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### CAESAREAN DELIVERY AT THE THRESHOLD OF VIABILITY: THE OBSTETRICIANS ATTITUDES IN EIGHT EUROPEAN COUNTRIES

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**Introduction**. The obstetricians attitudes towards caesarean delivery at the threshold of viability were explored in a European project (EUROBS) in eight countries: France, Germany, Italy, Luxembourg, Netherlands, Spain, Sweden and the UK.

**Methods**. In each country, NICU-associated obstetrical units were selected through census or random sampling. An anonymous self-administered questionnaire explored the obstetricians attitudes regarding the lowest gestational age at which they would perform a caesarean delivery in case of acute foetal distress of a single, non-malformed and normally grown fetus given that: a) parents want everything possible done to save the baby; b) parents favour non-aggressive management for fear of disability; and c) the obstetrician him/herself is one of the parents. Data collection took place in 2001–2002; 105 units and 1530 obstetricians participated (response rates 70% and 77% respectively).

**Results**. At 24 weeks of gestational age, 71% of the German, 52% of the Swedish, and 27% of the Italian and British obstetricians would perform a caesarean delivery given parental agreement, compared with only 17% of the French, 14% of the Spanish, and less than 1% of the Dutch ones. The intervention would be postponed by an average of 3.8 days (95% CI 2.9–4.7) in case of parental opposition to active management, and by 5.7 days (95% CI 4.1–7.3) if the obstetrician was one of the parents. Other factors significantly associated with a more advanced caesarean section threshold in a multivariate model were older age, being a woman, muslim and oriental religion, more pessimistic beliefs regarding neonatal prognosis, and consultation with neonatologist.

**Conclusions**. The lowest gestational age at which obstetricians would perform a caesarean delivery for fetal indication only varies according to country, parental views, and personal physician characteristics and beliefs. These findings have implications for neonatologists subsequent actions, and for the international comparison of perinatal statistics.

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### GESTATIONAL DIABETES: CORD BLOOD INSULIN, IGF-I AND IGF-II LEVELS IN RELATION TO ANTHROPOMETRIC PARAMETERS OF NEONATES BORN AS AGA OR LGA

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Insulin, IGF-1 and IGF-2 are considered as the main growth factors during fetal life. The aim of the study was to evaluate the relationship between cord blood insulin, IGF-I and IGF-II concentrations and antrophometric parameters in neonates of GDM mothers born with different birth weight categories: appropriate (AGA) or large (LGA) for gestational age.

**Material and methods**: The study covered 72 newborns born to GDM mothers divided into 2 groups - 35 LGA and 37 AGA. 40% mothers from LGA and 48,6% from AGA group were on diet only and the others on insulin. There was no significant difference in the mean GA between the groups (AGA -38,2 ± 2,2; LGA - 38,4 ± 1,8 weeks). Anthropometric measurement (body mass, length, head and chest circumference) was done at birth. Umbilical venous blood was taken after delivery and concentration of insulin (RIA), IGF-I (Immunoassay Quantikine) and IGF-II (ELISA Biosource) was estimated.

**Results**: Insulin and IGF-I levels were significantly lower in AGA than in LGA group (4,5 v. 6,8 $\mu$IU/ml and 64,9 v. 79,0 ng/ml). A significant positive correlation between IGF-I and insulin levels in LGA group was noticed ($r=0,33$; $p<0,05$). IGF-II and insulin levels correlates positively with body mass ($r=0,31$; $p<0,05$; and $r= 0,57$; $p<0,001$) as well as head circumference ($r=0,37$; $p<0,05$ and $r=0,44$; $p<0,01$) in LGA but not AGA group. In LGA group a positive correlation between insulin ($r=0,39$; $p<0,01$) as well as IGF-I ($r=0,31$;$p<0,05$) levels and chest circumference was found.

**Conclusion**: There is an association between normal birth weight and occurring of low cord blood insulin and IGF-I levels in neonates of the GDM mothers. Moreover unfavourable influence of insulin and IGF-I on body mass and proportion between head and chest circumference in LGA neonates born to GDM mothers may be balanced by beneficial IGF-II influence on head circumference.

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### TISSUE-SPECIFIC ACTIVATION OF THE ERYTHROPOIETIN GENE BY THE WILMS' TUMOR SUPPRESSOR WT1(-KTS)

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The mechanisms of the developmental-stage and tissue-specific regulation of erythropoietin (Epo) expression under normoxia are only partially understood yet. The Wilms tumor suppressor gene, Wt1, encodes a zinc finger transcription factor, which is required for the normal development of various organs, including the kidney, heart, and eye. Recent findings suggest a role of Wt1 in the development of the hematopoietic system. In our study, we tested the hypothesis that Wt1 is involved in Epo gene regulation. Using electrophoretic mobility shift assay and in vitro DNA-footprinting, we identified the binding of the Wt1(-KTS) variant, which acts as a transcription factor, to the minimal Epo promoter. Under normoxia, Epo mRNA and protein expression were significantly upregulated in human embryonic kidney HEK 293 cells, which had been stably transfected with Wt1. A reporter plasmid construct harboring the 117bp minimal human Epo promoter was activated more than 20-fold by the Wt1(-KTS) isoform in transient transfection assays. Mutations in the Wt1 binding site in the Epo promoter did not interfer with the hypoxic induction of reporter constructs harboring the downstream Epo enhancer. Hepatic Epo mRNA expression was significantly decreased in Wt1 -/- mouse embryos (e12.0). Immunohistochemical fluorescence-double-staining indicated also the co-expression of Wt1 and Epo in neuronal cells of the developing dorsal root ganglion. Co-expression has been also found in the adult testis were both genes may have antiapoptotic function. Preliminary data indicate furthermore that Wt1(-KTS) modulates the binding of other transcription factors, such as Sp1, to the Epo promoter. In conclusion, Wt1 is a novel transcriptional activator in the developmental-stage and tissue-specific regulation of Epo.

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### ABNORMAL ABCA3 EXPRESSION AND LAMELLAR BODIES FORMATION IN NEWBORNS WITH CONGENITAL SURFACTANT DEFICIENCY.

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**Background**: Besides surfactant protein B (SP-B), respiratory distress syndrome in term neonates is associated to mutations of ABCA3, a gene encoding a type II pneumocyte protein essential for intracellular surfactant metabolism.

**Study goal**: To correlate mutations in surfactant-related genes with specific tissue/cell structural anomalies and alterations of surfactant-related protein expression.

**Methods**: 4 neonates with primary, progressive respiratory failure unresponsive to exogenous surfactant. Optical microscopy (OM) on formalin-fixed lung biopsy: HE, PAS, Masson trichrome; immunohistochemestry with CD45, CD68, SP-B and SP-C antibodies; immunofluorescence with ABCA3 antibody. Electron microscopy (EM) on Karnowsky-fixed ultrathin sections. Direct sequencing of SP-B, SP-C and ABCA3 genes on PCR-amplified genomic DNA.

**Results**: Case 1, 2 and 3 were term-born infants dead at 68, 48 and 55d; case 4 was a 32-week preterm alive with severe respiratory failure at 4 months. OM: all cases showed marked interstitial thickening with monocyte infiltrate, type II pneumocyte hyperplasia, intra-alveolar proteinaceous material and macrophage accumulation. SP-B and SP-C protein expression was normal. ABCA3, abundantly expressed with a cytoplasmic granular pattern in normal subjects, was either absent (1), low with a diffuse cytoplasmic pattern (2,4), or apparently normal (3). EM: in all cases, type II pneumocyte lamellar bodies appeared much smaller than normal and filled with homogenous material with an eccentric, denser inclusion. Pseudomyelin structures, corresponding to intracellular surfactant, were virtually absent. Molecular genetics: SP-B and SP-C gene sequences were normal. In the ABCA3 gene, homozygous frameshift (1) or double heterozygote missense mutations (2,3,4) were found.

**Conclusions**: ABCA3 deficiency is a rare but relevant cause of progressive respiratory failure in newborns. Various recessive mutations are associated with this phenotype, leading in most cases to absent or aberrant ABCA3 protein expression and/or function. Whereas OM may be nonspecific, EM shows typical anomalies of the lamellar bodies that may contribute to early diagnosis.

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### INHALED NITRIC OXIDE IN PRETERM INFANTS OF LESS THAN 30 WEEKS' GESTATION WITH RESPIRATORY DISTRESS SYNDROME

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**Background**. Inhaled nitric oxide (INO) might favour the prevention of bronchopulmonary dysplasia (BPD) in preterm infants through its anti-inflammatory action, regulatory effect in pulmonary angiogenesis, and minimising lung injury through a reduction in oxygen and ventilatory requirements.

**Objectives**. To test the hypothesis that INO therapy can decrease the incidence of BPD and death in preterm infants with RDS; to evaluate the possible predictive factors of response to INO therapy.

**Study design**. Preterm infants (less than 30 weeks of gestation) received during the first week of life INO, or nothing, if they presented severe RDS ($FiO2 > 0.50$ and $a/APO2 < 0.15$), despite mechanical ventilation and surfactant treatment. Then, to evidence possible differences, the treated infants were classified as non responders and responders.

**Results**. Twenty infants were enrolled in the INO therapy group and 20 in the control group. BPD and death were lees frequent in the INO group than in the control group (50 vs. 90%, $p=0.016$). A birth weight lower than 750 grams had a significant predictive value for the failure to respond to INO therapy (OR 12; 95% C.I. 1,3 - 113.3).

**Conclusions**. Inhaled NO decreases the incidence of BPD and death in preterm infants with severe RDS without adverse effects. The birth weight may influence the response of preterm infants to INO therapy.

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### A PROSPECTIVE ECHOCARDIOGRAPHY EVALUATION IN INFANTS OF DIABETIC MOTHERS DURING THE FIRST YEAR OF LIFE.

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Infant of diabetic mothers (IDM) may be in circulatory failure due to hyperthrophic cardiomyopathy (HCM). HCM is thought to be related to high insulin levels in fetus as a consequence of poor controlled maternal diabetes.

**Design**: To analyze the relationship between morphological heart parameters and cardiac function assessed during echocardiography examination in IDM and cord blood insulin,and fructosamine concentration at birth as well as to follow the natural history of echocardiographic findings during the first year of life.

**Material and methods**: A 44 IDM and 30 control subject were prospectively evaluated by echocardiography from birth to 12 months of life. The diabetic group covered 7 PGDM and 37 GDM, among them 18 mothers treated with diet only (G1) and 19 treated with insulin (G2). 8 (18,2 %) out of 44 IDM were born as LGA while in control group all but one neonates were AGA. In IDM venous blood samples were collected at delivery and analyzed for insulin and fructosamine level.

**Results**: IVS diameter was significantly higher ($p<0,01$) in diabetic, especially G2 group, than in control newborns. In 17 out of 44 IDM enlargement of the IVS was noticed; in 15 out of 17 asymmetrical hypertrophy and in to other cases symmetrical hypertrophy was noticed. There was not found any significant correlation between cord blood insulin and fructosamine levels and occurrence of the features of HCM. The ratio of IVSd/LVPW in the control group was 1,03 +/- 0,14 while in IDM was significantly ( $p<0,001$) higher- 1,32+/- 0,52. During 12 months observation resolution of HCM was confirmed.

**Conclusion**: Infants born to mothers with diabetes first recognized during pregnancy and treated with insulin ( G2) are at high risk for developing HCM. Resolution of HCM to normality was confirmed during 12 months echocardiography observation of IDM.