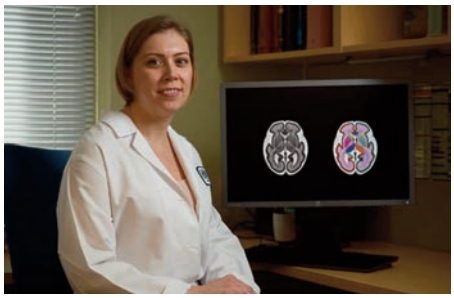
WINTER 2016

BRIGHAM AND WOMEN'S HOSPITAL

NEONATOLOGY ADVANCES



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HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Innovative Strategies to Improve Long-term Outcomes in High-risk Infants in the Neonatal Intensive Care Unit

Led by Terrie E. Inder, MBChB, MD, Chair of the Department of Pediatric Newborn Medicine at Brigham and Women's Hospital (BWH), a team including neonatologists, infant and child development experts, nutritionists, rehabilitation specialists, and providers in many other disciplines at BWH is employing a wide range of strategies to optimize long-term outcomes for high-risk infants who spend their first weeks and months in the neonatal intensive care unit (NICU).

"With medical advances, three out of four babies born between one and one and a half pounds today will survive, but many will suffer from long-term challenges, including developmental delays, learning difficulties in school, and other issues," said Dr. Inder, who is dual board certified in neonatology and pediatric neurology. "Using serial imaging, we have led extensive research in brain development in preterm and critically-ill babies to help guide our new initiatives and ensure that our NICU environment and practices are designed to support these babies' critical brain development."

Recent significant findings from serial brain imaging studies conducted by Dr. Inder and her team include:

- Preterm birth disrupts cortical development in a regionally specific fashion with abnormalities evident by term-equivalent postpartum age. This disruption is influenced by both antenatal growth and postnatal course. (*Ann Neurol*. 2015 Jan; 77(1):154-62.);
- A complex pattern of regional vulnerabilities in brain development may contribute to the diverse and long-lasting neurobehavioral consequences that can occur after very premature birth (*Neuroimage*. 2015 Apr 1;109:469-79.);
- White matter tract integrity is associated with later attentional abilities in very preterm children (*Neuroimage*. 2016 Jan 1;124(Pt A):75-84.).

Improving Outcomes through Technology and New Advances

Techniques used to enhance brain development in infants in the BWH NICU include:

- Magnetic resonance imaging (MRI) is typically performed on day four and day 10 for at-risk infants and is used to assess extent of injury, response to therapy, and recommendations for rehabilitation;
- Auditory exposure, such as reading to the baby and exposing them to a normally noisy environment in the NICU has been shown to benefit language development;
- Clinical trials, including the study of the bumetanide in the effectiveness in seizure control and a Phase II study using reinfusion of autologous stems cells from cord blood to more broadly study the impact on the brain environment in infants who have suffered brain injury. BWH will be the site for most of the MRI readings for this latter study.

Terrie E. Inder, MBChB, MD, leads an expert team to employ strategies that optimize outcomes for high-risk infants.

Groundbreaking NICU Redesign

BWH's NICU team cares for approximately 3,000 preterm and critically-ill infants each year. In 2017, BWH will open its newly redesigned NICU, built to specifically support the NICU team's goals and programs.

Advanced technological advances in the NICU include:

- Continuous electroencephalography (EEG) monitoring to optimize neurodevelopment;
- Near-infrared spectroscopy for cerebral blood flow monitoring;
- Dedicated magnetic resonance imaging (MRI).

Terrie E. Inder, MBChB, MD
Chair,
Department of Pediatric Newborn Medicine,
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Access and Information

For a consultation, more information on our neonatologists, or to refer a patient, please call **(617) 732-9894** or email **bwhreferrals@partners.org**.

The Impact of Nutritional Supplementation on the Metabolic Environment in Pregnant and Lactating Obese Women

In an effort to improve short- and long-term outcomes of babies and mothers impacted by maternal obesity, neonatologists in the Brigham and Women's Hospital (BWH) Department of Pediatric Newborn Medicine are devising strategic interventions to address metabolic dysregulation in pregnant and lactating obese women.

"Obesity has become one of the most pressing public health issues of our time and is associated with increased risks for preterm birth, birth defects, and the development of significant medical conditions in childhood," said Sarbattama Sen, MD, a neonatologist in the Department of Pediatric Newborn Medicine at Brigham and Women's Hospital (BWH). "We believe that the abnormal metabolic environment in obesity, which is characterized by increased inflammation and oxidative stress, may improve with tailored nutritional supplementation, thus reducing some risks posed by maternal obesity."

BMI-based Prenatal Vitamin Study (The PNV Study)

Dr. Sen is the Principal Investigator of a current double-blind randomized control trial including 100 obese women early in pregnancy and 100 obese women planning pregnancy. Trial participants receive either a standard prenatal vitamin and a placebo or a standard prenatal vitamin and a vitamin supplement with additional amounts of specific antioxidant micronutrients.

Primary outcomes of the study include:

- Vitamin levels;
- Markers of oxidative stress and inflammation in mothers and infants;
- Cord blood levels.

Secondary outcomes of the study include:

- Infant growth and adiposity via body composition assessment;
- Breastfeeding success and breastmilk composition;
- Infant development.

As part of the study, monthly urine samples are collected, and blood samples are taken at three points throughout pregnancy. Infant body composition is measured shortly after birth *(see sidebar)*, and the infants will then be followed at six months and at one year with samples to include blood for metabolic assays.

Maternal Obesity and Postnatal Health

The team also is examining the impact of maternal obesity on postnatal health of infants through breastmilk composition. Previously, Dr. Sen and colleagues measured pro-inflammatory nutritional substances in the breastmilk of lean and obese women one-to-two months postpartum and found:

- Ratio of omega-6 to omega-3 fatty acids increased as maternal BMI increased (*J Perinatal*. 2016 Jan 7. doi: 10.1038/jp.2015.199.);
- Lower concentrations of the neuroprotective substances DHA, ARA, and lutein (*J Perinatal*. 2016 Jan 7. doi: 10.1038/jp.2015.199.) in the breastmilk of obese women.

Follow-up research is being planned to assess whether maternal perinatal nutritional supplementation and targeted dietary modification can improve breastmilk composition in obese mothers.

"These studies are designed to test feasible and practical interventions to decrease inflammation pre- and post-natally and, hopefully, improve outcomes in children of obese mothers," said Dr. Sen.

Infant Body Composition Assessment

Neonatologists in the Neonatal Intensive Care Unit (NICU) at BWH employ an air displacement plethysmography system using whole body densitometry to determine body composition, including total weight, fat mass, and fat-free mass. Data derived from the system is being used in multiple research studies, including the breastmilk analyzer study described on page 5.

Sarbattama Sen, MD
Neonatologist,
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Brain Imaging Study Measures Fetal Brain Development in Congenital Heart Disease, Informs Neuroprotective Approaches

Neonatologists in the Department of Pediatric Newborn Medicine at Brigham and Women's Hospital (BWH) are leading studies to better understand underlying brain abnormalities in babies with congenital heart disease (CHD) and ultimately improve neurodevelopmental outcomes.

"Congenital heart disease is associated with long-term neurodevelopmental impairment, including deficits in attention, executive function, social cognition, and academic skills," said Cynthia M. Ortinau, MD, a neonatologist in the Department of Pediatric Newborn Medicine. "Through our research, we are striving to identify neuroprotective strategies to mitigate these risks in babies with congenital heart disease."

Large-scale Fetal Brain Development Study

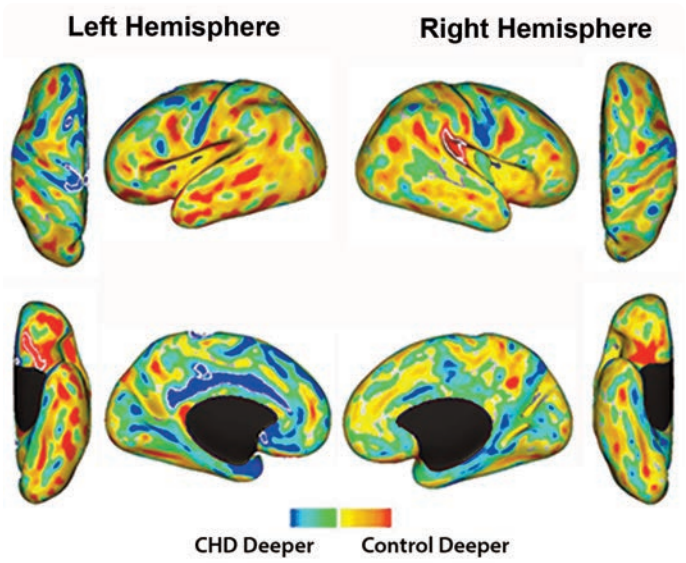
A research team at BWH led by Dr. Ortinau is collaborating with specialists at Boston Children's Hospital on a current large-scale fetal brain development study (Fetal Brain Development and Connectivity in Congenital Heart Disease) incorporating all forms of CHD that will likely require surgery during infancy. The study is enrolling up to 150 pregnant women, including 2/3 with fetal CHD and 1/3 as healthy controls.

"Most published data on CHD and brain development has been done after babies are born and are derived from smaller studies that are often restricted to a few select conditions," said Dr. Ortinau. "Our study is designed to understand brain development in many forms of CHD, beginning before babies are born, and categorize those conditions that pose the most risk for neurodevelopmental impairment."

As part of the study, fetal magnetic resonance imaging (MRI) is performed twice during pregnancy. The first fetal MRI is in the early third trimester. This MRI measures brain size, growth, and characteristics of multiple regions, including specific areas of the white matter, deep gray matter, and cortex. The second fetal MRI, performed just prior to delivery, determines how these regions change over time and whether abnormalities on the first MRI lead to further impairments in brain development, particularly of the deep gray matter and cortex.

"These images provide us with key information on the way the fetal brain changes over time," said Dr. Ortinau. "We also examine fetal brain development in association with specific aspects of heart physiology that may affect the way the brain is developing. These details will help us understand why brain development is different in CHD and identify who may benefit from neuroprotection."

To assess postnatal neurologic abnormalities, MRI is scheduled after birth (before surgery) and again between three and six months of age. Neurodevelopmental outcomes are measured between three and six months of age and again when the babies reach two years of age.



Maps comparing brain folding between infants with CHD and controls. Areas in yellow and red indicate regions where control infants had more folding.

Previous Findings

The current study builds on previous important findings by Dr. Ortinau and other BWH researchers, including:

- Infants with CHD have smaller brain measures in the frontal lobe, parietal lobe, cerebellum, and brain stem (*J Thorac Cardiovasc Surg*. 2012 Jun;143(6):1264-70.);
- Decreased surface area, less folding of the brain, and alterations in sulcal depth are evident prior to cardiac surgery (*J Pediatr.* 2013 Nov;163(5):1507-10.);
- Infants with CHD have the same rates of brain growth in the cerebellum as healthy term infants in the first three months of life after surgical repair for CHD. Nutritional factors appear to play an important role in this growth. (*Pediatr Cardiol.* 2012 Oct;33(7):1138-46.)

Cynthia M. Ortinau, MD
Neonatologist,
Department of Pediatric Newborn Medicine,
Brigham and Women's Hospital

Novel Studies Using Breastmilk Analysis Aim to Optimize Neurodevelopment in Preterm Infants

Studies led by neonatologists in the Department of Pediatric Newborn Medicine at Brigham and Women's Hospital (BWH) are analyzing the nutritional composition of breastmilk, with a goal of conducting future studies using individualized fortification of breastmilk for optimal growth and neurodevelopment of preterm infants in the BWH Neonatal Intensive Care Unit (NICU).

"We know that nutrition plays a large role in neurodevelopment and that preterm babies who achieve higher weight gain during their NICU stay have better neurodevelopmental outcomes," said Mandy Brown Belfort, MD, MPH, a neonatologist in the Department of Pediatric Newborn Medicine. "While breastmilk offers a myriad of advantages, preterm babies given breastmilk tend to gain weight at a slower rate than those given formula."

Currently, the standard of care for preterm infants who are given breastmilk in the NICU is fortification of the breastmilk based on the baby's gestational age, weight, and demonstrated growth pattern. This assumes, however, that all breastmilk contains the same nutritional components.

"The challenge with this practice is that the nutritional composition of an individual mother's breastmilk can be highly variable day-to-day or even throughout the course of one day," said Dr. Belfort. "Without analyzing each sample, we have no way of knowing its true nutritional composition."

Neonatologist Mandy Brown Belfort, MD, MPH, is leading a pilot study that utilizes specialized equipment to assess breastmilk composition, including macronutrients like protein and fat that are important for growth and neurodevelopment.

Pilot Study Supports Trial Design

A new pilot study led by Dr. Belfort is using specialized equipment to assess breastmilk composition, including macronutrients like protein and fat that are important for growth and neurodevelopment. The team is collecting data to compare the nutritional components of the breastmilk with the infants' growth patterns, body composition, and brain growth while they are in the NICU. The pilot study is expected to continue until mid-2016.

"Our initial study is designed to examine the babies' growth patterns based on the breastmilk's nutritional composition," said Dr. Belfort. "Those data will give us an indication as to whether individualized fortification of the breastmilk based on routine nutritional analysis is likely to improve the baby's growth and outcomes."

Data collected from the pilot study will be used to support future clinical trials that will compare the growth of infants given individualized fortification with the growth of infants that are fed following the standard-of-care guidelines. These studies are planned to include long-term follow up after the infants leave the NICU.

Building on Previous Findings

Current studies build on Dr. Belfort's previous research, which:

- Examined the association between growth patterns in preterm infants in the NICU with neurodevelopmental outcomes (*Pediatrics.* 2011 Oct;128(4):e899-906.);
- Determined a positive relationship between longer breastfeeding duration of healthy full-term infants and higher receptive language and verbal and nonverbal intelligence later in life (*JAMA Pediatr.* 2013 Sep;167(9):836-44.).

Mandy Brown Belfort, MD, MPH
Neonatologist,
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Access to our Neonatology Services

Our Physician Liaisons Ellen Steward and Tom Anderson can provide direct assistance with consultations. Ellen can be reached at **(617) 582-4733** or via email at **esteward@partners.org**. Tom can be reached at **(617) 582-4760** or via email at **tanderson0@partners.org**.

Watch Our Videos with BWH Neonatologists

Visit **brighamandwomens.org/neonatologyadvances** to view these videos:

Brain Development in Preterm Infants

Terrie E. Inder, MBChB, MD, Chair of the Department of Pediatric Newborn Medicine at Brigham and Women's Hospital, explains the impact of premature birth on neonatal brain development. In addition, she describes how brain imaging can help predict the likelihood of learning problems and discusses research examining the impact of auditory stimulation on neonatal brain development.

Newborn Brain Development Research

Terrie E. Inder, MBChB, MD, Chair, Department of Pediatric Newborn Medicine, Christopher McPherson, PharmD, clinical pharmacist in the Neonatal Intensive Care Unit, Cynthia M. Ortinau MD, and Sarbattama Sen, MD, neonatologists and clinical investigators in the Department of Pediatric Newborn Medicine, present research on neurodevelopment in high-risk infants. Areas of research covered include focusing on accurate, early diagnosis of brain injury as well as developing treatments and preventive strategies to reduce subsequent disabilities; the impact of drugs on the developing newborn brain; brain magnetic resonance imaging before and after birth to understand the nature and timing of alterations in brain development and neurodevelopmental outcomes in infants born with congenital heart disease; and devising and trialing dietary interventions to improve pregnancy outcomes for obese women and their infants.

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