We have shown that EFW or AC <10th or 5th centiles should no longer be used to define pregnancies at high risk for adverse outcome, but instead a more selective definition is suggested. To no longer subject pregnancies with EFW or AC <10th or 5th centiles to increased surveillance, unless also accompanied by abnormal UA Dopplers, will have significant impact on resource utilization in contemporary obstetric practice and will allow for more efficient targeting of obstetric resources.

Predictors of adverse perinatal outcome*

Predictor	Adverse outcome* (n=65)	NICU admisson (n=324)	Normal outcome (n=991)	P-value
EFW <3rd	58 (89.2%)	282 (87.0%)	721 (72.8%)	0.0034
EFW <5th	62(95.4%)	311 (96%)	926 (93.4%)	0.5363
EFW <10th	65 (100%)	324 (100%)	991(100%)	N/A
AC <3rd	59 (90.8%)	292 (90.1%)	814 (82.1%)	0.0750
AC <5th	60 (92.3%)	308 (95.1%)	892 (90.0%)	0.5470
AC <10th	63 (96.9%)	318 (98.1%)	958 (96.7%)	0.9121
EFW <3rd + oligo	13(20.0%)	66 (20.4%)	115 (11.6%)	0.0445
EFW <5th + oligo	13 (20.0%)	76 (23.5%)	177 (17.9%)	0.6636
EFW <10th + oligo	15 (23.1%)	82 (25.3%)	214(21.6%)	0.7787
AC <3rd + oligo	14 (21.5%)	70 (21.6%)	165 (16.6%)	0.3089
AC <5th + oligo	14 (21.5%)	73 (22.5%)	189 (19.1%)	0.6249
AC <10th + oligo	14 (21.5%)	77 (23.8%)	214(21.6%)	0.9915
EFW <3rd + oligo + abnormal Doppler	45 (69.2%)	159 (49.1%	209 (21.1%)	<0.0001
EFW <5th + oligo + abnormal Doppler	48 (73.8%)	172 (53.1%)	295 (29.8%)	<0.0001
EFW <10th + oligo + abnormal Doppler	50(76.9%)	183 (56.5%)	351 (35.4%)	<0.0001
AC <3rd + oligo + abnormal Doppler	45 (69.2%)	163 (50.3%)	272 (27.4%)	<0.0001
AC <5th + oligo + abnormal Doppler	46 (70.8%)	172 (53.1%)	303 (30.6%)	<0.0001
AC <10th + oligo + abnormal Doppler	49 (75.4%)	180 (55.6%)	344 (34.7%)	<0.0001

*Includes composite outcome of IVH, PVL, HIE, NEC, BPD, sepsis and perinatal mortality. Abnormal Doppler refers to AEDF in the umbilical artery or pulsatility index greater than 95th centile.

20 Maternal allopurinol administration during term labor for neuroprotection in case of fetal asphyxia: a multicenter randomized controlled trial

Joepe Kaandorp[1], Manon Benders[2], Ewoud Schuit[3], Carin Rademaker[4], Martijn Oudijk[2], Martina Porath[5], Sidarto Bambang Oetomo[6], Maurice Wouters[7], Ruurd Elburg[8], Maureen Franssen[9], Arie Bos[10], Timo de Haan[12], Janine Boon[13], Inge de Boer[14], Robbert Rijnders[15], Corrie Jacobs[16], Liesbeth Scheepers[17], Danilo Gavilanes[18], Kitty Bloemenkamp[19], Monique Rijken[20], Gerard Visser[2], Ben Willem Mol[11], Frank van Bel[2], Jan Derks[2]

[1]University Medical Center Utrecht, Dutch Consortium for Studies in Obstetrics, Fertility and Gynaecology, Utrecht, Netherlands, [2]University Medical Center Utrecht, Perinatology, Utrecht, Netherlands, [3]University Medical Center Utrecht, Julius Center for Health Sciences, Utrecht, Netherlands, [4]University Medical Center Utrecht, Clinical Pharmacy, Utrecht, Netherlands, [5]Maxima Medical Center, Obstetrics, Veldhoven, Netherlands, [6]Maxima Medical Center, Neonatology, Veldhoven, Netherlands, [7]VU University Medical Center, Obstetrics, Amsterdam, Netherlands, [8]VU University Medical Center, Neonatology, Amsterdam, Netherlands, [9]University Medical Center Groningen, Obstetrics, Groningen, Netherlands, [10]University Medical Center Groningen, Neonatology, Groningen, Netherlands, [11]Academic Medical Center, Obstetrics, Amsterdam, Netherlands, [12]Academic Medical Center, Neonatology, Amsterdam, Netherlands, [13]Diakonessenhuis, Obstetrics, Utrecht, Netherlands, [14]Diakonessenhuis, Neonatology, Utrecht, Netherlands, [15]Jeroen Bosch Hospital, Obstetrics, Den Bosch, Netherlands, [16]Jeroen Bosch Hospital, Neonatology, Den Bosch, Netherlands, [17]Maastricht University Medical Center, Obstetrics, Maastricht, Netherlands, [18]Maastricht University Medical Center, Neonatology, Maastricht, Netherlands, [19]Leids University Medical Center, Obstetrics, Leiden, Netherlands, [20]Leids University Medical Center, Neonatology, Leiden, Netherlands

OBJECTIVE: Hypoxic-ischemic encephalopathy due to perinatal hypoxia-induced free radical formation is an important cause of neurodevelopmental disabilities. Allopurinol (ALLO) reduces the formation of free radicals, which potentially limits hypoxia-induced brain damage. With this trial we aimed to assess whether maternal ALLO treatment during fetal hypoxia would reduce the release of biomarkers associated with neonatal brain damage.

STUDY DESIGN: We performed a randomized double blind placebo controlled multicenter trial (NCT00189007) studying laboring women at term with imminent fetal hypoxia. Fetal distress was suspected in case of an abnormal fetal heart rate, significant ST-changes on fetal ECG or fetal scalp pH <7.20. Women were allocated to receive ALLO 500 mg IV or placebo immediately prior to delivery. Primary endpoint was S100B in cord blood, neuroketal was a secondary endpoint. Both are tissue-specific biomarkers for brain damage. Because S100B followed a very skewed distribution we performed quantile regression to estimate the difference in median between the treatment groups (DiM). For neuroketal we report geometric mean differences (GMD). Because both S100B and neuroketal approached physiological values, we also examined the difference in infants with an S100B or neuroketal value < p75.

RESULTS: Between Oct 2009 and Dec 2011 we randomized 222 women to ALLO (n=111) or placebo (n=111). No significant differences were found between the two groups for both S100B (DiM -7.69 (95%CI -24.9;9.52), RR<p75 0.85 (95%CI 0.53-1.36)) and neuroketal (GMD -7.53 (95%CI -15.5;3.62), RR<p75 0.85 (95%CI 0.51-1.4)). Post-hoc subgroup-analysis however showed a marked gender difference in treatment effect in favor of girls for both S100B (RR<p75 0.37 (95%CI 0.14-0.99)) and neuroketal (GMD-16.4 (95%CI -24.6;-1.64)).

CONCLUSION: Maternal treatment with ALLO during fetal hypoxia reduces damage to neuronal cells as indicated by brain-tissue-specific chemical biomarkers, but only in girls.

21 Sex-specific genetic susceptibility to adverse neurodevelopmental outcome after early preterm birth

Erin A. S. Clark[1]

[1]Maternal Fetal Medicine Units Network, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Bethesda, MD

OBJECTIVE: In-vivo and in-vitro data suggest neurobiological differences between male and female susceptibility and response to brain injury. We aimed to determine if sex-specific genetic susceptibility loci are associated with adverse neurodevelopmental outcome after early preterm birth.

STUDY DESIGN: Secondary case-control analysis of a randomized trial of magnesium sulfate (MgSO4) before anticipated early preterm birth (<32 weeks) for prevention of cerebral palsy (CP). Cases died by age 1 year or developed CP, mental or psychomotor delay (defined as Bayley MDI or PDI <70) by age 2. Controls were survivors with normal neurodevelopment. Neonatal DNA was evaluated for 80 polymorphisms (33 genes) in inflammation, coagulation, vasoregulation, excitotoxicity and oxidative stress pathways using Taqman assays. Cases and controls were matched by maternal race and infant sex. Conditional logistic regression determined the odds ratio for each polymorphism (additive model) by sex stratum and adjusted for gestational age at birth, maternal education level, and exposure to MgSO4 and antenatal corticosteroids. An interaction term between infant sex and genotype tested heterogeneity across strata. Holm-Bonferroni method was used to adjust for multiple comparisons (p<7.3x10-4).

RESULTS: Analysis included 211 cases (134 males and 77 females) and 215 controls (130 males and 83 females). A polymorphism in the inflammatory cytokine interleukin-6 (IL6) gene (rs2069840) was associated with adverse neurodevelopmental outcome in females (OR 2.6, 95% CI 1.5-4.7; p=0.001), but not in males (OR 0.8, 95% CI 0.5-1.2; p=0.33). The effect difference between males and females was significant (p=7.0x10-4). MgSO4 exposure did not modify this association. The remaining gene-sex associations were not significant after correction for multiple comparisons.

CONCLUSION: An IL6 gene locus may confer sex-specific susceptibility to adverse neurodevelopmental outcome in females after early preterm birth.