

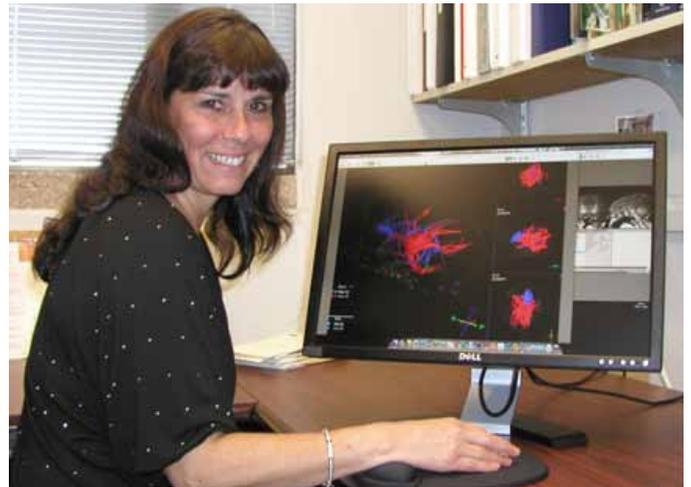


## Epo May Provide Breath of Life to Newborns Experiencing Severe Oxygen Deprivation

by Joel Schwarz

Every year between 5 and 10 percent of babies born around the world experience perinatal asphyxia (or severe oxygen deprivation). In the United States the picture isn't as bleak but asphyxia is one of the leading causes of neonatal death and brain injury, with effects more dire among extremely preterm babies. A therapeutic regime is sorely needed to mitigate and even reverse some of the devastating neonatal brain injuries caused by asphyxia as well as by stroke and intracerebral hemorrhage. Among those scientists searching for a treatment is Sandra Juul, M.D., Ph.D., an associate professor of pediatrics at the University of Washington and a research affiliate of the Center on Human Development and Disability (CHDD).

Juul is investigating new, safe, and effective approaches for treating neonatal brain injury and much of her work focuses on erythropoietin (Epo), a hormone produced in the kidneys that controls and stimulates the production of oxygen-transporting red blood cells. Epo also has been found in the spinal fluid of newborns and its receptors have been located in the brain and spinal cord. There are two forms of Epo, a naturally occurring type and a synthetic form, recombinant erythropoietin (also commonly called Epo). Epo has been used to treat anemia in chronic renal disease for more than two decades. There is also a darker side to Epo usage, as an illegal "blood doping" agent to improve athletic performance. Epo is approved for treating anemia in infants, but not in neonates or preterm infants. This is not unusual, according to Juul, because most available drugs have not been studied on the patient group with which she works. More recently, Epo has been found to have neuroprotective effects. Research using high doses of Epo to treat perinatal asphyxia was delayed for nearly two years in the U.S. after increased mortality was reported in elderly stroke patients who were given the hormone in German trials. After determining these risks were not pertinent to neonates, the Federal Drug Administration hold was lifted last year and Juul is involved in two new studies. The NEAT trial is a phase I/II study of term and near-term infants with perinatal asphyxia treated at Seattle Children's Hospital. The other is a larger randomized controlled phase II/III study of 475 extremely preterm babies at 15 medical centers across the country.



Sandra Juul studies images to measure the extent of brain damage caused by perinatal asphyxia, a condition that can cause death or severe life-long disabilities including seizures, cerebral palsy and intellectual disabilities.

Perinatal asphyxia can occur when a newborn has difficulty initiating and maintaining breathing after birth or if the placenta malfunctions before birth. This prevents oxygen and carbon dioxide from being exchanged, leading to a significant drop in the baby's blood oxygen and a build up of carbon dioxide. If this is not fixed quickly, blood pressure falls and the heart rate slows, preventing adequate blood flow from reaching critical organs, especially the brain, and causing damage. The brain damage caused by this oxygen deprivation can lead to severe life-long disabilities among survivors including intellectual disability, seizures, and cerebral palsy. At present, the only treatment that has shown any effectiveness in mitigating the effects of perinatal asphyxia is hypothermia, but its efficacy is limited. Hypothermia works by interfering with and slowing down the cascade of events that occurs after a brain injury and thus preventing further damage. "In term and near-term neonates 65 percent who have brain injuries will suffer death or lifelong impairment," Juul said, "with hypothermia treatment, that goes down to 50 percent. But that's not good enough and there is no data on hypothermia use with preterm babies."

Epo works to counteract the effects of asphyxia by decreasing inflammation resulting from the brain injury and decreasing cell death. It also helps by promoting red blood cell precursor cells in bone marrow to mature into red blood cells that transport oxygen. The increased production of red blood cells also increases iron utilization, a process that decreases oxidative injury to the brain. In addition, Epo is believed to provide protection to oligodendrocytes, cells that make the myelin to sheath neurons. Oligodendrocyte precursor cells can be damaged in preterm babies leading to brain injury. One unanswered question that Juul is working on is determining the dosage needed to effectively treat term and preterm babies. Epo is administered into the bloodstream in high doses because very little of the hormone passes through the brain-blood barrier. "With an intact brain-blood barrier only about 1 percent of the Epo gets across the barrier. But if you have an injured brain, the Epo gets across better." In her current work she is comparing doses of 500 and 1000 units of Epo per kilogram of infant weight. Also still to be determined in the new studies are the optimal timing of treatment and number of doses required to mitigate damage initiated by asphyxia.



Sandra Juul heads a team of researchers investigating new, safe, and effective approaches for treating neonatal brain injury caused by severe oxygen deprivation. Much of her work centers on effectiveness of the hormone erythropoietin, or Epo.

"Once we can determine the best dosing regimen for Epo, I believe we can significantly improve the lives of eight or nine thousand premature babies a year in this country plus many more term babies," said Juul. "Today most babies who survive asphyxia face big challenges. We want to improve the outcomes of babies that survive. Epo has great potential because it is likely to be effective and safe, is readily available, is not very costly and is easy to administer."

CHDD is an interdisciplinary center dedicated to the prevention and amelioration of developmental disabilities through research, training, clinical service, and community outreach. CHDD includes the University Center of Excellence in Developmental Disabilities and the Eunice Kennedy Shriver Intellectual and Developmental Disabilities Research Center.

#### CHDD Outlook

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