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A Neuroprotective Agent for Extremely Preterm Infants

by Sally James

Sandra Juul, M.D., Ph.D., has spent 18 years chasing down a way to help minimize the health and developmental effects for babies who are born too early or sometimes suffer low oxygen before, during, or after birth. A new grant of more than \$9 million may finally get her to the finish line. “This is a dream come true,” she said, during an interview. Juul, a professor of pediatrics and a research affiliate of the Center on Human Development and Disability (CHDD), studies many different reasons that babies can suffer brain damage.

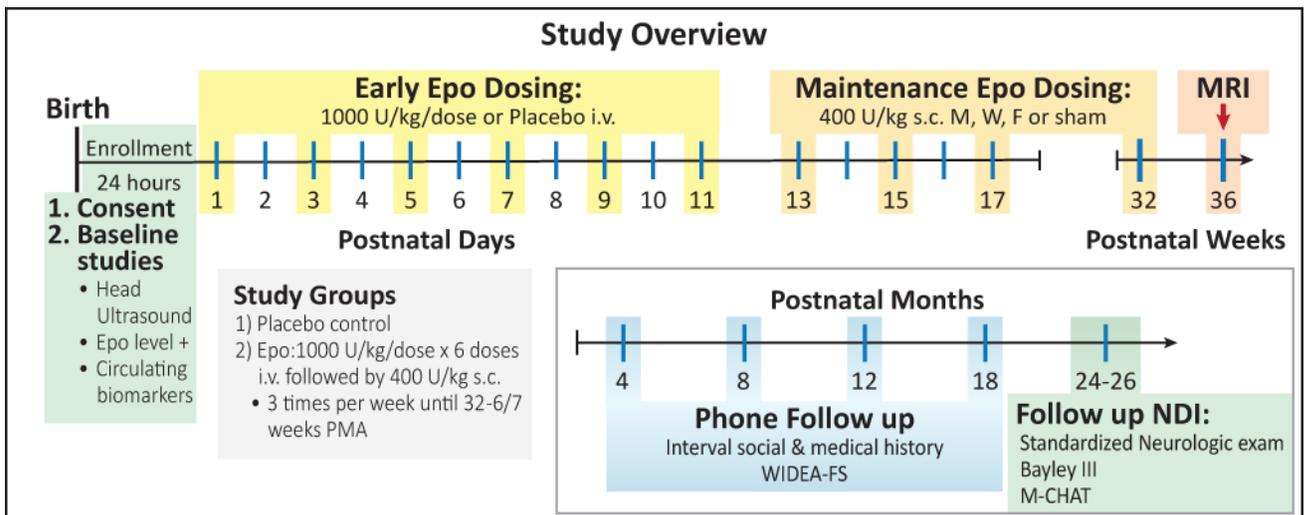
Juul’s most recent grant focuses on preterm infants in neonatal intensive care units at 16 different sites across the country. The program may enroll about 100 families in Washington who receive care from the University of Washington and receive medical and developmental assessments at CHDD’s Neonatal Intensive Care Unit Follow-Up Clinic. In all, the study will enroll 940 babies over a three year period, with plans to evaluate them at two years of age. Babies chosen for this research are those born early – specifically before 28 weeks of gestation. Forty weeks is normal gestation. As a group, these infants are called Extremely Low Gestational Age Neonates or ELGANS. One in five of them will die before leaving the hospital. Cerebral palsy, deafness, blindness, and/or intellectual disability is present in approximately 50% of survivors at school age. Those chosen for the experimental group in this study will receive erythropoietin, (also shortened to Epo), a hormone produced in the kidneys that stimulates red-blood cell production in the human body, and has also been shown to have protective effects on the brain. There are two forms of Epo, a naturally occurring type and a synthetic recombinant form.

Research previously carried out by Juul in animals has shown that Epo decreases brain injury by decreasing inflammation and programmed cell death. It also promotes the regeneration of neurons and protects a special cell known as an oligodendrocyte. The oligodendrocyte is crucial to normal brain development in preterm children. Improving outcomes for these preterm infants can have a profound impact on the individual, their families, and on society.

Epo has already been used for treating anemia in infants and adults, so it is a medication well known and widely available. In fact, if Epo sounds familiar it is because the same compound has been used by high-performing athletes for a different purpose in what is called “blood-doping.”



Sandra Juul’s research goal is to improve the lives of preterm babies and their families by utilizing a hormone produced in the kidneys and widely available in a synthetic form.



Recently there was a highly publicized admission of such illegal use by bicyclist Lance Armstrong, once a respected international star for his triumphs in the Tour de France race.

One other hope of the trial is that researchers will establish some biomarkers in the blood that help predict the level of disability that the children will experience as 2-year-olds. Researchers will be taking sequential blood samples from study participants and using MRI (magnetic resonance imaging) tests to measure brain development. It is possible that the carefully sequenced testing and sampling might lead to a reliable predictor for developmental disorders.

If this research proves the effectiveness of Epo treatment, Juul has high hopes that physicians may adopt the new approach quickly. Since the medication is widely available already in neonatal intensive care units, and it is not expensive, she believes clear results of a large study could lead to widespread adoption. Winning over practicing physicians could benefit thousands of babies, if the treatment lives up to expectations in the large clinical trial. "If Epo is proven to safely reduce combined morbidity and mortality of ELGANS, we anticipate a shift in neonatology practice that would improve the lives of babies and their families, and decrease the cost of health care," she wrote in her grant application. Juul remembers the skeptics at her presentations, which began in the 1990s. Her first paper on using Epo for babies was published in 1997. "The idea has moved from crazy to obvious," she said.

Besides this ELGANS study, she also hopes to receive a grant that would allow treatment of babies who suffer perinatal asphyxia. Asphyxia is one of the leading causes of neonatal death and developmental disability and can happen to both babies born early (preterm) and babies born at full term. Perinatal asphyxia can occur when a newborn has difficulty beginning and maintaining breathing after birth or if the placenta malfunctions before birth. This prevents oxygen and carbon dioxide from getting exchanged, leading a significant drop in the baby's blood oxygen. There is a cascade of symptoms that can lead to a slower heart rate and less blood to the brain, which can cause permanent brain damage. Approximately 7000 babies per year are affected by this problem each year in the United States.

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.

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