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EFFECT OF HIGH VERSUS STANDARD EARLY PROTEIN INTAKE ON EXTREMELY LOW BIRTH WEIGHT INFANTS

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Background: Growth failure remains a significant cause of morbidity among premature infants. Early provision of protein has been shown to limit catabolism and could improve growth. Our objective was to determine whether early aggressive protein intake improved growth outcomes of ELBW infants

Methods:ELBW infants admitted to our NICU during 2001- 2003 were included in the study if they had no major congenital anomalies or renal failure and were still hospitalized at 36 wks PMA. In 25 infants, defined as high protein group (HP), the start protein intake was 2g/kg/d and the planned peak metabolizable protein intake was 3.5g/kg/d; the 31 historical controls, defined as standard protein group (SP), received 1g/kg/d in the first day of life and 3g/kg/d as the peak metabolizable protein. The primary outcome measure was Z score change from birth to discharge. Multiple regression analysis was used to identify significant predictors of postnatal growth

Results: The two groups were similar in GA (HP 27.7±1.9 vs SP 27.2±1.5 wks), BW (817±113 vs 838±89 g), CRIB score (4.2 ±3.0 vs 4.3 ±3.6), exposure to antenatal steroids (72 vs 64,5%), male gender (48 vs 38.7%) and SGA infants (8 vs 9.7 %). The mean metabolizable protein intake of the HP was 28.6% greater at postnatal week 1 (2.68±0.29 vs 1.91±0.22 g/kg/d; p<0.0001) and 18.8% greater (3.08±0.16 vs 2.50±0.20g/kg/d; p<0.0001) at postnatal week 2. HP group showed a trend toward reduced postnatal weight loss (8.8±4.9 vs 11.6±6.1%) and earlier regain of BW (9.2±3.9 vs 13.3±5.5 days; p=0.0062). During hospitalization the HP group experienced less cumulative protein deficit (-0.4±7.6 vs -24.0±12.7;p<0.0001) and had a significant reduced fall in ZsW (-0.36 ±0.64 vs -0.92±0.98;p=0.0135) and ZsL (-0.24±0.83 vs -0.75±0.80;p=0.0311). Multiple regression analysis indicated that the mean protein intake at week 2 was a significant positive predictor of ZsW (coeff 0.77, p=0.007) and ZsL (coeff 0.73, p=0.041) changes; GA was a negative predictor for ZsW and ZsL changes; Z score at birth and CRIB score were negative predictors for all Z-score changes

Conclusion: Early high protein intake was associated with improved weight and length growth outcomes at discharge. These findings highlight the benefits of aggressive protein intake immediately after birth

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PERINATAL FACTORS INFLUENCING LATER GROWTH OUTCOME IN ELBW INFANTS

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Background: Poor growth during the early years is well documented in children born prematurely but the relation between perinatal morbidity and subsequent growth retardation is poorly understood. Our aim was to determine, in children born appropriate for gestational age and with BW ≤1000 g, the main perinatal factors predictive of growth patterns at corrected age of 24 months

Methods: The growth outcome of 70 of the 87 ELBW AGA infants (GA 27.2±1.5 wks, BW 850±108 g) discharged from our NICU between 1998 and 2001 was assessed at 24 months of corrected age. Multiple regression analysis was used to assess several potential predictors of growth

Results: At birth the mean (SD) Z scores were -0.45±0.76 for W, -0.70±0.76 for L and -0.62±0.73 for HC. During hospitalization there was a significant fall in ZsW (-0.94 95%CI -1.24 to -0.63; p <0.0001) and ZsL (-0.85 95%CI -1.16 to -0.54; p <0.0001) but not in ZsHC (-0.24 95%CI -0.51 to 0.04; p =0.0944). At discharge (39,6±1,9 wks PMA) the prevalence of infants with Zs <-2 was 28.6% for W, 34.3% for L and 10.0% for HC. From discharge to 24 months of age, catch up growth was documented in 44.3% of infants for W, in 67.1% for L and in 35.7% for HC; during this period overall mean difference in Z scores was negative but not significant for W (-0.22 95%CI -0.59 to 0.16; p =0.2602), negative for HC (-0.42 95%CI -0.76 to -0.08; p =0.0157) and positive for L (0.42 95%CI 0.07 to 0.77; p =0.0186). At 24 months of age 37.1% of infants had Zs < -2 for W, 21.4% for L and 28.6 % for HC and the children were smaller on average in each of the three growth measures: Z scores were -1.61±1.22 for W, -1.17±1.16 for Height and -1.29±1.11 for HC. Multiple regression analysis identified days of oxygen therapy (coeff -0.008, p=0.032), NEC (coeff -1.40, p=0.032) and ZsW at discharge (coeff 0.64, p<0.0001) as the best predictors for ZsW at 24 months (r2 0.41). Days of oxygen therapy (coeff -0.011, p=0.010) and ZsL at discharge (coeff 0.28, p=0.040) were significant predictors for ZsL at 24 months (r2 0.33). ZsHC at discharge (coeff 0.65, p<0.0001) was the only predictor for ZsHC at 24 months (r2 0.44)

Conclusion: Poor growth during early postnatal period is common in ELBW infants and could predict the growth retardation at 2 years of age

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EARLY HEMODYNAMIC EFFECT OF PATENT DUCTUS ARTERIOSUS IN PRETERM INFANTS WITH INTRA-UTERINE GROWTH RESTRICTION OF PLACENTAL ORIGIN

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Background: Significance of patent ductus arteriosus (PDA) is low during the first hours of life because of high pulmonary vascular resistance (PVR). However, clinical symptoms of significant PDA such as systemic hypotension, oliguria, hyperpulsatile pulses. . . are described early after birth in preterm infants with intra-uterine growth restriction (IUGR) of placental origin. We therefore hypothesized that significant ductal shunting can occur early after birth in IUGR. We compared the hemodynamic effects of PDA between 6 and 10 hours of life in IUGR versus eutrophic preterm infants.

Methods: Infants from 24 to 32 weeks of gestational age (GA) admitted to our unit were prospectively studied. Exclusion criteria were: DA closure between 6 and 10 hours of life, premature rupture of membranes > 1 week, malformations, severe respiratory disease (FiO2 30 % and/or need for high frequency oscillatory ventilation), no antenatal corticosteroids, materno-fetal infection, need for vasoactive drugs, non-placental IUGR. The following parameters were assessed using bidimensional and Doppler echocardiography: left atrial aortic root ratio (LA:Ao), mean (mLPA) and telediastolic (tLPA) velocities in the left pulmonary artery, left ventricle shortening fraction (SF), DA diameter, mesenteric resistance index (MRI). Mean arterial blood pressure (MABP) and blood lactate level were also recorded.

Results: 30 eutrophic and 19 IUGR infants were included (GA: 28.9±0.4 vs 28.9±0.5 weeks, NS ; BW : 1300±60 vs 800±40 g, p<0.05, respectively). MABP, mLPA and SF were similar in both groups. The other parameters were significantly increased in IUGR infants: DA diameter (2.7±0.1 vs 2.1±0.1 mm, p<0.05), LA:Ao (1.5±0.08 vs 1.2±0.06, p<0.05), tLPA (0.23±0.02 vs 0.16±0.01 m/s, p<0.05), MRI (0.86±0.04 vs 0.7±0.02, p<0.05), lactate level (4.7±0.6 vs 3.1±0.3 mmol/l, p<0.05).

Conclusion: Our results indicate that significant PDA may occur during the first 10 hrs of life in preterm infants with IUGR of placental origin. The hemodynamic consequences of PDA are higher in IUGR than in eutrophic preterm infants. The data suggest also that poor tolerance of PDA in IUGR infants is not due to an altered ventricular contractility but to a higher shunt flow through the DA. The significance of PDA should be assessed early after birth in IUGR.

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EFFECTS OF PHOSPHODIESTERASE 5 INHIBITOR ON PULMONARY VASCULAR REACTIVITY IN THE FETAL LAMB

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Background: Nitric Oxide (NO) released by pulmonary vascular endothelium is a potent vasodilator related to increased cGMP content. Hydrolysis of cGMP is achieved predominantly by cGMP–specific phosphodiesterases (PDEs). Sildenafil (SILD) is a selective phosphodiesterase–5 (PDE–5) inhibitor. The purpose of the study was to assess the effects of sildenafil on pulmonary vascular circulation during the perinatal period.

Methods: 12 pregnant ewes were operated on between 128 and 130 days gestation (term = 145 d). Catheters were placed into the ascending aorta, superior vena cava, main pulmonary artery and left atrium. An ultrasonic flow transducer was placed around left pulmonary artery (LPA). An inflatable vascular occluder was placed around ductus arteriosus (DA). Acute DA compression increases pulmonary artery pressure (PAP) causing an increase in pulmonary blood flow (Q) and a progressive decline in pulmonary vascular resistance (PVR). Fetal lambs were divided in two groups: 1) a SILD group infused continuously with SILD at a rate of 24 mg/day (n=6) and; 2/ control group (CONT) infused with saline (n=6). After 24 hrs of infusion, we compared the hemodynamic response of LPA to: 1) increased fetal PaO_2 (maternal O_2 inhalation for 30 min), and; 2) increase in vascular shear-stress (flow-induced pulmonary vasodilatation related to DA compression).

Results: Mean PAP, Q and PVR were similar in both groups before and after 24 h of SILD or saline infusion. Despite similar baseline values, PVR during maternal O_2 inhalation was lower in SILD than in CONT group (0.23±0.01 vs 0.27±0.01 mmHg/ml.min^{-1} respectively) (p<0.01). Furthermore, drop in PVR during acute DA compression was greater in the SILD group (from 0.54±0.03 to 0.26±0.02 mmHg/ml.min^{-1}) than in the CONT group (from 0.55±0.04 to 0.39±0.02 mmHg/ml.min^{-1}) (p<0.01).

Conclusion: Although no difference was found in the basal pulmonary vascular tone, sildenafil increases pulmonary vascular reactivity in the ovine fetus. These data suggest that PDE–5 is involved in the regulation of pulmonary vascular reactivity during the perinatal period. We further speculate that specific inhibitor of PDE–5 may potentiate birth related pulmonary vasodilator stimuli and could improve conditions associated with failure to circulatory adaptation at birth.

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EXPRESSION OF ANGIOPOIETIN-2 AND ENDOSTATIN IN INTRAUTERINE GROWTH RESTRICTION DURING THE PERINATAL PERIOD

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Background: Angiopoietin-2 (Ang2) is an endothelial cell-specific growth factor, which acts by blocking stabilization and maturation of vessels allowing them to remain in a more plastic state and respond to sprouting signals provided by other angiogenic factors. Ang2 gene expression is up-regulated by hypoxia, present in intrauterine growth restriction (IUGR) pregnancies. On the contrary, hypoxia down-regulates production of endostatin (End), a potent angiostatic factor derived from collagen XVIII. This study aimed at investigating circulating Ang2 and End levels in maternal blood (MS) during the first stage of labor, in the doubly clamped umbilical cord (UC) at delivery, representing fetal state and in the neonate in the first (N1) and fourth (N4) day of life, reflecting transition and stabilization to extrauterine life, respectively

Methods: Ang2 and End were determined by enzyme immunoassay methods in serum, deriving from 20 fullterm appropriate for gestational age (AGA) and 40 fullterm IUGR infants, as well as from their mothers.

Results: Statistical significant difference was noted in N4 Ang2, being higher in IUGR (p=0.030), (while in N1 Ang2 was only indicative-p=0.057) and in UC End, being lower in IUGR (p=0.002), as compared to AGA cases. Statistical significant correlations existed for Ang2 between: MS and UC, N1, N4 (p=0.000, p=0.001, p=0.017 respectively), UC and N1, N4 (p=0.000, p=0.000 respectively), N1 and N4 (p=0.000) and for End between N1 and N4 (p=0.006). In the IUGR group variables presenting a statistically significant association with: a) MS Ang2, were gestational age (p=0.011), placental weight (p=0.013), gender (p=0.002) and birth length (p=0.023), b) UC Ang2, was gestational age (p=0.042), c) N1 Ang2, were gestational age (p=0.000) and birth weight (p=0.003) d) N4 Ang2, were gestational age (p=0.000) and birth weight (p=0.023), e) MS End, were gender (p=0.003), gestational age (p=0.007) and birth length (p=0.006), f) UC End, were placental weight (p=0.038) and gender (p=0.031), g) N1 End, was gender (p=0.050).

Conclusion: High neonatal Ang2 and low fetal End is documented in IUGR infants, possibly due to intrauterine action of hypoxia on these factors. In IUGR fetuses End is associated with placental weight. Similarly, Ang2 in IUGR fetuses is associated with gestational age and in IUGR neonates with gestational age and birth weight, in general indicating the impact of these factors on angiogenesis and tissue growth.

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PERINATAL ACTIVITY OF ANGIOGENIC GROWTH FACTORS IN INTRAUTERINE GROWTH RESTRICTION

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Background: Vascular endothelial growth factor (VEGF) and placenta growth factor (PlGF) are expressed, among other organs, in the placenta and play cardinal roles in angiogenesis. Production of VEGF, in contrast to PlGF, is enhanced by hypoxia, which is present in intrauterine growth restriction (IUGR) pregnancies. This study aimed at investigating circulating VEGF and PlGF levels in maternal blood (MS) during the first stage of labor, in the doubly clamped umbilical cord (UC) at delivery, representing fetal state and in the neonate in the first (N1) and fourth (N4) day of life, reflecting transition and stabilization to extrauterine life, respectively.

Methods:VEGF and PlGF were determined by enzyme immunoassay methods in serum, deriving from 15 fullterm appropriate for gestational age (AGA) and 15 fullterm IUGR infants, as well as from their mothers.

Results: Statistical significant difference was noted in MS PlGF, being lower in IUGR as compared to AGA cases (p=0.014). Statistical significant correlations existed for VEGF between: UC and N1 (p=0.04), UC and N4 (p=0.011) and N1 and N4 (p=0.009) and for PlGF between N1 and N4 (p=0.018). In the IUGR group variables presenting a statistically significant association with: a) MS VEGF, were placental weight (p=0.031) and birth length (p=0.049), b) UC VEGF, was placental weight (p=0.016), c) N4 VEGF, were gestational age (p=0.028) and birth weight (p=0.026), d) UC PlGF, was head circumferance (p=0.036), e) N1 PlGF, was birth weight (p=0.023), f) N4 PlGF, was gestational age (p=0.011) and birth length (p=0.040).

Conclusion: Low MS PlGF was associated with IUGR, while no differences were found between IUGR and AGA fetuses and neonates concerning PlGF and VEGF circulating levels. In IUGR fetuses VEGF is associated with placental weight, while in IUGR newborns with gestational age and birth weight. Similarly, PlGF in IUGR newborns is associated with gestational age and birth weight, in general reflecting the implication of angiogenic factors in angiogenesis and tissue growth.