenafil. Within a week of commencing sildenafil the infant required less ventilation with a decrease in the oxygen requirement from 80% to 40%. She was successfully extubated to CPAP 4 weeks later. She has subsequently been discharged home on nasopharyngeal CPAP facilitated by home carers.

DISCUSSION PPHN occurs in 1-2/1000 live births PPHN is associated with significant mortality of up to 20%. Sildenafil is a specific PDE-5 inhibitor and is mostly known for its use in the treatment of erectile dysfunction. Preliminary findings suggest that sildenafil is effective in the long-term therapy of pulmonary hypertension and is particularly effective in reducing rebound hypertension after discontinuation of NO in patients with arterial pulmonary hypertension. Preliminary but limited data suggests that there might be a role for sildenafil in the treatment of PPHN. Randomised-controlled trials are required to determine its efficacy and safety.

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DOUBLE TROUBLE: A CASE OF PROXIMAL TUBULAR DYSGENESIS IN A DONOR SURVIVOR OF TWIN-TO-TWIN TRANSFUSION SYNDROME

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Background: In twin pregnancies complicated by twin-to-twin transfusion syndrome (TTTS) blood passes through unidirectional vascular shunts from the donor to the recipient twin. The donor twin consequently exhibits reduced growth velocity and oliguria. Proximal renal tubular dysgenesis (RTD) has been reported as a post mortem diagnosis in donor twins. We report a case of proximal RTD in a surviving donor twin.

Case Report: Monozygotic male twins were delivered at 30 weeks gestation for severe TTTS. The donor twin was initially hypotensive requiring inotropic support. He was oliguric for 12 days with a urine output of 0.1 ml/kg/hour. There was no acidemia or significant hyperkalemia. On day 20 his creatinine and urea peaked at 811 micromols/L and urea 39 mmols/L respectively. He developed hypertension and was managed with labetalol. By 30 days of life his urine output had normalised, although his creatinine remained elevated at 200 micromols/L. A renal biopsy performed at 12 weeks of age showed a paucity of proximal renal tubules consistent with proximal RTD.

Discussion: TTTS causes significant perinatal mortality and morbidity. In post mortem examination of donor twins with RTD a complete or near complete absence of proximal tubules and ischaemic glomeruli has been described. It is postulated that RTD occurs as a consequence of chronic hypovolaemia resulting in hypoperfusion of the kidney and up-regulation of renin synthesis. Increased renin causes elevated levels of angiotensin II and subsequent vasoconstriction. Active apoptosis has also been described in RTD pathophysiology. Cardiovascular changes in survivors of TTTS are consistent with abnormalities of the renin-angiotensin system. The donor twin shows a protracted tendency towards vasoconstriction and hypertension that may lead to renal failure. Fetal renin gene expression may influence renal haemodynamics and amniotic fluid volumes in TTTS and thus may present an avenue for therapeutic interventions.

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PLACENTAL CULTURES IN THE ERA OF PERIPARTUM ANTIBIOTIC USE. K BHOLA^{1,3}, H AL-KINDI^{2,3}, JE DAHLSTROM^{2,3}, A KENT^{1,3} ¹DEPT OF NEONATOLOGY, THE CANBERRA HOSPITAL, WODEN, ²DEPT OF ANATOMICAL PATHOLOGY, THE CANBERRA HOSPITAL, WODEN, ³AUSTRALIAN NATIONAL UNIVERSITY MEDICAL SCHOOL, CANBERRA (AUSTRIA)

Background: Examination of the placenta can yield valuable information that may be clinically significant for both mother and baby. In-utero infection may have serious long-term sequelae in the neonate. With the advent of intrapartum antibiotic prophylaxis for at risk pregnancies, the number of positive placental cultures may be decreased and significant infections may not be identified.

Aim: To determine whether placental culture rates are affected by antibiotic administration in the intrapartum period.

Methods: A review of all placentas submitted for histopathology in 2003 was performed. The clinical records were reviewed for: gestation at delivery, duration of rupture of membranes prior to delivery, intrapartum antibiotic use, placental culture result and histological findings.

Results: 425 cases were identified. Of these 282 (66%) were cultured and 12 (4.3%) had positive culture results. Five (41.7%) of the women with positive placental cultures had received intrapartum antibiotics. All of these placentas had histopathological evidence of in-utero inflammation with chorioamnionitis and funisitis. Three of these cases were preterm deliveries (gestation < 37 weeks). Of the seven positive culture results without intrapartum antibiotics, 4 had evidence of in-utero inflammation on histological evaluation. 104/425 (24%) had histopathological evidence of in-utero inflammation, 51 (49%) had received intrapartum antibiotics. Bacteria cultured included Group B streptococcus, Bacteroides, Enterobacter cloacae, E. coli, Klebsiella, Morganella morganii and a coliform.

Conclusion: Despite a significant proportion of placentas noted to have evidence of in-utero inflammation, only a small proportion had positive placental cultures. The presence or absence of intrapartum antibiotics did not appear to significantly affect the number of positive culture results. Other possible reasons include a non microbiological cause of the inflammation or culturing techniques that cannot detect all possible causative organisms. A review of culture techniques is required to determine whether alternative methods may improve culture growth.

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PLACENTAL ASSESSMENT: SIMPLE TECHNIQUES TO ENHANCE BEST PRACTICE.

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Background: Pathological assessment of the placenta provides a method of auditing clinical judgement by clinicopathological examination.

Aim: To improve the number of placentas submitted for histopathological evaluation meeting certain inclusion criteria and to improve the clinical history provided to pathologists.

Methods: A placenta information form was devised collecting the following clinical history features: preterm infant (gestational age box provided), prolonged rupture of membranes (>18 hours), suspected maternal/fetal bacterial or viral infections, swabs taken for culture, IUGR, perinatal death, pre-eclampsia, essential hypertension, diabetes, placenta praevia, multiple pregnancy and cytogenetics. An extra box was provided for other relevant clinical history. A table was introduced into the midwifery placenta policy detailing the inclusion criteria for histological assessment: preterm infant (> 37/40), prolonged rupture of membranes, suspected fetal/maternal infection, IUGR, perinatal death, pre-eclampsia, twins, placenta praevia. This table also detailed whether microbiology or cytogenetics was required. Records for a 6-month period (January-June 2002) were compared to a similar time period following introduction of the information form and policy (January-June 2003). Following this review a placenta poster was designed and placed in the delivery suite to act as a reminder to staff of the inclusion criteria for placental histopathology. A further review of records was performed for a 6-month period following introduction of the placenta poster (March-August 2004).

Results: The total number of placentas submitted for histopathological examination (and meeting the inclusion criteria) increased from 40% (115/288) to 61% (161/266) to 82% (262/319). Positive placental pathology was found in 64% of placentas in 2002, 55% in 2003 and 60% in 2004. Pathologists were very pleased with the improved clinical information.

Conclusions: The number of placentas meeting the inclusion criteria submitted for histopathological evaluation increased 100% following these interventions. Continued education in-service programmes will inform new staff of the policy and act as a reminder to continuing staff members.

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NEONATAL NECROTISING ENTEROCOLITIS: RESULTS OF A RETROSPECTIVE STUDY ON 128 PATIENTS OVER 25 YEARS

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Introduction: Necrotising enterocolitis (NEC) is the most common neonatal surgical emergency with a high mortality. However frequency is low and even in perinatal centers NEC is observed rarely. Thus, retrospective studies are substantial to analyse large patient cohorts.

Material and methods: Over a 25 year period (1978-2003) data were available from 128 patients and entered into a database.

Results: Main results were:

1. Low birth weight (BW) and gestational age (GA), severity of NEC, elevated lactate concentration and the need for intraoperative erythrocyte transfusion had influence on survival.
2. Manifestation of NEC was significantly earlier in children < 1000g birth weight (BW) than in children > 1500g BW (P<0.05).
3. Infants < 1500g BW required more postoperative medication and treatment than infants > 1500g.
4. Changes in hemoglobin concentration, CRP and leukocyte or thrombocyte count were not of diagnostic or prognostic value in NEC.
5. Gestational age (GA) (p<0.005) and BW (p=0.026) were significantly lower in infants with small bowel involvement than in infants with large bowel affections.
6. Infants with only mucosal (P=0.02) or mucosal plus submucosal involvement (P<0.001) had lower GA and BW than infants with transmural necrosis. BW and GA had more impact on prognosis than histological findings as survival was higher in infants with elevated BW and GA despite an increased rate of transmural necrosis.