Many evidences have correlated neonatal diseases with oxidative stress (OS) caused by the harmful effect of free radicals (FRs). FRs are reactive oxygen and nitrogen species formed as a result of normal cellular metabolism and have many roles in cell signaling pathways. FRs can be also produced in the course of hypoxia, ischemia, ischemia-reperfusion, hyperoxia, inflammation and as consequence of exposition to many endogenous and exogenous oxidising agents. OS injury occurs when tissues, cells and biomolecules undergo an excessive exposition to oxidising agents, both endogenous (substances produced by inflammatory cells) and exogenous (environmental toxins). The FRs production exceeds antioxidant defences and OS occurs. OS is on the basis of several human pathologies such as stroke, hypertension, diabetes, rheumatic diseases, multiple sclerosis, neurodegenerative diseases and cancer. In Neonatology, OS is involved in the development of several FR-related diseases (FRRD) such as oxidative hemolysis, intraventricular haemorrhage, necrotizing enterocolitis, retinopathy of prematurity, chronic lung disease, renal failure. The damaging effect of FRs in perinatal period may be demonstrated by measuring OS biochemical markers in amniotic fluid and in cord blood. Intrauterine hypoxia induces OS in pregnancies with fetal growth restriction (FGR). Prostaglandins concentration, actually considered as the best biomarker of OS, are particularly elevated in amniotic fluid of pregnancies with Down syndrome affected fetuses and in cord blood of newborns from maternal chorioamnionitis. They also have a significant predictive value to early detect pregnancies at high risk of perinatal fetal hypoxia and newborns who will develop the FRRD.

**Ischemia-Resuscitation Pathway**

XO-derived superoxide occurs upon reoxygenation after asphyxia, a trial with allopurinol to the mother with signs of perinatal fetal hypoxia has been started. Activation of inflammatory factors after asphyxia is recognised to be related to post-aphyxic brain damage.

Rather than monotherapy directed to one pathway, a combination of drugs intervening in various pathways in relation with the time-profile of these pathways, might achieve optimal reduction of reperfusion injury.

**Long-term Outcome After Critical Illness: The Need for Appropriate Care Continues After Discharge from the ICU**

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**Antioxidant Strategies: Where Are We Now?**

F. van Bel. Neonatology, University Medical Center Utrecht, Utrecht, Netherlands

Part of asphyxia-related brain damage occurs upon reoxygenation. Renewed availability of oxygen activate biochemical pathways and neuronal cell death. Important pathways are: 1) Calcium-induced formation of neurotransmitters; 2) formation of (pro-) radicals; 3) activation of inflammation; 4) induction of apoptosis; 5) depletion of growth factors. Four important sources of free radicals are: 1) Nitric oxide (NO)-related formation of peroxynitrite. It is reported that selective iNOS/eNOS inhibitor 2-aminobiotin induced neuroprotection after asphyxia in animal models. 2) Pro-radicals, such as non proteinbound-iron (NPBI), lead to formation of hydroxyl free radicals. NPBI chelation with deferoxamine, which has also a stabilising effect on HIF1-α and stimulates trophic factors, showed encouraging results in experimental models. 3) Formation of superoxide radical by metabolism of xanthine-oxidase (XO) can be blocked by XO-inhibitors such as allopurinol. 4) Metabolisation of arachidonic acid to prostaglandin leading to superoxide can be blocked by cyclo-oxygenase inhibitors. Since XO-derived superoxide occurs upon reoxygenation after asphyxia, a trial with allopurinol to the mother with signs of perinatal fetal hypoxia has been started. Activation of inflammatory factors after asphyxia is recognised to be related to post-aphyxic brain damage.

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**Neonatal Extracorporeal Membrane Oxygenation, Risk Factors for the Brain and Long Term Neurological Outcome**

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