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neonatal INTENSIVE CARE

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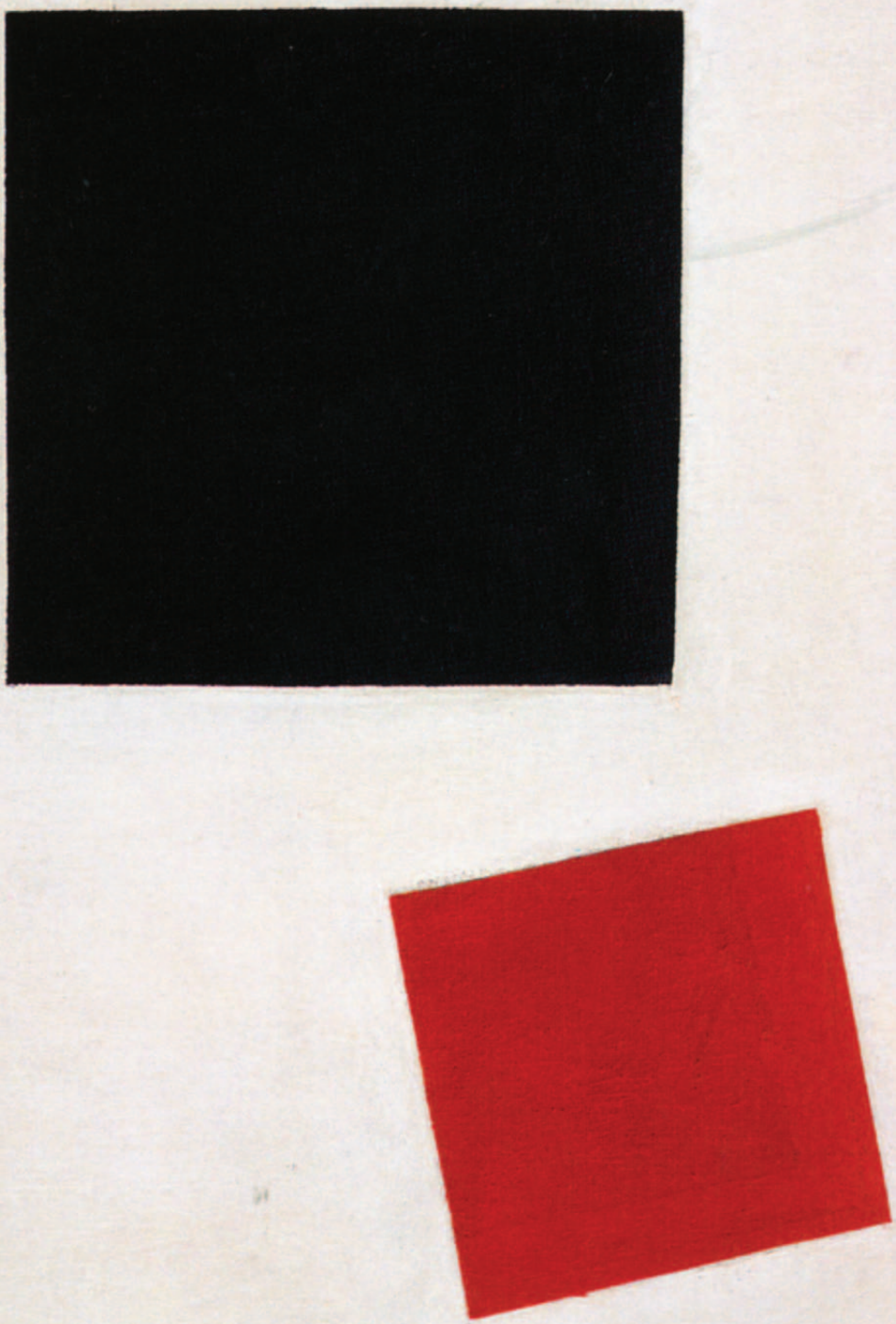

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Human milk makes all the difference

The American Academy of Pediatrics' (AAP) policy recommends the use of human milk for all preterm infants, whether mother's own milk (MOM) or pasteurized donor human milk when mother's own milk is unavailable.[1]

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1. American Academy of Pediatrics. Breastfeeding and the Use of Human Milk. Section on Breastfeeding. [originally published online February 27, 2012]. Pediatrics. DOI: 10.1542/peds.2011-3552

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News

☐ Winter 2017

Dräger Unveils Groundbreaking Babyleo

Dräger, a leader in neonatal care, officially unveiled its Babyleo IncuWarmer at the 2016 NANN ConferenceFeaturing the latest innovation in neonatology since a decade-long dry spell, Babyleo is the first hybrid warmer to deliver a unique combination of three different heat sources – ensuring optimal thermoregulation for neonates at all times including open care, closed care, and transition. In addition to better protecting the littlest patients, Babyleo features a family-centric design and easy and efficient workflow for care teams – creating the optimal conditions for neonatal development in the NICU. In designing its new IncuWarmer, Dräger conducted extensive research to identify the optimal conditions for pre-term babies to thrive in the NICU. This included assessing the baby's own environment as well as that around it, including how the family is involved and how the medical team can provide care. Babyleo's advances include: Creating a more stable environment for developing babies to grow; supporting the central role in the family in neonatal care; and making workflow easier and more efficient for hospital staff

Fetal Cells Could Lead to New Test

Researchers at Baylor College of Medicine and RareCyte, Inc., have determined that it is feasible to develop a prenatal, noninvasive genetic test based on rare fetal cells that are present in the mother's blood. The study appears in the October issue of the journal Prenatal Diagnosis. Fetal cells were first reported in the circulation of pregnant women more than 40 years ago, and people have been hoping since that time to be able to use them for prenatal diagnosis. RareCyte has developed a platform that identifies individual fetal cells using an automated image scanner that mechanically retrieves them with an extremely precise needle having a tip opening less than half the width of a human hair. About two tablespoons of maternal blood has hundreds of billions of red blood cells and hundreds of millions of white blood cells but only 20 to 40 fetal cells. The research group commonly recovered 3 to 10 or more fetal cells for analysis by various molecular methods, including next generation DNA sequencing. Although other noninvasive methods for genetic testing are currently widely available, they have limitations. For instance, cell-free DNA testing cannot reliably detect very small changes in the fetal genome. The authors reported identification of a gene deletion between 2 and 3 million base pairs long, which was described as "well below the limits of resolution" for currently available plasma-based non-invasive pre-natal testing. If the test can become routine practice in current and future forms, the firm anticipates that it could be transformative for prenatal diagnosis, offering comparable information to that which can be obtained by amniocentesis and chorionic villus sampling. He estimates that a test might be available to the public in one to two years.

Illuminating Discovery Unveiled

The NEOSCAN transilluminator is a new handheld LED transilluminator. Features include a flexible fiberoptic distal attachment and rechargeable batteries. A ruggedized all metal housing is water resistant and drop resistant and is easily sterilizable using any hospital disinfectant. The brilliant cold white light output offers great contrast when searching for a vein, diagnosing hydrocephalus, pneumothorax or hydrocele and for frontal sinus examination. Contact Sylvan Corporation for more information at www.sylvanmed.com.

Paternal Exposure to Phthalates Studied

Paternal exposure to phthalates before conception might be more harmful to the baby than maternal exposure, researchers have shown in the first study of its kind. "Up until recently, paternal environmental exposure has been a largely unexplored determinant of offspring health," said Carmen Messerlian, PhD, from the Harvard T.H. Chan School of Public Health in Boston. But she and her team found that paternal — not maternal — preconception urinary concentrations of di-(2-ethylhexyl) phthalate (DEHP) metabolites were associated with significant decreases in birth weight. For every log-unit increase in DEHP concentration, birth weight decreased by 113 g (P = .01), the

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author reported during a prize paper presentation at the American Society for Reproductive Medicine 2016 Scientific Congress. The researchers analyzed 178 singleton births from couples who underwent in vitro fertilization at the Massachusetts General Hospital Fertility Center from 2005 to 2015. As part of the prospective Environment and Reproductive Health study, urine samples from the couples were analyzed for 11 individual phthalate metabolites. Both men and women provided a sample on study entry, the women provided up to two additional preconception samples per treatment cycle and pregnancy samples at each trimester, and the men provided a preconception sample at the time of egg retrieval. The average birth weight of the babies born was 3400 g, and about 3% were below 2500 g, which is slightly less than the national average.

Bariatric Surgery Impacts Studied

Infants born to mothers with prior bariatric surgery had significantly higher risks for prematurity, small-for-gestational-age (SGA) status, and neonatal intensive care unit (NICU) admission, according to a new study. The highest risks for prematurity and NICU admission were seen in those born to mothers with operation-to-birth (OTB) intervals of less than 2 years, and the risks decreased with longer OTB intervals. Brodie Parent, MD, from the Department of Surgery, University of Washington Medical Center, Seattle, and colleagues report their findings in JAMA Surgery. Several observational studies have shown that bariatric operations before pregnancy are associated with a reduced prevalence of macrosomic infants, maternal diabetes, and hypertension relative to the prevalence found among obese women who did not undergo a bariatric operation, the authors wrote. However, "because bariatric operations can result in nutritional deficiencies in the mother, there has been some concern that surgery may adversely influence fetal development and infant outcomes. Outcomes, such as [NICU] admissions, Apgar scores, and congenital malformations, are likely to be affected by maternal metabolic and nutritional derangements." The researchers analyzed data from birth certificates and maternally linked hospital discharge data for 1859 mothers with prior bariatric surgery (postoperative mothers [POMs]) and their infants, and a population-based random sample of 8437 nonoperative mothers and their infants, matched by birth year. Bariatric surgeries included banded gastroplasty, adjustable gastric banding, sleeve gastrectomy, or Roux-en-Y gastric bypass.

Antidepressant Could Increase Complications

Children exposed to a common type of antidepressant in the womb may be at an increased risk of complications soon after birth and years later, according to two new studies. One study suggests newborns are more likely to need intensive care after birth if their mothers take selective serotonin reuptake inhibitors (SSRIs) during pregnancy. A second study finds those same children may be at an increased risk for speech and language disorders years later. Links between SSRIs and these types of birth outcomes have been seen before in previous studies that weren't as reliable, said Dr Eva Pressman, chair of obstetrics and gynecology at the University of Rochester Medical Center in New York. Even with these associations, she said, women should make decisions about their SSRI use only after talking with their healthcare providers about their specific circumstances. Ulrika Norby of Lund University in Sweden and colleagues analyzed data on nearly 750,000 births in that country from 2006 through 2012. About 2 percent of the children had been exposed to SSRIs while in the womb. About 14 percent of newborns exposed to SSRIs were admitted to the neonatal intensive care unit (NICU) after birth, compared to about 8 percent of those not exposed to the drug, according to the results in the journal Pediatrics. The increased risk was more pronounced when mothers took SSRIs late in pregnancy. In the second study, researchers analyzed data on more than 56,000 children, most under the age of 9, to see if those who'd been exposed to SSRIs in the womb were more likely to have cognitive problems. The children were born between 1996 and 2010 in Finland. About 28 percent had been exposed to SSRIs during pregnancy. Another 17 percent were born to mothers who had depression but did not purchase SSRIs during pregnancy. The remaining 55 percent were born to mothers who didn't take SSRIs and did not have depression.

TcB Could Be Safe: Study

Transcutaneous bilirubinometry (TcB) is feasible and safe for evaluation of jaundiced neonates, researchers report. TcB is a valid method for assessing the severity of jaundice, but it is

uncommonly used in sick neonates because blood sampling in these children is often done for other indications and serum bilirubin can be measured simultaneously. In a randomized trial involving 430 hospitalized jaundiced newborns, Amalia Children's Clinic, Zwolle, The Netherlands sought to quantify the reduction in blood draws as a result of implementing TcB from 32 weeks' gestational age, compared with visual assessment with subsequent blood sampling for determination of serum bilirubin. Use of the Air-Shields Jaundice Meter-103 (Drager Konica Minolta, Lubeck, Germany) was associated with a 38.5% reduction in the number of blood draws per neonate (21.1% of those in the neonatal ward for sick neonates and 44.4% of those in the maternity ward). There were no significant differences in secondary outcomes (highest serum bilirubin level, phototherapy, severe serum bilirubin, length of hospitalization, and serum bilirubin value above exchange transfusion threshold) between the TcB and control groups. There were no cases of clinical kernicterus, and none of the measured serum bilirubin values was extreme (at or above 425 umol/L) or hazardous (at or above 512 umol/L). In 158 paired samples, TcB bilirubin values were an average 7.0 umol/L higher than the respective serum bilirubin levels, with limits of agreement between -56.9 and 71.0 umol/L.

Milk Types Studied

Very low birth weight (VLBW) infants fed fortified donor human milk as a supplement to maternal milk showed neurodevelopmental outcomes similar to those of infants supplemented with formula instead, according to a new study. Deborah L. O'Connor, PhD, RD, from the Department of Nutritional Sciences, University of Toronto, the Hospital for Sick Children, Toronto, Ontario, Canada, and colleagues, found both groups of infants also received their mothers' milk, for an average of 58.4% of feedings in the donor milk group (interquartile range, 13.6% - 96.0%) and 63.3% in the formula group (interquartile range, 9.6% - 97.2%; P = .96). Although this is the largest double-blind randomized trial to date, "[t]his trial does not definitively answer the question of whether donor human milk has an effect similar to that of maternal milk in improving neurodevelopmental outcomes," writes Tarah T. Colaizy, MD, MPH, from the Stead Family Department of Pediatrics at the Carver College of Medicine, University of Iowa, Iowa City. She points out that a larger trial is under way in the National Institute of Child Health and Human Development Neonatal Research Network. In that trial, infants will receive a larger proportion of donor milk compared with the newly reported trial. That said, this is the only trial reported thus far in which neurodevelopment was a primary outcome, Dr Colaizy notes. At 18 months' corrected age, the children underwent testing on the cognitive composite portion of the Bayley Scales of Infant and Toddler Development, third edition. Overall, there was no statistically significant difference between the two groups. Scores after adjusting for randomization strata were 92.9 in the donor milk group and 94.5 in the formula group (mean difference, –1.6; 95% confidence interval [CI], –5.5 to 2.2). The results were also nonsignificant when the researchers excluded infants who did not receive supplements and infants with severe brain injury.

Study Looks at Meth Damage in Infants

Infants exposed in utero to methamphetamine or whose mother smoked tobacco while pregnant display delays in motor development and white matter maturation, a new study found. The findings provide additional evidence that maternal use of methamphetamine and tobacco during pregnancy may lead to altered brain development in fetuses that are evident on the quantitative neurological examination in neonates. The researchers assessed, over a period of 4 months following birth, white matter microstructure and neurologic development of infants exposed to methamphetamine and/or tobacco prenatally and those of healthy control infants who were not exposed to those substances. Participants included 36 infants exposed prenatally to both methamphetamine and tobacco, 32 exposed to tobacco, and 71 unexposed control infants. According to the researchers, methamphetamine and tobacco-exposed infants showed delayed trajectories on active muscle tone. Male infants who were exposed to both stimulants also had significantly delayed trajectories in superior and posterior corona radiata that normalized by age 3 to 4 months. Female infants exposed to both stimulants had persistently lower FA in anterior corona radiata. Tobacco-exposed infants also showed persistently lower axial diffusion in the thalamus and posterior limb internal capsule.

Brave Beginnings

Brave Beginnings, along with presenting speakers, actress Zoe Saldana, Raj Dasgupta, MD, Assistant Professor of Clinical Medicine, Division of Pulmonary Critical Care and Sleep Medicine at University of Southern California KECK School of Medicine and 'Dr Raj' from the television show, "The Doctors," and Philippe S. Friedlich, M.D., Interim Chief of the Division of Neonatology and Director of the Center for Fetal and Neonatal Medicine at Children's Hospital Los Angeles, recently joined forces to raise awareness and funds for the benefit of the Neonatal Intensive Care Unit at Children's Hospital Los Angeles. Brave Beginnings, a program initially

part of the Will Rogers Institute (WRI), works to improve the lives of premature babies by providing hospitals with grants for purchasing life-saving neonatal equipment and supporting critical care pulmonary services. Guests consisting of members of the medical community and patrons of Brave Beginnings and Children's Hospital Los Angeles enjoyed an afternoon that featured a special introduction by Saldana, who shared her NICU experience as the mother of twins born prematurely and encouraged the audience to support Brave Beginnings so that every parent and child has the access to the best medical equipment and care available. Physician speaker presentations by Friedlich and Dasgupta both articulated the critical need for proper medical equipment to not only save the lives of newborns, but to also be able to send babies home without a chance of developing lifelong disabilities or disorders. Premature birth accounts for 35% of all infant deaths in the US, more than any other single cause. Since 2006, Brave Beginnings (formerly the Will Rogers Institute Neonatal Program) has provided essential ventilator equipment to neonatal intensive care units (NICUs) across the country. To date, the neonatal program has contributed $7 million in grants to 148 hospitals. Each year, the program issues 20 to 30 grants for a total of $1 million – and the demand increases every year. To date, 73,000 babies have been helped by the Brave Beginnings program.

Stillbirth Prevention Studied

Giving levothyroxine to more pregnant women with mild hypothyroidism could prevent more stillbirths, low-birth-weight babies, and early cesarean sections, results from a new study indicate. The findings were presented by Peter Taylor, MBChB, from the departments of diabetology and epidemiology at University of Cardiff in Wales, at the UK Society for Endocrinology Annual Conference in Brighton. Thyroid hormones are critical for fetal brain development, but fetuses can't make their own until the second trimester so they depend on maternal supplies. Suboptimal thyroid function in pregnancy is associated with adverse obstetric outcomes, but it is unclear whether levothyroxine treatment, initiated during pregnancy, is beneficial, say Dr Taylor and colleagues. And the issue of screening for subclinical hypothyroidism in pregnancy is the subject of debate due to conflicting data on the benefits. New American Thyroid Association guidelines addressing the issue are expected to be published in coming months. In this new analysis, Dr Taylor and colleagues retrospectively examined a cohort from the Controlled Antenatal Thyroid Screening (CATS) study and linked that data with routinely collected obstetric outcomes in the Secure Anonymised Information Linkage (SAIL) databank. The cohort included 13,224 women who were 12 to 16 weeks pregnant. Of those, 340 had subclinical hypothyroidism (SCH) and 305 had isolated hypothyroxinemia (IH). Of the women with abnormal thyroid function, 518 were randomized to either receive levothyroxine at the end of the first trimester (n = 263) or to receive no treatment (n = 255). The researchers looked primarily at a composite of stillbirths and neonatal deaths; preterm delivery (less than 34 weeks); length of hospital stay (more than 5 days); and APGAR score at 5 minutes (less than 7).

Less Pain, Less Crying

Infants who nurse during vaccinations may cry less and feel less pain than babies who are soothed in other ways, a research review suggests. Researchers examined data on breastfeeding and infant pain during needle sticks from 10 previously published studies with a total of 1,066 babies ages one to 12 months. On

average, breastfeeding babies cried for 38 seconds less than babies who didn't nurse during vaccinations, researchers report in the Cochrane Database of Systematic Reviews. Pain scores based on observations of babies' behavior were also lower when infants were breastfed during needle sticks than when they were not. To assess the potential for breastfeeding to curb pain in babies after the first month of life, researchers analyzed data from studies that compared nursing to alternative pain relief methods such as bottles of formula, pacifiers, cuddling, distraction, topical analgesics, and skin-to-skin contact. These previously published studies looked at a variety of needle stick procedures in addition to vaccinations, including blood draws and intravenous line insertions. The 38-second reduction in crying time during vaccinations was found in a pooled analysis of six studies of 547 infants who were breastfed, given water or offered no interventions during the shots. Breastfeeding didn't consistently result in changes in physical indicators of pain such as heart rate, however. Pain scores were also lower for babies who nursed during vaccinations, although the authors note it's difficult to gauge discomfort in young infants.

Zika Could Still Be Lurking

Infants with laboratory-confirmed congenital Zika virus infection but who do not have microcephaly at birth may experience slow postnatal head growth that can develop into microcephaly. Therefore, the absence of microcephaly in a neonate does not rule out Zika virus infection or its potential teratogenic effects, according to an article in Morbidity and Mortality Weekly Report. From October 2015 to January 2016, researchers at two Brazilian referral centers evaluated 13 babies (nine male) who tested positive for congenital Zika virus infection. The infants had normal head size at birth; circumferences ranged from 0.30 to 2.00 standard deviations below the mean for gestational age and sex. By age 5 months, however, they had experienced decelerated head growth, and 11 developed microcephaly, defined as a head circumference greater than 2 standard deviations below the mean for age and sex. Clinical evaluation included neurologic and orthopedic evaluation; brain imaging; hip radiography, to identify congenital dislocation; assessment of dysphasia; ophthalmologic and auditory assessment; and confirmatory electroencephalogram in infants suspected of having seizure activity.

Impacts of Early Developmental Intervention

An early developmental intervention program for very premature infants and their parents has few long-term effects on children's neurodevelopmental outcomes, but it does improve parents' mental health, according to new research. Parental mental health problems can have a negative effect on preterm children's development and mental health, and thus the results from the current study demonstrating improvement in parental mental health after the intervention are clinically important and have the potential to also improve children's outcomes in the longer term, Dr Alicia Spittle of the University of Melbourne in Victoria, Australia, and her colleagues state in their report. About half of children born very preterm have long-term neurobehavioral problems, Dr Spittle and her team note, while parents of these children face an increased risk of anxiety and depression. Intervention programs have short-term benefits for these families, the researchers add, but studies of their long-term effects have had mixed results. In the new study, the researchers followed up with 100 children born before 30 weeks' gestation who had been randomly assigned to receive a nine-visit home-based intervention in the first year of life or usual care. The intervention focused on infant development, parents' mental health and the infant-parent relationship. At eight years' corrected age, the 47 children who had received the intervention were less likely to have problems with mathematics than the 53 children in the control group, but there were no other differences in other developmental outcomes between the groups. Parents in the intervention group had fewer symptoms of depression and were less likely to have mild to severe depression (odds ratio 0.14). Twenty percent of the parents in the intervention group had anxiety and 5% had depression, similar to rates of depression and anxiety seen among parents of children born at term, the authors note. However, in the standard care group, 42% had depression and 27% had anxiety.

Some Infants Take Longer to Gain Weight

Even though doctors often tell parents that newborns will regain weight lost after birth within a week or two, many infants take much longer to achieve this milestone, a US study suggests. Nearly all newborns lose weight during the first days after birth, regardless of whether they are breastfed or formula fed. Many doctors expect babies to regain those lost ounces and surpass their birth weight within 10 to 14 days. But by 14 days, 14 percent of babies born vaginally and 24 percent of infants delivered via cesarean section surgeries didn't return to their birth weight, the study of almost 144,000 newborns found. It is normal for newborns to lose a significant amount of weight in the first 1 to 3 days after delivery due to both urinating excess fluid and limited intake, according to research from State College of Medicine in Hershey, Pennsylvania. C-section babies may lose more weight after birth because they come into the world more hydrated than other infants due to intravenous fluids given to women prior to and during the surgery.

Comprehensive Care for Newborns

The new HAMILTON-C1 neo combines a range of therapy options with maximum mobility in a highly versatile ventilator designed specifically for neonates. With over 30 years of experience in developing intelligent ventilation solutions for patients of all ages, Hamilton Medical has now channeled that wealth of expertise and proven neonatal technology into their most compact device to create the HAMILTON-C1 neo. Combining invasive and noninvasive modes with the options of nCPAP in a very small footprint, this dedicated neonatal ventilator makes it easier for caregivers to help the most fragile of patients. The HAMILTON-C1 neo provides tidal volumes as low as 2 ml for effective, safe, and lung-protective ventilation even for the smallest patients. Both the proximal flow sensor, designed to minimize the dead space, and the neonatal expiratory valve were developed specifically for neonates. The precise measurement of pressure volume, and flow directly at the airway opening ensures the required sensitivity and a quick response time. Your most fragile patients should benefit from a better synchronization and less work of breathing as a result. Using the IntelliTrig leakage compensation function, the HAMILTON-C1 neo identifies the leak by measuring the flow at the airway opening and uses this data to automatically adjust the gas delivery, while still remaining responsive to the set inspiratory and expiratory trigger sensitivity (ETS). This ensures adaptive synchronization with the neonate's breathing pattern in both invasive and noninvasive modes. The nCPAP modes of the HAMILTON-C1 neo are engineered in such a way that you only need to set the desired CPAP/PEEP. The flow is subsequently adjusted automatically based on the patient condition and potential leaks. This prevents unintended peak pressures and

guarantees highly efficient leak compensation. In addition to the standard nCPAP mode, the HAMILTON-C1 neo also features the biphasic nCPAP-PC (pressure controlled) mode. This mode allows you to set two pressure levels as well as the rate and inspiratory time.

Opioid Issues Hit Rural Areas

Opioid-related problems among pregnant women and infants in the US are rising at a faster rate in rural communities than in urban settings, underscoring the terrible toll the addiction crisis is taking on small towns. A new study from the University of Michigan C.S. Mott Children's Hospital found births of infants exposed in the womb to heroin and other addictive opioids grew more than sixfold in rural communities between 2004 and 2013, versus more than threefold in urban areas, according to results. The researchers looked at babies who were diagnosed with neonatal abstinence syndrome, or NAS, a condition marked by painful withdrawal symptoms from narcotics, including tremors, high-pitched crying and seizures. Over the same period, the rate of hospital deliveries complicated by the mother's opioid use grew more than sixfold in rural areas, versus threefold in urban areas. Widespread abuse of opioids has hit all corners of the US, but the impact has been particularly acute in rural areas, where treatment and prevention programs often lag behind those of cities. Largely due to opioid abuse, death rates from drug overdoses are now higher in rural areas than in big cities. The researchers examined a nationally representative sample of hospital discharge records. They found cases of NAS grew from 1.2 to 7.5 per 1,000 hospital births in rural areas, and from 1.4 to 4.8 per 1,000 hospital births in urban areas. Hospital deliveries complicated by the mother's opioid use grew from 1.3 to 8.1 per 1,000 deliveries in rural areas, and from 1.6 to 4.8 per 1,000 in urban areas. The growth could in part reflect the health-care system's growing awareness of opioid-related problems, the researchers said, but this was "unlikely to account for the rural/urban disparities we found."

Grant to Fund Commercialization of New NICU Tech

Invictus Medical, the San Antonio, Texas-based medical device company dedicated to providing newborns with healthy developmental milestones, has been awarded a prestigious National Science Foundation (NSF) Phase II grant to develop a new noise attenuation technology aimed at making neonatal intensive care units (NICUs) more conducive to newborn infants' cognitive development. The NSF Phase II grant provides funding of about $735,000 to complete the development of the noise attenuation technology, a process anticipated to be completed in 2018. Invictus states that it has assembled a set of world-renowned experts in the field of active noise attenuation to assist in this effort.

Helping Boost Patient Satisfaction and Increase Parental Confidence to Care for their Baby in the NICU

In this feature, Neonatal Intensive Care interviews clinicians and healthcare providers about the actual application of specific products and therapies. This interview is with Laura M Daly, RN, CPHQ, LHRM, Associate Director of Quality & Patient Safety at Holtz Children's Hospital & The Women's Hospital at Jackson Memorial and Kylie Rowlands RN, CNM, MSN, SANE A, Director NBSCC & Pedi/NICU Transport Team at Holtz Children's Hospital.

How did you find out about the Safer Way to Sleep hospital program?
We were at a conference for neonatal nurses and ran into someone who was representing HALO® and their Safer Way to Sleep® Hospital Modeling Program. I (KR) had also worked at another facility where they were already using the HALO® SleepSack® Swaddle, but I was unaware of the various elements of the program.

How do you use the HALO SleepSack Swaddle?
We use them for any baby 35 weeks and above because prior to that we position them for developmental growth and for other medical reasons. At 35 weeks corrected age the babies are stable, and this milestone coincides with the time when we can put baby on his back and use the HALO SleepSack Swaddle. (We also use these safe sleep wearable blankets on all full-term babies in the well-baby nursery.)

Did you find the use of a SleepSack Swaddle facilitated care of the babies? Did parents feel more comfortable holding their baby in a HALO SleepSack Saddle as there was no longer the fear of a blanket coming undone?
We found that when we started using the HALO SleepSack Swaddle in the NICU, parents became more relaxed about handling and caring for their baby. They no longer worry about baby getting cold as there is no need to totally undress baby for a diaper change as the HALO SleepSack Swaddle unzips bottom to top so baby remains clothed when changing a diaper. The garment actually helps the baby retain his body warmth. There is also a huge advantage when parents do skin-to-skin contact with baby — an important part of the bonding process. This is particularly true for mothers who are often undressed from the waist up. The fact that the HALO SleepSack Swaddle remains on the baby and is open not only keeps the baby warm but it also provides some coverage/modesty for the mother, often eliminating the need for total privacy. The HALO SleepSack Swaddle is hassle-free and actually gives parents greater confidence when holding their baby.

If you would like to participate in this feature, as a company or healthcare provider, please contact Steve Goldstein at s.gold4@verizon.net.

How do you use the tools of the program to teach safe sleep to parents?
At the onset of the baby's stay in the NICU we state that we maintain a safe sleep environment, we practice safe sleep and we ask for a commitment from the parents to do the same. We have many teaching materials available to us from HALO, Cribs for Kids and the Jackson Health Foundation to properly teach safe sleep to parents. We found flip charts to be the most effective, and at the end of the baby's stay parents receive a certificate of graduation that certifies that they know how to use a HALO SleepSack Swaddle and how to create a safe sleep environment at home. (We have also learned that through the Jackson Health Foundation all babies in the well-baby nursery and step-down NICU in our three hospitals, Jackson Memorial, Jackson North Medical Center, and Jackson South Community Hospital, will receive a new HALO SleepSack Swaddle as a gift to encourage and support all they have learned in the hospital about safe sleep. Our three hospitals combined deliver nearly 10,000 babies per year.)

Prior to the implementation of the program did you regularly review safe sleep protocol with your NICU nurses?
We are always reviewing safe sleep protocol and practice with the nurses in the NICU and in other areas of maternity in the hospital. It's a process of reinforcement and re-education which is ongoing.

Did the program have an impact in terms of patient satisfaction and their experience in the NICU?
Definitely – parents like things that are visual and look nice, and obviously seeing their babies dressed in a HALO SleepSack Swaddle is a pleasing sight. But far more importantly, they understand the benefit of what we are doing to keep their baby safe. It makes them feel confident that the staff is looking out for their baby's safety. The use of the HALO SleepSack Swaddle also gives parents the confidence to participate in baby's care in terms of bonding and diaper change…it provides a sense of ease that they will transfer to the home.

What other safety programs have you implemented in the hospital and have you seen positive results?
We have an active injury prevention program with community outreach that is ongoing. Among the areas we have focused on are fire safety and bicycle (helmet) safety. As a result of these

efforts we have seen a measurable reduction in ER visits for fire and/or bicycle accidents.

Are you a safe sleep certified hospital?
We are currently in the process of seeking the designation as a Safe Sleep Certified Hospital through Cribs for Kids. We are very close to completion, and using the HALO SleepSack Swaddle is an important part of the process.

Would you recommend the program to other hospitals?
Absolutely. We definitely think the Safer Way to Sleep Modeling program makes it easier for parents to care for baby which also makes for happier parents. We are aiming for a happy, healthy home for our babies after they leave the hospital, and this helps to contribute to that goal.

The HALO SleepSack Swaddles are aesthetically more pleasing to everyone including the staff, but they are first and foremost helping us keep babies safe and secure. That's the parents (and our staff's) top priority. In addition the program allows us to demonstrate the safe sleep techniques we want the parents to mimic at home, so seeing us use a wearable blanket they can also use at home helps to make the parents feel more confident after they leave the hospital. Parents put a lot of trust in healthcare professionals, particularly when it comes to learning how to care for baby properly.

We have also found that the concept of modeling behavior that you want the parents to adopt helps our staff understand the tremendous impact they have on these parents and on the health and well-being of their patients. It's a mindfulness that is present among the staff that we have not seen before.

Helping Parents and Professionals Handle Trauma in the NICU

In this feature, Neonatal Intensive Care interviews clinicians and healthcare providers about the actual application of specific products and therapies. This interview is with Cheryl Milford, NICU Psychologist and National Perinatal Association Board Member.

Deb Discenza: As a NICU parent myself, I naturally had a huge amount of stress watching my daughter struggle through her stay in the unit. I witnessed the same with my fellow patient families surrounding me. It never dawned on me how the NICU professionals themselves were also trying to cope with what is a daily onslaught of stress and trauma. Their professional demeanor was amazing but now I can look back and see the cracks within the façade of professionalism.

Mental health in the NICU has become a new drumbeat in neonatal medicine. Gone are the days of "holding up" and "dealing" for both patient families and professionals. The research is clear that trauma has lasting effects with the patient, the patient's family and, yes, the professional team.

I was fortunate to meet and participate in a recent conference panel with NICU Psychologist and National Perinatal Association Board Member Cheryl Milford. I asked her to delve into more detail around this topic.

DD: Tell us a bit about your background and how you came into the NICU arena.
Cheryl Milford: I am trained in educational psychology and I spent the first three years of my career in a public school setting. I had worked with toddlers and preschoolers during graduate school and I enjoyed the younger children. I became interested in working in health psychology and initially was part of an adult behavioral pain management program. An opportunity arose to work in an NICU, specifically the follow-up program and I took the chance. That was nearly 34 years ago and I have never regretted the career change. I have worked in NICUs in Oklahoma, California and Pennsylvania. Since 1997, I have also consulted in many units around the country. Working with NICU professionals, families and their neonates has been my life's work and I get great satisfaction from it every day.

DD: There is research surrounding depression and trauma for families but also for staff in the NICU. What research have you found that is most insightful to you?
CM: Research has emerged over the last 15 years that initially found the NICU to be a traumatic and overwhelming environment for families and their infants (Hynan et. al, 2015; Pace et al. 2016). I believe for staff, the work from Europe on the psychological and emotional energy and work expended by NICU professionals has enabled me to have a better understanding of their experiences and how their work impacts their mental health (Cricco-Lizza, 2014; Sansbury et al 2015). With this knowledge, I have developed self-care education and provided one-on-one intervention with bedside nurses. In addition, the research on both families and staff has informed my interactions with them. The trauma-informed care model with its tenets of safety, empowerment, trust, collaboration and choice (Sansbury et al 2015; Coughlin 2016) is the foundation of the education, modeling and interactions I engaged in with families and staff. Much of the early work I did was with the family-centered care model and the trauma-informed care model expands on FCC and acknowledges that the NICU environment, practices and procedures can be traumatic, not only to the neonate but to the parents and the professional caregivers.

DD: With an emotionally laden environment, I have to imagine that the staff members have a hard time and that impacts the team in a variety of ways in terms of emotion, of day-to-day work and being in an organization long-term, yes? What do you see consistently with impacts to staff?
CM: NICU professional staff are caring, empathic individuals. It is these attributes that attracted them to this work. These attributes also make the work challenging and emotionally laden on a daily basis. The staff develop significant relationships with families and their neonates. When caregivers engage in the procedures and practices that cause pain and distress for their patients and families it impacts them (Coughlin, 2016). The caregiver also is traumatized by the family and infant experience, leading to feelings of powerlessness and frustration. I often see caregivers being tense and agitated when they feel unable to decrease pain and distress in their patients and the families. This can lead to negative feelings and attitudes and becoming emotionally unavailable with decreased empathy over time. NICU professionals need to be supported, encouraged and nurtured in their work. This can be accomplished by a supportive administration that is sensitive to the issues the staff deal with every day in their work and in providing opportunities to de-brief and receive education on their own needs and self-care as well as effective practices and behaviors to support families and infants (Coughlin, 2016). Providing mental health support services in the NICU is important for families and staff in dealing with their emotions and their experiences (Hynan et al, 2015)

DD: Your focus is mental health for all being helpful to families but also training staff to handle mental health issues with

Input on questions was provided by Deb Discenza. If you would like to participate in this feature, as a company or healthcare provider, please contact Steve Goldstein at s.gold4@verizon.net.

families while also focusing on self-care too. What is your approach to change? And how have you seen these changes positively affect families, and staff care and retention?
CM: My approach to change is to be caring and supportive, modeling positive, nurturing behavior and genuine caring for the staff and families. Knowledge is power, so I use education, one-on-one opportunities for discussion, de-briefing and role-playing. I interact with families to model behaviors that families find to be comforting and empowering in their interactions with professional staff (Hall et al, 2015). My observations have been that parents have less anxiety and distrust in professional staff when they are treated with genuine respect and caring. The relationship is positive and parents feel comfortable discussing their questions and concerns in a respectful and attentive way. This supports the staff feeling competent and respected in their work with families. My experience has been that when you nurture staff, make their self-care and needs important to their co-workers and the administration and provide them with education to enhance their practice, they feel empowered, safe and respected as the amazing professionals they are.

DD: Anything else you would like for readers to know?
CM: Being a NICU professional is both challenging and rewarding. To be able to provide the optimal care to neonates and families, all NICU professionals need to be self-aware and engage in good self-care practices to support their own mental health. People are counting on you, please take good care of yourself.

DD: Thank you, Cheryl.

In this enlightened age of helping families and professionals better cope with the NICU experience, I find Cheryl Milford's work to be key to patient family satisfaction as well as to employee satisfaction. Cheryl Milford provides consulting to NICUs nationwide. You can learn more about this topic and get more information at her website: www.CherylMilford.com

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Using Therapeutic Hypothermia to Improve Neurological Outcomes

In this feature, Neonatal Intensive Care interviews clinicians and healthcare providers about the actual application of specific products and therapies. Participating in the interview is Greta Simmons, BSN, RNC-NIC, a Clinical Education Specialist, Neonatal Intensive Care Unit at Huntsville Hospital, Women and Children's.

Neonatal Intensive Care: What are the common causes of neonatal encephalopathy?
Greta Simmons: Anything that decreases oxygen supply to the brain can cause encephalopathy. There can be maternal causes like cardiac arrest, or shock. Some other common causes are placental abruption, cord prolapse, nuchal cord, or due to a prolonged or difficult delivery.

NIC: How are these babies identified/diagnosed?
GS: We assess babies that have experienced high risk or difficult deliveries for low apgars, metabolic acidosis, and neurological signs—like seizures.

NIC: How does therapeutic hypothermia improve neurological outcomes?
GS: Severe hypoxic events can cause cerebral edema, cell death, inflammation and free radical production, which can result in brain injury. Cooling the patient decreases the inflammatory process, reduces edema, and stabilizes the blood brain barrier which has shown to improve outcomes.

NIC: What are the common criteria needed to initiate cooling?
GS: Babies <6 hours old, >36 weeks, and >1800 grams can be considered for treatment. We look for an acute perinatal event, with apgars <5 at 10 min, acidosis, and a poor neurological exam.

NIC: How long are the babies cooled for?
GS: 72 hours

NIC: What temperature are the babies cooled to?
GS: Between 32-34 degrees. Our protocol uses a set point of 33 degrees.

NIC: Are there any other treatments currently being researched in addition to cooling therapy for these babies?
GS: There are some trials looking at expanding the criteria for cooling to include premature babies <35 weeks, extending the window of cooling greater than 6 hours, and for longer than 72 hours. There are also groups researching the protective effect of stem cell, and cord blood transplantation.

NIC: What type of medical follow up should these babies receive after discharge from the NICU?
GS: These babies should be followed by a pediatric neurologist or follow-through clinic, and be followed closely so therapy can be initiated early for any developmental delays.

NIC: How can the families be included in the care of a patient diagnosed with HIE and undergoing cooling therapy?
GS: Mothers are encouraged to pump breastmilk for her baby. We use this for colostrum oral care, and feeding. Parents are welcome at the bedside, and can participate in hands-on care with the nurse as the baby is stable. It's important to involve the family early in the baby's plan of care. Explaining the causes, and symptoms of HIE, as well as the way treatment works facilitates a parents feeling of involvement. This knowledge also helps with the ability to recognize signs and symptoms of neurological and developmental problems that can occur after discharge.

If you would like to participate in this feature, as a company or healthcare provider, please contact Steve Goldstein at s.gold4@verizon.net.

Improving Feeding Tolerance in VLBW Infants

In this feature, Neonatal Intensive Care interviews clinicians and healthcare providers about the actual application of specific products and therapies. Participating in the interview is Maushumi Assad, MD, MPH, who will be answering questions about a study she conducted while at Sinai Children's Hospital in Baltimore, MD.

Neonatal Intensive Care: Can you start by defining "Exclusive Human Milk Diet"?
Maushumi Assad: An exclusive human milk (EHM) diet consists of mother's own milk or donor human milk that is fortified with donor milk-based fortifier for preterm or very low birth weight infants (VLBW), classified as less than 1500 grams. This is an important distinction especially for preterm infants since breast milk alone would not provide sufficient nutrition for optimal growth.

NIC: You recently published a study in the Journal of Perinatology. What was the purpose of the study?
MA: An EHM diet is the preferred form of nutrition for premature infants and results in better feeding tolerance and a lower incidence of NEC which was previously demonstrated by Sullivan S in J Pediatr 2010 Apr;156:562-7. Despite these benefits, the most common fortifier used in the neonatal intensive care unit (NICU) is derived from a bovine protein. The majority of NICUs are currently not providing an exclusive human milk diet due to the high costs associated with providing such a diet. Thus, the purpose of our study was to assess the benefits and cost of an exclusive human milk (EHM) diet in very low birth weight (VLBW) infants in a community level III NICU. Our study was unique due to its focus on cost.

NIC: Can you describe the methodology?
MA: This was a single-center retrospective chart review study from March 2009 until March 2014 in a level III community NICU in Baltimore, MD. Starting in March of 2012 all infants ≤29 weeks or infants classified as VLBW were provided an EHM diet. Two hundred and ninety-three infants were divided into four feeding groups as follows: group H (entirely human milk based, born March 2012 to 2014), group B (bovine-based fortifier and maternal milk, born March 2009 to 2012), group M (mixed combination of maternal milk, bovine-based fortifier and formula, born March 2009 to 2012) and group F (formula fed infants, born March 2009 to 2012). No significant changes to clinical practice, feeding strategies, respiratory management or attending physician staffing occurred during the study period.

Maushumi Assad is a 2nd year Neonatal Perinatal Fellow at Connecticut Children's Medical Center. The study took place at Sinai Children's Hospital in Baltimore, MD. If you would like to participate in this feature, as a company or healthcare provider, please contact Steve Goldstein at s.gold4@verizon.net.

NIC: What were the study outcomes?
MA: The primary objective was to examine the effect of an exclusive human milk diet on length of stay, incidence of feeding intolerance and time to achieve full feeds. The secondary objectives were to determine the effect of the diet on the incidence of NEC and to determine the cost effectiveness of an EHM diet.

NIC: What were the cost savings for your institution with this diet?
MA: Total hospitalization costs were significantly lower by $27,387-$106,968 in the exclusive human milk diet. Cost information was unavailable for 10 infants, 3 of whom developed necrotizing enterocolitis and incurred even higher costs. Therefore, total hospitalization cost is likely a considerable underestimation of cost savings. A second cost analysis was performed using provider charges as an indirect marker for cost. In the exclusive human milk group, we included the cost of donor milk and donor milk-derived fortifier (Prolact+H²MF Prolacta Bioscience, City of Industry, CA, USA) that can range from $125 to $250 per 100 ml bottle. The analysis of physician charges showed significantly higher charges in the bovine and mixed group ($14,490 to $25,765), despite adding the cost of the fortifier and donor milk to the exclusive human milk group.

NIC: Can you elaborate on the significance of decreased feeding intolerance, shorter time to full feeds to cost?
MA: Feeding intolerance was defined as feeds being interrupted and held for 24 hours or longer due to emesis, abdominal distension, bloody stools or suspicion of NEC. This study went further to classify feeding intolerance we further subdivided infants into three groups: 0 interruptions, 1 interruption, or 2 or more interruptions in feeding for 24 hours or more. The EHM diet showed 94% of infants did not have a feed held for greater than 24 hours during their entire hospitalization compared to the other groups. The EHM diet was shown to decrease feeding intolerance, shorten time to full feeds to between 9-10 days and shorten length of hospital stay to between 4-22 days, which translates to lower overall hospital cost for extremely premature and VLBW infants.

NIC: Additional days to full feeds, additional days of hospitalization and total cost of hospitalization costs were lowest in EHMD group but highest in the mixed group (compared to the bovine group). How do you explain this?
MA: Infants in the mixed group were provided premature formula as well as breast milk fortified with Similac HMF liquid.

An abrupt change in the type of feedings the neonatal gut is exposed to may set off an inflammatory cascade that leads to a higher rate of feeding intolerance, increased length of stay and overall cost of hospitalization.

NIC: Your results corroborate the results of published RCT for reduction of NEC and NEC surgery using an EHMD compared to cow milk-based diets. Did you have other unexpected outcomes?
MA: Long-term benefits such as decreased incidence of bronchopulmonary dysplasia (BPD) and retinopathy of prematurity (ROP) were also seen. The study was not powered for these outcomes. In addition, there were no significant respiratory management changes or oxygen-targeting protocol changes implemented during the study period. Infants who have shorter lengths of stay and who reach full feeds more rapidly could be presumed to be healthier overall. An EHM diet may lower incidences of BPD and ROP by decreasing inflammation through out the body or by decreasing the inflammation in the gut reducing feeding intolerance improving health and further reducing comorbidities associated with prematurity. An EHM diet may have additional benefits beyond reducing NEC.

NIC: Some hospitals have been hesitant to implement an EHMD due, in part, to the cost of the human milk products. Based on your institution's experience and study findings with an EHMD, would you recommend an EHMD to other community level III NICUs?
MA: We have known for a long time that breast milk provides many benefits in both term and preterm infants and is recommended by the American Academy of Pediatrics (AAP Breastfeeding and the Use of Human Milk. Section on Breastfeeding originally published online February 27, 2012). Being able to provide an EHM diet further adds to the potential benefits that we may see. As this study has shown not only does it decrease overall hospital cost but it improves the health and well being of preterm very low birth weight infants by decreasing feeding intolerance and decreasing time to full feeds and hospital stay. Providing optimal nutrition for preterm and VLBW infants during this critical time period of rapid growth is important. It promotes important neurocognitive growth and likely improves long term clinical outcomes by decreasing comorbidities associated with preterm birth. Based on current research and our findings, I would strongly encourage clinicians to recognize the benefits of an EHM diet and further promote its use in our premature infants.

Exploring the Link Between Neonatal Brain Injury and Sucking

Early detection of injury leveraging emerging technologies

Christos Papadelis, PhD and Eleonora Tamilia, PhD

Problem: Current methods of identifying infants with neonatal brain injury (NBI) may not be sensitive enough to detect in the neonatal period and others are too costly to be used routinely.

Study Design: Longitudinal cohort.

Expected Outcomes: Demonstrate clear evidence of the association between early abnormalities in feeding performance and underlying brain injury.

Every year in the United States, approximately 500,000 babies are born preterm. Advances in technology and neonatal care have increased survival rates of premature infants up to 90%.[1]

Despite these advances, the incidence of neonatal brain injury remains high.[15] It is estimated that 50% or more of very low birthweight preterm infants will be diagnosed with periventricular leukomalacia (PVL)[2] and the number of preterm infants who will be diagnosed with some form of intraventricular hemorrhage (IVH) is reported to be 12,000 annually.[3]

Because of the documented high incidence of brain injury among preterm infants, the association of prematurity with neurodevelopment and disability remains a significant concern.[4] Premature infants have a documented increased risk for adverse neurodevelopmental outcomes including:

- Cerebral palsy
- Cognitive impairment
- Speech and language delay
- Sensory dysfunction

All of these adverse neurodevelopmental outcomes can affect long-term physical health with a higher risk of disease.[2]

The basis of concern regarding the association of prematurity with neurodevelopment and disability, is the fact that during the third trimester of gestation, the brain goes through rapid expansion and folding.

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This cerebral cortical maturation has been shown to be disrupted by preterm birth[5] and underscores the importance of developmentally supportive practice in the NICU during a time of extreme vulnerability.[6] A primary healthcare goal becomes identifying and intervening in those infants at highest risk, as early as possible, in order to take advantage of neuroplasticity; the peak time period when the brain can compensate for injury and disease.[7]

Detecting Neonatal Brain Injury

A major challenge to early identification of infants with neonatal brain injury (NBI) is the fact that current methods for diagnosing brain injury may not be sensitive enough to detect an injury in the neonatal period (e.g. cranial ultrasound) or may be too costly for routine identification of brain injury (i.e. magnetic resonance imaging).[8] Therefore, identifying a common neonatal behavior that reflects the overall integrity of the central nervous system and correlating that behavior with advanced neuroimaging capabilities, would be a substantial advancement in early identification of NBI. To that end, we have partnered with NFANT Labs LLC to study the challenge of early identification of neonates at risk for brain injury and poor, long term developmental outcomes.

Sucking as a Neurodevelopmental Biomarker

Successful infant feeding is a complex neonatal behavior that requires integration of physiologic function and neurobehavioral ability.[9,10] Sucking is considered the most precocious purposeful motor skill of the newborn[11] and is considered an early window into the overall integrity of the central nervous system.[12]

A number of researchers have demonstrated that early sucking performance is predictive of later neurodevelopmental outcomes.[13-15]

However, previously reported methods have been a limiting factor in the ability to interpret and generalize findings. Limiting methods include sensory degrading modifications to nipples, cumbersome equipment, and subjective measures of sucking performance.

Neuroimaging Techniques Offer Opportunity for Early Diagnosis and Treatment

Research on human brain development has seen an upturn in the past few years due to increasing use of noninvasive neuroimaging tools for studying the anatomy and function of the developing brain. We are witnessing advances not only in the

instrumentation optimized for the pediatric population, but also in research focused on the human fetuses in utero, neonates, and older children.[16] MRI methods such as volumetric T1 imaging and Diffusion Tensor Imaging (DTI) are being used more frequently in children to determine the gross anatomy and structural connectivity of the developing brain. On the other hand, to study the brain function, functional neuroimaging techniques, such as magnetoencephalography (MEG), electroencephalography (EEG) and near-infrared spectroscopy (NIRS) can be used to assess electrophysiological functions of the developing human brain. Findings from multiple neuroimaging methods can be combined to answer specific scientific questions regarding pediatric pathology[17-19] or typical human brain development. Neuroimaging can offer critical information about both normal as well as abnormal human brain development. Although most of the currently available tools are designed for adult use, at Boston Children's Hospital we have developed and refined hardware and methods especially tailored for pediatric use. Such technological advancements address specific issues relevant to pediatric populations and will promote wider adoption of neuroimaging for both clinical and research purposes.

Our group is uniquely positioned to perform pediatric multimodal neuroimaging studies. To date, there are only 5 MEG systems available worldwide for use on children. Our unique MEG system is tailored specifically for young children birth-3 years old, and to employ pioneering neuroimaging methods to integrate anatomical and functional neuroimaging findings.

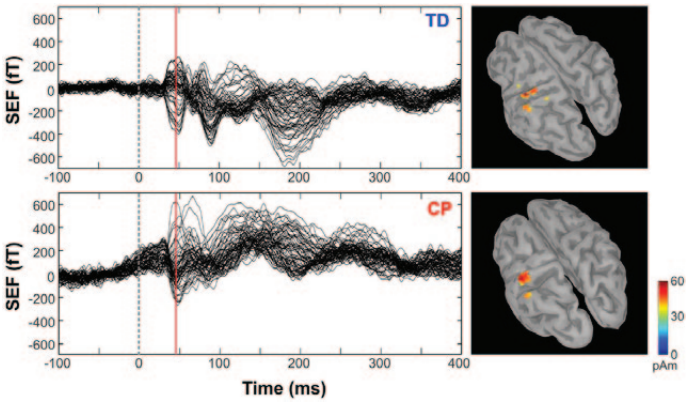
This research program will provide clear evidence of the association between early abnormalities in feeding performance and underlying brain injury.

MEG and MRI/DTI

Foundation: More than 95% of children with CP have sensory deficits that limit their tactile abilities. The development of fine motor skills depends heavily on the somatosensory system. Tactile feedback from mechanoreceptors in the skin is critical to the online modulation of fine motor skills, such as feeding. Previous work by Dr Papadelis et al. examined sensory processing in typically developing (TD) children and children with cerebral palsy (CP) using MEG and DTI.[16] This was the first study combining findings from multiple neuroimaging techniques to examine the functional (Figure 1) and anatomical (Figure 2) integrity of the somatosensory systems in children with spastic CP.

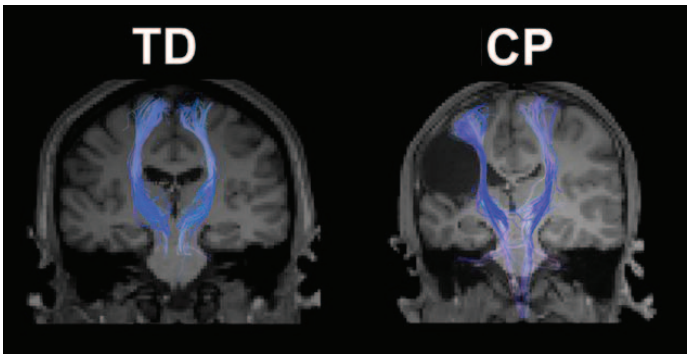
Functional: Somatosensory fields evoked by the tactile stimulation of the right thumb through a pneumatic stimuli for a TD child vs a child with CP with left hemisphere more affected (Figure 1). The left panels show the somatosensory-evoked fields recorded with MEG, while the right panels show the underlying generators localized using minimum norm estimates (MNE) overlaid on the child's cortical surfaces at the peak of the most prominent early deflection evoked by the tactile stimulation at around 40–50 ms (M50).

Figure 1. Study of the functional integrity of the somatosensory system. Somatosensory-evoked fields evoked by the tactile stimulation of the right D1 (left panels) for a TD and a child with CP (left hemisphere more affected) child from 100 to 400 ms after the onset of the tactile stimulus. Source localization with Minimum Norm Estimates (in pico ampere meter) overlaid on participant cortical surfaces at the peak of the M50.



Anatomy: Brain fibers that control the sensation of touch projecting from the thalamus to the post-central gyrus of a TD child (left) vs a child with CP is reconstructed from DTI data (Figure 2).

Figure 2. Study of the structural integrity of the somatosensory system. Thalamocortical fibers projecting from thalamus to the post-central gyrus for both sides of the brain for a TD and a child with CP (left hemisphere more affected).



Combination: We now can present results from an advanced multimodal neuroimaging method developed by our group to reconstruct functionally-defined sensory tracks by integrating findings from MEG and DTI. Using MEG, we mapped the functionally active regions in the primary somatosensory cortex during tactile stimulation of the thumb (D1), middle (D3), and little fingers (D5) of both hands of children with CP due to periventricual white matter injury (Figure 3). The functionally active regions then were used as anatomical regions of interest for the deterministic DTI analysis. The figure shows the results for a child with unilateral periventricular white matter injury. We can observe that the affected right hemisphere where the brain lesion is visible on the MRI, presents less sensory fibers than the less affected left one.

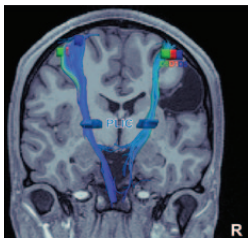


Figure 3. Functionally-defined Sensory Tracks of a child with unilateral periventricular white matter injury during tactile stimulation of the thumb (D1), middle (D3), and little fingers (D5). The functionally active regions in the primary somatosensory cortex during tactile stimulation of D1, D2, and D3 are displayed with red, green, and blue color respectively. Such functionally active regions were then used as anatomical regions of interest for the deterministic DTI analysis to reconstruct the sensory tracks shown in the figure. The right hemisphere, where the brain lesion is visible on the MRI, shows less sensory fibers compared to the left hemisphere.

nfant®Feeding Solution is a noninvasive FDA cleared medical device that objectively measures nipple dynamics during feeding.

nfant Feeding Solution overcomes the limitations of previously reported methods as it is scalable and easily integrated into routine care. nfant Feeding Solution uses standard bottle nipples and so supports the individualized nature of neonatal feeding and respects the importance of sensory feedback in the development of feeding skill. It is an objective tool for the quantitative assessment of nutritive sucking in infants.[20]

Nipple movement is captured in real time and displayed visually on a tablet via the nfant® Mobile App. Feeding data is stored in the nfant® Patient Database for later analysis. Early studies from NFANT Labs[20,21] supports the work of others[14,22] who have suggested that sucking patterns are an early marker for neurodevelopment.

Correlating Sucking and NBI

MEG data will be used to identify any functional abnormality in the infant's brain network. MRI/DTI data will allow us to reconstruct the brain neural tracts that control feeding process and to estimate any possible structural abnormality. Using the nfant® Feeding Solution and our in- house software for sucking assessment,[27] we will assess the infant's sucking pattern (Figure 4) and identify the infants showing early oral-motor abnormalities while feeding. The sucking assessment will be conducted during the infant's stay in the NICU whereas the neuroimaging scans will be conducted prior to discharge. This will allow us to correlate the sucking performance evaluated early during the NICU stay using the nfant Feeding Solution (Figure 5) with the brain functional and structural abnormalities evaluated later at the time of discharge using our advanced multimodal neuroimaging technique.

Figure 4. Algorithms objectively identify key features and metrics to describe the suck pattern.

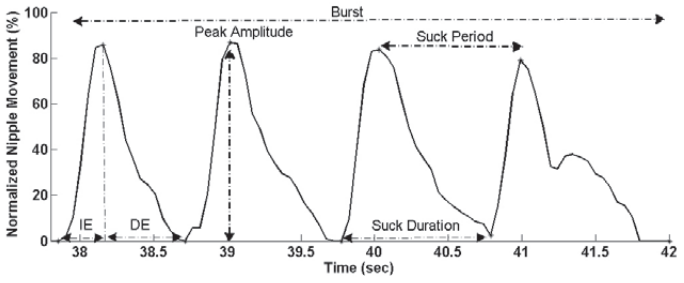
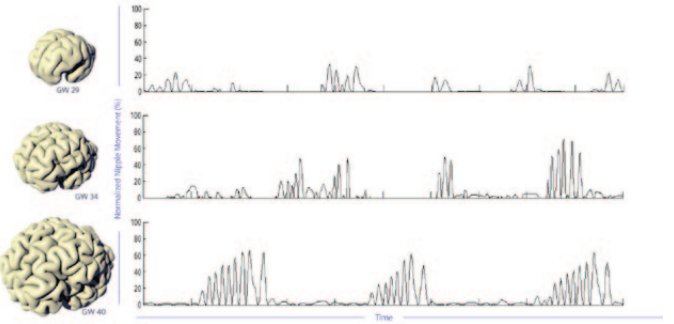


Figure 5. Sucking performance is evaluated throughout NICU stay and maturation using nfant Feeding Solution. Metrics are generated from the sucking patterns for each feeding and correlated to maturation.[28]



Hypotheses and Potential Outcomes

We plan to run neuroimaging studies with MEG and MRI/DTI using advanced tools available at Boston Children's Hospital, in order to assess the complex brain network that controls feeding and sucking in neonates. We will then correlate any deficits in the feeding brain network with early abnormalities identified in patterns of sucking performance during bottle feeding, via nfant Feeding Solution. This research program will provide clear evidence of the association between early abnormalities in feeding performance and underlying brain injury. Similarly, this work will give clinicians robust insights into the brain deficits that possibly underlie the feeding problems they encounter in practice. Furthermore, using an objective tool to assess infant oral feeding in practice, we will insure that feeding problems reflecting early symptoms of brain injury will not be missed. We will combine NFANT Labs experience in the technology-aided clinical assessment of feeding, with the cutting-edge pediatric neuroimaging techniques we use at Boston Children's Hospital to study brain injury in infants.[17,23]

About the authors

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Breastfeeding Promotion in Infants of Substance Abusing Mothers

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While the occurrence of substance abuse in pregnant women has increased dramatically over the last several years, it is not new. Happel first published a report of neonatal withdrawal in 1900.[1] Which substances are abused has changed from time to time with the most recent concerns centered around abuse of prescription drugs and heroin.

The 2013 National Survey on Drug Use and Health reported that 5.4% of all pregnant women were current illicit drug users.[2] This included 14.6% of women between 15 and 17 years of age and 8.6% between 18 and 25 years of age, all pregnant. Rates of neonatal abstinence syndrome have increased from 2009 to 2012 from 3.4/1000 live births to 5.8/1000 hospital births.[3] Rates for census regions are also available and range from 16.2/1000 live births in the East South Central states to 2.6 in the West South Central states. Notice that this reflects the incidence of neonatal abstinence syndrome (NAS) and not necessarily the rate of substance exposure. Infants exposed to marijuana, for instance do not usually demonstrate the symptoms associated with NAS. Therefore, the actual rate of exposure is likely much higher. Many women are polysubstance abusers and frequently have alcohol and tobacco use during the pregnancy and limited or no prenatal care, all of which increase the risk of poor outcome. A baby is now born every 25 minutes who is suffering from opioid withdrawal.[3]

This issue emotes strong emotional responses from caregivers. Comments from healthcare staff like "this mother doesn't deserve this baby" and recommendations that these women be reported for child abuse demonstrate this attitude.[4,5] However, today, we are encouraged to see substance abuse as a chronic health condition equal to type II diabetes, hypertension or asthma.[6] One must understand that substance abuse is an illness that requires medical and social intervention and life-long support. These women have a substance abuse problem, in most cases, long before the pregnancy. Pregnancy rarely, if ever, is the stimulus that results in substance abuse. Some women report using substances of abuse as self-medication for psychological conditions including post-traumatic stress disorder, bipolar disease and depression. In order to stop the abuse, these underlying conditions must be treated. Prescription drugs are sometimes used after an injury in which opioids are legitimately prescribed but continued long after the injury-associated pain is gone. Prescribing practices have been targeted in efforts to decrease this type of abuse. Regardless of the underlying history of the abuse, it occurs in all races, cultures and populations but rates vary.

If mothers are receiving prenatal care, every attempt is made to transition her to methadone or buprenorphine treatment from heroin or other opioid abuse. This results in a known dose of drug during the pregnancy, regular screening to ensure this is the only drug being taken and continued prenatal care. However, methadone and buprenorphine cross the placenta and are found in the fetus. The infant may still have NAS even if the mother is properly managed on these replacement drugs during the pregnancy. The controlled dose given in a monitored program, however, leads to more predictable onset and course of withdrawal in the infant. Since these drugs cross the placenta, they are also found in breast milk, although in small quantities.

Patrick et al[3] report length of stay at 2.1 days for infants without NAS and 16.9 days for infants with NAS. Cost of care is estimated at $3500 for infants without NAS and $66,700 for infants with NAS. Infants with NAS are more likely to be born prematurely, have neonatal respiratory disease, feeding difficulty, seizures and low birth weight.[3,7] These infants often have difficulty post-discharge as well including continued feeding difficulties and developmental and growth delay.[8] As the number of infants with NAS increases, costs increase. Therefore, many facilities have protocols to manage NAS more efficiently and decrease length of stay. By decreasing length of stay and NICU admissions, cost of care is decreased as is separation from mothers. Providing breast milk or, more specifically direct breastfeeding has been shown to result in a decrease in the need for pharmacotherapy for withdrawal as evidenced by a lower score on a standardized withdrawal scoring tool such as the Finnegan tool.[9,10]

The benefits of breastfeeding are many and have been well documented for both the infant and mother (Table 1). These benefits are more important in NAS infants. A drug-abusing mother does not automatically exclude the possibility of breastfeeding. The Academy of Breastfeeding Medicine's (ABM) guidelines for breastfeeding in this population states that each case must be evaluated individually.[13] There are several advantages for mother and baby when breastfeeding, some different than what is seen in non-substance abusing women. For instance, breastfeeding may increase the bond between mother and infant due to the release of oxytocin during breastfeeding

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Table 1

With breast feeding, these conditions are seen less in the infant	With breast feeding, these conditions are seen less in the mother
Respiratory illnesses Otitis media Gastritis and diarrhea UTIs Asthma Atopic dermatitis Obesity Crohn's disease Ulcerative colitis Diabetes type I & II Childhood leukemia & lymphoma SIDS	Breast cancer Ovarian cancer Diabetes type II Hypertension Rheumatoid arthritis Depression Cardiovascular disease
15, 16	11,12

which may also protect the mother against addiction relapse and stress.[14,15] In some cases, the focus of providing for an infant, including breastfeeding helps the mother stay in a treatment program, receive counseling and other support that aids in continued sober living. Besides the benefits of the infant receiving breast milk that contains a small amount of opiate, resulting in more gradual weaning of the drug rather than a sudden discontinuation upon delivery, infants who are direct breastfed also get other interventions that are helpful in supporting hyperactive, irritable infants. The skin-to-skin holding or swaddling during breastfeeding and rooming-in may also result in a lesser need for withdrawal treatment.[15]

The Academy of Breastfeeding Medicine, the American Academy of Pediatrics (AAP) and American Congress of Obstetrics and Gynecology (ACOG) recommend breastfeeding for mothers receiving opioid maintenance therapy during and after pregnancy provided there are no other contraindications to breastfeeding.[13,16,17] The ABM recommends that mothers who meet the following criteria be supported in their decision to breastfeed their infant:

- Women already in a substance abuse treatment program who intend to continue the treatment program in the postpartum period
- Women whose substance abuse counselors confirm that the women are continuing in the treatment program
- Women who have been abstinent from the illicit drug for at least 90 days before delivery in an outpatient setting
- Women who have a negative drug screen at delivery except for prescribed medications and who have received consistent prenatal care
- Women who have stable methadone maintenance should be encouraged to do so regardless of maternal methadone dose

Historically, it was believed that a methadone dose of over 20 mg would contraindicate breastfeeding. However, many researchers have found that the amount of drug excreted into the breast milk is minimal for both methadone and buprenorphine, regardless of dosage that the mother receives.[18,19,20,21] Furthermore, the dosage that the mother needs in order to prevent withdrawal symptoms during the pregnancy must be increased during the third trimester. Without this increase, she is more likely to relapse. Therefore, maintaining a lower dose in order to allow breastfeeding is counterproductive, may result in relapse and does not make a significant difference in amount of exposure to drug in the breast milk.[22]

Liu and collegues[14] evaluated the effect of mode and type of feeding on onset of NAS as well as need for pharmacologic management of NAS. They compared infants who were fed directly at the breast, those fed expressed breast milk and those fed formula. They found no difference in requirement for pharmacologic management based on mode/type of feeding in the first 2 days of life. However, infants who were fed directly at the breast had a significantly delayed onset of NAS. It was not reported if these infants continued to be fed directly at the breast and the sample size was small so any effect of the mode of feeding may not have been seen in this sample. Malpas, Horwood & Darlow[23] found that breastfed infants had a shorter stay by 8 days than infants who were formula fed due to lesser requirement for NAS treatment. Pritham, Paul & Hayes[24] found infants who were breastfed as compared to formula fed were less likely to need treatment for NAS and had a significantly shorter stay by 9 days.

However, even if healthcare providers realize the benefit and encourage mothers to breastfeed, it has been found that breastfeeding rates remain low in this population.[25] Wachman, Byun & Philipp[25] published results of a retrospective chart review to determine how many substance-abusing mothers began breastfeeding and how long the breastfeeding continued. Their criteria for allowing substance abusing mothers to breastfeed included a negative urine drug screen on admission, no illicit drug use in the third trimester and a negative HIV screen. They found that 68% of the mothers were eligible to breastfeed but only 24% actually breastfed in an environment they felt was supportive of breastfeeding. Sixty-percent of these mothers stopped breastfeeding in less than 1 week. Tsai & Doan[26] reported the results of a literature review in which studies were included that evaluated breastfeeding in mothers receiving opioid maintenance treatment including either methadone or buprenorphine. They found 9 studies that met their inclusion criteria. There were 5 studies that reported breastfeeding rates in the United States. The initiation of breastfeeding in these studies ranged from 24% to 81% and duration, where reported 8% at discharge to 50% at 6-8 weeks postpartum.[26] Most of the studies did not differentiate partial or exclusive breastfeeding. These authors also undertook an analysis of type of medication used for opioid maintenance therapy (OMT), either methadone or buprenorphine and possible influences on initiation and duration of breastfeeding. No conclusions could be drawn about the effect of these drugs on breastfeeding as not all reported the type of maintenance therapy, percentage of breastfeeding and continuation based on this criteria. We know that maintaining exclusive breastfeeding for the recommended 6 months after delivery often requires encouragement and support for women who are not substance abusers. It is logical that for these women, the support needed to initiate and maintain breastfeeding for any length of time

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Table 2: Measures to support breast feeding in the infant with NAS

Combined obstetric and addiction treatment
Current knowledge regarding safety of breast feeding in the presence of OMT
Rooming in
Address maternal anxiety
Smaller, more frequent feedings
Put to breast while drowsy and swaddled

would be different than for women who are not substance abusers.

Measures to Support Breastfeeding

Various studies have reported the effect of various measurements on initiation and maintenance of breastfeeding. Two studies in the US reported the effect of combined obstetric and addiction treatment. The sites included in these two studies also practiced rooming in during the post-partum period.[27,28] Combined obstetric and addiction treatment is likely to be valuable to these mothers since transportation and child care are often issues. Making multiple appointments after the infant's discharge can result in insurmountable problems and loss to follow up. These two reports are from the same hospital in different time periods, all women were treated with buprenorphine and the hospital was designated Baby Friendly. The Baby Friendly designation alone, however, did not result in an increase in breastfeeding rates. The one study that reported on breastfeeding outcomes in a Baby Friendly hospital without other interventions showed one of the lowest rates of breastfeeding for these women at 24.1%.[25] While breastfeeding support is part of the Baby Friendly designation, there is no specific education regarding the needs of women who are substance abusers. In another study, these women expressed guilt over having methadone in their breast milk, felt they were discouraged from breastfeeding because of this and felt a lack of support for breastfeeding from health care staff.[15]

It can also be quite challenging to breastfeed an infant who is irritable and hyperactive. Maternal anxiety may be more pronounced in this population. Addressing anxiety related to breastfeeding before attempting to provide breast milk may be helpful.[29] Many of these mothers may suffer from anxiety disorders already and therefore, may need additional assistance in this area. In addition, smaller, more frequent feedings at breast as would be the practice for bottle-fed infants who are substance exposed may be helpful.[29] Finally, infants should be put to the breast while still drowsy and swaddled to prevent symptoms of irritability which will make breastfeeding more difficult[29]. Measures that may be helpful in supporting breastfeeding in these infants are listed in Table 2.

It is well known that health care providers' attitudes impact rates of breastfeeding for non-substance exposed infant/mother dyads. Attitudes about substance abuse in general and particularly in pregnancy as well as lack of knowledge about breastfeeding safety can impact breastfeeding rates in this population. Making judgments about a substance abusing mother after the baby is born is pointless and certainly not helpful to the baby. Kohsman[6] discussed the three levels of prevention in NAS. Health care providers can intervene at the primary level of prevention by attempting to prevent exposure. Primary prevention occurs before pregnancy. Most neonatal providers will not have this opportunity but exposure for a future infant may be possible. As secondary prevention, women who present for prenatal care and who are substance abusers should be recognized and treatment provided in order to minimize exposure of this infant. Neonatal providers can intervene as part of tertiary prevention that seeks to minimize long-term consequences for both mother and infant. This would include mental health and social work referrals and supporting breastfeeding thus decreasing the signs of withdrawal in the infant. An additional benefit is to impart many other advantages of breastfeeding as has been found in studies involving infants not exposed to illicit substances. Studies not specific to the NAS infant have been shown to improve bonding with early continued contact and breastfeeding, something that may be in jeopardy for these substance exposed infants due to separation (infants with extended inpatient stays or admission to the NICU) and social factors.

While substance abuse and addiction are issues fraught with morality, these are more common and especially in women of child-bearing age. As neonatal providers, making judgment against the abuser equals judgment against an innocent child. Encouraging breastfeeding can impart advantages beyond decreasing withdrawal for these infants. Mothers should be supported in their role in the infant's life, in spite of illicit drug exposure. For mothers maintained on methadone or buprenorphine, it appears that breastfeeding is safe and should be supported. Pregnancy provides a window of opportunity to intervene and while not all abusers will take advantage of this opportunity, it does happen and is more likely to happen with appropriate referrals and support. In addition, we must recognize that substance abuse is often a sign of underlying mental health or social issues that must be addressed concurrently.

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Cell Phones: Be Aware Of The Risks To The Fetus

B M Petrikovsky, MD, PhD

Introduction

An increased incidence of adverse pregnancy outcomes in doctors who have become pregnant during their training has been reported by numerous investigators.[1-4] The original explanation was that unlimited work hours, stress, and fatigue were the main causes of such adverse outcomes.[4] To reduce stress fatigue, the Accreditation Council for Graduate Medical Education instituted new rules regulating work hours for trainers. Effective July 1, 2013, residents are limited to working a maximum of 80 hours in one week, with at least one 24-hour day free per week, and a minimum of 10 hours off between calls. These changes, however, didn't lead to a significant decrease in complication rates for pregnant trainers. When the hours worked by female residents who had adverse pregnancy outcomes were calculated, no correlation was observed between their workloads and the corresponding incidence of adverse outcomes. Therefore, factors other than stress and long hours may contribute to adverse outcomes, especially a threefold increased rate of fetal growth restriction. Residents are exposed to noise and vibrations from their cell phones and/or beepers at a higher rate than other pregnant women. The goal of the study was to assess the effect of frequent noise and vibrations caused by beepers and cell phones on fetal behavioral patterns.

Materials and methods

Pregnant trainers undergoing antenatal fetal assessment for accepted clinical indications were candidates for this prospective study conducted between June 10, 2011 and March 13, 2015. Inclusion criteria were as follows:

1. Gestational age of 27 and more weeks determined by a first trimester ultrasound
2. Singleton pregnancies.
3. No evidence of fetal congenital abnormalities.

All study subjects were asked to stay away from consuming caffeinated beverages and smoking on the day of testing. All tests were done in a quiet room. All study participants were randomly assigned to either a study or control group. Cell phones and beepers were attached to the scrub pants around the waists of the subjects of the study group and in the chest pocket in the subjects of the control group. Informed consents were obtained as approved by the IRB. All study subjects underwent fetal heart rate (FHR) monitoring and biophysical profiling for 20 minutes before and after each sound stimulation. The sound pressure level of the beepers and cell phones used in the study is between 30 and 95 decibels and the frequency of the vibrations was 900MHZ. The beepers and cell phones used in the study are the sort routinely used by physicians on call. The cell phones and beepers were all set to audible mode. The criteria used for determining the fetal behavioral states were the ones proposed by Nijhuis, et al.[5] Response components included: head turning, mouth opening, tongue protrusion, hand to head movement, and eyelid blinking. Oblique, sagittal or lateral coronal views were used. For this study, response decrement was defined as the cessation of all components of startle response, except eye blinking, over two sequential stimuli. Statistical analysis of the data included one and two way analyses of variance, Student t tests and Chi square analyses whenever appropriate.

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Results

One hundred and twelve pregnant trainers were enrolled in this prospective study. The study included 68 low risk pregnant women in whom a beeper or cell phone was attached to the waist and 44 low risk pregnant women in whom it was attached to the chest pocket. The mean maternal mass was 84.2 ±0.6 kilograms, the mean gestational age was 35.2 ±0,4.2. All the fetuses in the study group developed startle responses compared to 12% in the control group. Table 1 reflects response decrements in both groups for different gestational ages. Changes in behavioral startle response to the first acoustic stimulation were detected in 80% of fetuses in the study group versus 12% of fetuses in the control group.

Table 1. Fetal response decrements in different gestational ages

Gestational age (in weeks)	Study group	Control group	p value
27-32	62%	11%	P<0.05
33-36	81%	7%	P<0.01
37-41	90%	12%	P<0.01

Discussion

The widespread use of cell phones by pregnant women poses a question as to the effect of such use on developing fetuses. We chose a trainer model to address this issue since physicians in training are frequent users of cell phones and beepers. Multiple studies have revealed less than optimum pregnancy outcomes experienced by physicians in training. Thus, Grunebaum et al[6] reported a 7.5-fold increase in fetal growth restriction during residency compared with pre and post residency pregnancies.

Previous cohort studies had also demonstrated an increased risk of low birth weight and stillbirth in pregnant residents.[7,8] Recently, Behbehani et al[9] analyzed the rate of obstetrical complications in pregnant medical and surgical residents and reported much higher rates of fetal growth restriction. Previous studies have also shown that doctors in training are more likely to have small for gestational age (SGA) babies.[6,9] The frequency of fetal complications had no relationship to the residents' workload. We therefore decided to explore the effects of beepers and cell phones frequently used by trainers on fetal behavioral patterns. Previously, we studied the effects of sound waves on fetal swallowing and amniotic fluid index. Fetal swallowing is the major mechanism for the disposal of amniotic fluid and may play a key role in the progressive diminution of fluid near term and beyond. In our series, seven of seventeen subjects with a borderline AF index developed oligohydramnios (AFI<5) after fetal acoustic stimulation. Four of these fetuses demonstrated variable decelerations, which persisted in two and served as an indication for delivery. Thus, the increase in fetal swallowing activity after fetal acoustic stimulation can lead to a decrease in amniotic fluid. These findings can be even more significant in fetuses with preexisting oligohydramnios, who are prime candidates for fetal acoustic stimulation.[10] In these cases, intensive fetal swallowing in response to vibroacoustic stimulation may be another potential mechanism for the development of iatrogenic fetal compromise. In the current study, fetuses were exposed to noise and vibration generated by cell phones and beepers located in the close proximity to the fetal head. Healthy fetuses undergo sleep-wake patterns with most of the time spent in stage 1F (quiet sleep) and 2F (active sleep).[5,11,12] Frequent acoustic stimulation by cell phones and beepers was accompanied by a startle response manifested by head turning towards the source of the sound, increased swallowing and frequent eye blinking. Startle responses were observed in all fetuses of the study group and only in 12% of the fetuses in the control group. Besides causing startle response, acoustic stimulations were associated with changes in behavioral states, most notably, from quiet and active sleep into an awakening state.

In conclusion, until further research establishing the safety of cell phones and beepers for the fetus, they should be used with caution and worn away from fetal compartment.

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Circadiance Introduces the NeoPAP Neonatal CPAP System – Advanced Technology Delivered Simply

David Groll

NeoPAP is a sophisticated respiratory support system that boasts patient comfort, high functionality, and ease of use. NeoPAP represents a major departure from the traditional time-intensive approach to infant CPAP therapy that demands continuous monitoring. It is advanced technology, delivered simply.

The NeoPAP System is intended to provide continuous positive airway pressure (CPAP) for use in hospitals to treat newborns and infants weighing less than 5kg, with RDS (respiratory distress syndrome) or for those who are recovering from RDS.

Circadiance NeoPAP infant respiratory support system sets a new standard for neonatal respiratory care through the use of a lightweight, comfortable, easy-to-adjust patient interface that does not require a perfect fit to the infant's face to function properly.

Unlike competitors' NICU CPAP products that cover the infant's face, NeoPAP's low-profile nasal cannula and mask maximize clinician efficiency, while minimizing the obstructed view of the baby's face during therapy.

NeoPAP utilizes an innovative system called Baby-Trak. Using proportional solenoids, pressure and flow transducers and a microprocessor to regulate pressure, the Baby-Trak leak compensation algorithm quickly responds to patients' changing respiratory requirements related to leaks and to fluctuations in breathing patterns. During exhalation, the CPAP level is maintained, but the flow rates are automatically reduced to decrease the resistance on exhalation to the baby. During inspiration, if there is a reduction in pressure as the infant inhales, NeoPAP increases flow to maintain the set pressure.

The innovative Baby-Trak leak compensation algorithm also helps to reduce pressure on the infant's sensitive skin by eliminating the need for a closely-fitted interface seal, while maintaining the target CPAP level. There's no need to repeatedly tighten the bonnet, risking facial deformation and tissue damage.

Coupled with a small profile patient interface and unique bonnet design, Circadiance's Baby-Trak technology allows for therapy delivery with a minimal number of leak-related nuisance alarms, providing caregivers the freedom to accommodate the unique therapeutic needs of their smallest patients.

David Groll is the CEO of Circadiance. Contact david.groll@circadiance.com.

NeoPAP offers the versatility of three therapy modes: CPAP mode, flow mode, and resuscitation mode. FiO2 concentration can be set between 21% and 100% while operating in any mode. Standby mode allows clinicians to set up the unit in anticipation of admitting a baby needing CPAP, and is useful when an interruption of therapy is required.

Utilizing feedback from the pressure line at the patient interface, NeoPAP can regulate and monitor the level of pressure delivered and provides adjustable alerts with both visual and audible alarms.

The NeoPAP low-profile nasal cannula and mask is made of medical-grade silicone that offers added comfort. The nasal cannula and mask contain no BPA, DEHP, or natural rubber latex. There are no hard plastic parts to cause irritation to delicate newborn skin.

The tapered nasal prong design reduces contact with the patient's nasal mucosa, providing a clear view and minimizing the patient interface from irritating the nasal septum. Because the cannula and mask can be used with both CPAP and Flow modes, the NeoPAP system helps maximize clinician efficiency and reduces patient disruption during therapy.

NeoPAP's unique lining material helps stabilize the bonnet on the patient's small head. The smart Circadiance design preserves the orientation of the patient interface to help reduce nuisance alarms. With its adjustable, single connection point, the bonnet is easy to secure and adjust on the infant patient. The opening at the top of the bonnet provides patient visibility and access for other therapeutic procedures.

Circadiance's tubing fixation is designed for maximum flexibility. The adjustable, Fabrifoam-lined bonnet clips secure the tubing to help reduce the need for adjustments. The tubing fixation incorporates a hook and loop backing for ease of tubing placement and ease of adjustment when necessary. The design allows customization of interface orientation to meet the individual needs of each patient.

The NeoPAP device base configuration includes:

- NeoPAP Device with O_2 and Air Regulators and Market-Specific Fittings
- Quick Start Guide
- User Manual pdf
- IV Pole Cover Mount Plate with 7/8 inch (22mm) shim

- Battery
- Oxygen Sensor
- Oxygen Sensor Removal Tool
- Power-On-Self-Test (POST) Start-up Adapter/Part
- Allen Keys for Mounting of Device to IV Pole – Two Sizes Included

NICU physicians and caregivers from a growing number of prominent healthcare facilities in the United States have discovered that NeoPAP is the ideal solution for infant CPAP therapy. NeoPAP allows medical and nursing staff to spend more time caring for patients and less time tending to the device.

Circadiance designs, manufactures and markets innovative respiratory devices. The NeoPAP System has leveraged Circadiance's experience and expertise by creating a product that incorporates developmental care principles into neonatal and infant CPAP care. Circadiance NeoPAP infant respiratory support system. Design-driven by focusing on clinician workflow with an eye always on patient comfort and care.

The NeoPAP Neonatal CPAP System. Advanced Technology Delivered Simply.

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Nosocomial Outbreak of KPC-2- and NDM-1-Producing Klebsiella Pneumoniae in a Neonatal Ward: a Retrospective Study

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Abstract

Background: The spread of resistance to carbapenems among Enterobacteriaceae has become a major public health problem in recent years. In this study, we describe an outbreak of Klebsiella pneumoniae in the neonatal ward. First, we aimed to study the drug resistance, genetic relatedness, and transmission mechanism of carbapenem-resistant K. pneumoniae; second, we implemented infection control measures to contain the outbreak.

Methods: We investigated 27 non-repetitive strains isolated from neonates and five strains cultured from around the neonatal ward. Polymerase chain reaction (PCR), the agar dilution method, and multilocus sequence typing (MLST) were used to analyze the resistance gene(s), antimicrobial susceptibility, and homology, respectively. Health-care personnel education, hand hygiene, outer gown changing, and infected patient isolation were strictly enforced.

Results: Our antimicrobial susceptibility results show that all strains were multidrug-resistant. MLST and PCR results revealed that, in this study, all of the KPC-2-producing strains are Sequence Type (ST) 11 (ST11) (n = 22) and all of the NDM-1-producing strains are ST20 (n = 4) or ST888 (n = 1). The environmental strains were identified as KPC-2-positive K. pneumoniae ST11 (n = 3) and NDM-1-positive K. pneumoniae ST20 (n = 2). The percentages of isolates with the extended-spectrum-β-lactamases CTX-M-15, blaCTX-M-14, blaTEM-1 were 9.4, 84.3, and 68.8 %, respectively. AmpC β-lactamase genes were not detected in our isolates.

Conclusions: KPC-2-positive K. pneumoniae ST11 and NDM-1-positive K. pneumoniae ST20 were associated with this outbreak. The identification of these isolates in samples from radiant warmers and nurses suggests that hospital cross-transmission played a role in this outbreak. Active infection control measures were effective for controlling this multidrug-resistant K. pneumoniae outbreak.

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Keywords: Multidrug-Resistant, Klebsiella pneumoniae, KPC-2, NDM-1, Nosocomial Infection, Neonate

Background

Carbapenem-resistant Enterobacteriaceae (CRE) have increasingly been found to cause nosocomial infections during the past decade; they primarily affect critically ill patients [1]. Carbapenem-resistant Klebsiella pneumoniae (CR-KP) is one of the most important types of CRE, and it has spread extensively around the world [2]. Carbapenems are the most effective drug for treating infections caused by K. pneumoniae that produce extended-spectrum beta-lactamases (ESBLs). However, with the increase of carbapenem resistance in K. pneumoniae, options for treatment have become limited [3].

Carbapenemases, including KPC, GES, SME, NMC, IMI NDM, IMP, VIM, and OXA-48, are the main mechanisms of carbapenem resistance in CRE. Other mechanisms of carbapenem resistance in these bacteria include the absence or decreased expression of outer membrane proteins and mutations in the ampC enzyme or ESBLs [4].

Outbreaks of hospital-associated CRE infections are not rare [5, 6]. In recent years, outbreaks of CRE infec- tions in neonates have been rising and have attracted increasingly more attention [7, 8]. Here, we noted that the frequency of K. pneumoniae isolated from newborns in our neonatal ward had dramatically increased compared with that of previous years. Therefore, we collected CR-KP in 2015 from January to November to study the resistance and transmission mechanisms of carbapenem-resistant strains in the neonatal ward.

Methods

Setting of the study

A retrospective study was conducted in an 11months period between January 2015and November 2015 in the neonatal ward of Tongji Hospital (TJH). The neonatal ward of TJH receives approximately 1750 admissions per year and it has six rooms (60 beds) for newborns. The 60 % of patients come from maternity ward and 30 % of neonates were outpatients.

Bacterial isolates collection and identification

Thirty-two carbapenem-resistant K. pneumoniae were included in this study. Twenty-seven isolates were collected from different patients. At the same time, according to previous investigation, hospital infection control staff collected environmental samples from high frequency contact areas in neonatal ward in

Table 1. Characteristics of multi-drug resistance K. pneumoniae

Isolate No.	sex	Specimen	Date of Detection	STs	Carbapenemase	ESBL
TJ1	F	Sp	23/1/2015	ST11	KPC-2	CTX-14,TEM-1
TJ2	M	Bl	1/2/2015	ST888	NDM-1	CTX-15,TEM-1
TJ3	M	Ca	6/3/2015	ST11	KPC-2	CTX-14,TEM-1
TJ4	M	Bl	7/3/2015	ST11	KPC-2	CTX-15
TJ5	M	Sp	15/7/2015	ST11	KPC-2	CTX-14,TEM-1
TJ6	M	Sp	16/7/2015	ST11	KPC-2	CTX-14
TJ7	F	Ur	18/7/2015	ST20	NDM-1	TEM-1
TJ8	M	Ca	4/8/2015	ST11	KPC-2	CTX-14
TJ9	M	Ca	8/8/2015	ST11	KPC-2	CTX-14,TEM-1
TJ10	F	Bl	11/8/2015	ST11	KPC-2	CTX-14,TEM-1
TJ11	M	Ur	26/8/2015	ST11	KPC-2	CTX-14,TEM-1
TJ12	M	Bl	31/8/2015	ST11	KPC-2	CTX-15
TJ13	M	Bl	4/9/2015	ST11	KPC-2	CTX-14,TEM-1
TJ14	F	Ca	13/9/2015	ST20	NDM-1	CTX-14,TEM-1
TJ15	M	Sp	13/9/2015	ST11	KPC-2	CTX-14,TEM-1
TJ16	M	Ca	22/9/2015	ST20	NDM-1	CTX-14
TJ17	F	Sp	25/9/2015	ST11	KPC-2	CTX-14,TEM-1
TJ18	F	Ur	30/9/2015	ST11	KPC-2	CTX-14,TEM-1
TJ19	M	Bl	2/10/2015	ST11	KPC-2	CTX-14,TEM-1
TJ20	F	Ur	6/10/2015	ST11	KPC-2	CTX-14,TEM-1
TJ21	M	Ur	8/10/2015	ST11	KPC-2	CTX-14,TEM-1
TJ22	F	Ur	12/10/2015	ST11	KPC-2	CTX-14,TEM-1
TJ23	M	Bl	25/10/2015	ST11	KPC-2	–
TJ24	M	Bl	28/10/2015	ST20	NDM-1	CTX-14
TJ25	F	Ur	20/11/2015	ST11	KPC-2	CTX-14,TEM-1
TJ26	F	Bl	20/11/2015	ST11	KPC-2	CTX-14
TJ27	M	Ur	21/11/2015	ST11	KPC-2	CTX-14,TEM-1
TJ28[a]	–	Radiant warmer	8/9/2015	ST11	KPC-2	CTX-14,TEM-1
TJ29[a]	–	Radiant warmer	8/9/2015	ST20	NDM-1	CTX-14
TJ30[b]	–	Nurses hand	8/9/2015	ST11	KPC-2	CTX-14,TEM-1
TJ31[c]	–	Radiant warmer	8/9/2015	ST11	KPC-2	CTX-14,TEM-1
TJ32[b]	–	Nurses hand	8/9/2015	ST20	NDM-1	CTX-14

F female, M male, Sp sputum, BL blood, Ur urine, Ca aspiration catheter
[a]65 bed radiant warmer; [b]nurses hand; [c]55 bed radiant warmer

September 8, 2015, including bed railing, stethoscope, personal digital assistant, suction apparatus, venous catheter, radiant warmer, nurses' hand, thermostat button and ventilator machine. Samplings were accomplished before routine cleaning, 89 environmental samples and 40 samples from nurses' hands were obtained. All isolated strains were identified by conventional biochemical methods, then were confirmed by PCR amplification of 16S rRNA gene and sequencing [9].

PCR and DNA sequence analysis of resistance gene

PCR were performed to detect drug-resistance genes, including carbapenemases (blaKPC-2, blaGES, blaIMP-4, blaVIM-1, blaNDM-1, blaOXA-48), common ESBL genes (blaCTX-group1, blaCTX-group2, blaCTX-group8, blaCTX-group9, blaTEM-1, and blaSHV), and ampC genes (MOX, FOX, DHA, CIT, AAC and EBC) [10–12]. The PCR products were sequenced and analyzed using BLAST (http://www.ncbi.nlm.nih.gov/BLAST).

Susceptibility testing

Antibiotic susceptibility testing was assayed by agar dilution method to determinate the minimum inhibitory concentration (MICs) of ampicillin, ceftazidime, cefotaxime, cefepime, cefuroxime, cefoxitin, gentamicin, levofloxacin, amikacin, ciprofloxacin, aztreonam, imipenem, meropenem, trimethoprim-sulfamethoxazole, piperacillin- tazobactam, tigecycline and colistin. All antibiotics, except tigecycline and colistin, were interpreted according to the standard of the Clinical and Laboratory Standards Institute (CLSI) document M100-S22. For tigecycline and colistin, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint was used. E. coli ATCC 25922 and P.aeruginosa ATCC27853 were used as quality control.

Multilocus sequence typing (MLST)

Epidemiological relatedness was carried out by multilocus sequence typing (MLST). Multilocus sequence typing (MLST) for clinical K. pneumoniae isolates was performed following the methods described previously [13]. The allelic profiles and sequence types (STs) were assigned using online databases (http://www.pasteur.fr/recherche/ genopole/PF8/mlst/ Kpneumoniae.html).

Infection control interventions

Strict infection control measures were implemented according to the Guidance for Control of CRE in November, 2015 [14]. Healthcare personnel are familiar with proper hand hygiene technique and wash their hands properly before entering and upon leaving patient rooms. Hand hygiene adherence was monitored by video. Patients who are suspected or confirmed with CRE should be placed in a private room in which staff

Table 2. Antibiotic susceptibility of K. pneumoniae

Minimal inhibitory concentration (ug/ml)		
Antibiotics	K. pneumoniaeST11 (n = 25) range	NDM-1positiveK. pneumoniae (n = 7) range
AMP	≥512	≥512
CAZ	≥512	≥512
CTX	128- > 512	64- > 512
FOX	64–256	64–256
FEP	64–256	16–64
CXM	≥512	≥512
ATM	≥512	1–2
GN	64–256	0.25–0.5
LEV	32–128	0.06–0.25
AK	≥512	1–2
CIP	≥32	0.06–1
TZP	64/4- > 256/4	128/4- > 256/4
SXT	1/19–2/38	≥256/4864
IPM	8–64	1–16
MEM	4–32	1–32
TGC	0.06–0.5	0.06–0.5
CO	0.03–0.5	0.06–0.25

AMP ampicillin (0.06–512), CAZ ceftazidime (0.06–512), CTX cefotaxime (0.06–512), FEP cefepime (0.06–512), CXM cefuroxime (0.06–512), FOX cefoxitin (0.06–512), GN gentamicin (0.06–512), LEV levofloxacin (0.06–512), AK amikacin (0.06–512), CIP ciprofloxacin (0.004-32), ATM Aztreonam (0.06–512), IPM imipenem (0.03–256), MEM meropenem (0.03–256), TZP piperacillin-tazobactam (0.25/4–256/4), SXT trimethoprim-sulfamethoxazole (0.25/4.75–256/4864), TGC tigecycline (0.03–256), CO colistin (0.03–256)

and visitors are required to don gloves and gowns for entry. Extensive cleaning of shared equipment and the use of disposable materials (when feasible) were implemented.

Results

Epidemiological characteristics of K. pneumoniae isolates

The molecular epidemiology of carbapenem-resistant Enterobacteriaceae was studied from January to November 2015. During this period, There were 1519 patients admitted to hospital,including 590 females (38.9 %) and 929 males (61.1 %). The sex ratio of all patients is similar to infection group (61.1 vs 63.0 %). The average age of the CR-KP infection (32.5 ± 22.7) ws older than all patients (11.2 ± 23.4).27 consecutive CRE were isolated from 27 different patients. The characteristics of the CR-KP isolated in this study are shown in Table 1. Twenty seven of the isolates are from new- borns in the neonatal unit, including 17 males and 10 females, with a mean age of 32.5 days (range, 1–85 days). The sources of these specimens were blood (n = 9), urine (n = 8), aspiration catheter (n = 5), and sputum (n = 5). Meanwhile, ten suspicious colonies were found and further identified by biochemical method, and finally five CR-KP isolates were cultured from radiant warmers or nurses' hands during the peak of the outbreak.

Antimicrobial susceptibility patterns of K. pneumoniae isolates

The results of minimum inhibitory concentration (MIC) assays are shown in Table 2. All K. pneumoniae isolates were non-susceptible to ampicillin, cefoxitin, cefuroxime, cefotaxime, cefepime, ceftazidime, imipenem, meropenem, and piperacillin tazobactam, but were highly sensitive to tigecycline and colistin. The antibiotic resistance rates to gentamicin, amikacin, levofloxacin, ciprofloxacin, aztreonam, and trimethoprim-sulfamethoxazole were 78.1, 78.1, 78.1, 84.1, 78.1, and 21.9 %, respectively. Notably, strains producing NDM-1carbapenemase show different antibacterial susceptibility spectra from strains producing KPC-2 carbapenemase, including gentamicin, amikacin, levofloxacin, ciprofloxacin, aztreonam, and trimethoprim-sulfamethoxazole (see Table 2).

Sequence typing and expression of drug-resistance genes

Based on the multi-locus sequence typing (MLST) results, the 27 isolates from unique patients were identi- fied as Sequence Type (ST) 11 (ST11) (n = 22), ST20 (n = 4), and ST888 (n = 1), and the five environmental isolates were identified as ST11 (n = 3) and ST20 (n = 2).

The percentages of isolates with carbapenemases KPC-2 and NDM-1were 81.5 % (22/27) and 18.5 % (5/27), respectively. All KPC-2-producing strains were ST11, and most of the NDM-1-positive strains were ST20 (n = 4). Three of the five environmental strains were KPC-2- positive K. pneumoniae ST11, and the other two environ- mental isolates were NDM-1-positive K. pneumoniae ST20. The rates of the ESBLs CTX-M-15, CTX-M-14, and TEM-1 were 9.4, 84.3, and 68.8 %, respectively. AmpC genes and other carbapenemases were not detected.

The effect of infection control interventions

We monitored for neonatal infection with K. pneumoniae in future 4 months, and we detected multidrug-resistant K. pneumoniae in five patients, three patients, one patient and one patient, respectively, over these 4 months.

Discussion

K. pneumoniae is an important nosocomial pathogen that can cause pneumonia, sepsis, and meningitis [15]. The emergence of CR-KP has created a challenge for treating K. pneumoniae infections, the mortality caused by CR-KP incection was high [16]. However, one infected neonate has died in our study. Mortality from K. pneumoniae infection is associated with a variety of factors, including underlying disease, nutritional status, and medical treatment, which may explain the discrepancy in mortality among different studies.

Underlying disease, low birth weight, antibacterial drug treatment, invasive procedures, and prolonged hospitalization have all been reported as extremely important risk factors of CRE infection [17, 18]. Of the 27 patients in this study, the percentages of subjects who had a low birth weight, who were treated with antibacterial drugs, and who underwent invasive procedures were 74.1 % (n = 20), 100 % (n = 27), and 77.8 % (n = 21) (data was not show), respectively. Additionally, we noticed that each nurse needed to take care of several infants and that each newborn was usually cared for by several nurses due to scheduling reasons. Overall, the newborns in our study possessed high risk factors for CRE infection, and this outbreak was likely spread by cross-infection.

As results showed, no significant differences in sex ratio and age between infection patients and non-infection patients. The CR-KP infection probably has no relation with age and gender in our study,which was similar with other study [19]. In addition, the average days for hospitalization in TJH is 11.8 days at present. However, the average hospital stay of the 27 patients including in this study was 29.9 days. Prolonged hospitalization may contribute to spreading of the ST11 and ST20 strains in neonatal ward.

The first KPC-2-producing K. pneumoniae isolate (TJ1) was

isolated from a 23-day-old boy that was confirmed as infected with multidrug-resistant K. pneumoniae at another hospital. He was transferred to our hospital for treatment on January 23, 2015, and a sputum culture confirmed his infection with a multidrug-resistant K. pneumoniae. We learned that his mother had suffered from a respiratory tract infection for 2 weeks and 4 days. Through combination therapy with cefoperazone sulbactam, amoxicillin clavulanic acid, fluconazole, and meropenem, the child recovered and was discharged on February 5, 2015. Subsequently, KPC-2-positive strains with the same phenotype appeared in the same ward. All KPC-2-positive strains were detected in patients who had been hospitalized for more than 48 h, so we speculate that the origin of the KPC-2-positive K. pneumoniae ST11 was probably TJ1. Rodloff MD and his colleagues found that carriage of KPC-2-producing K. pneumoniae can last for 3 years [20]. It probably explain continuous outbreak after index case. Regrettably, the origin of the NDM-1-producing isolates in our study is still unknown.

The number of infection with K. pneumoniae decrease sharply in future 4 months. These declining numbers suggest that our efforts to control the continuous outbreak of multidrug-resistant K. pneumoniae were at least partially effective. However, there was one or two CR-KP detected after infection control interventions. It is difficult to eradicate the CR-KP by infection control measures [21]. Infection control measures were still need to improve, including routine screening of hospitalized patients, pathogens culture of medical equipment and screening the colonization status of contemporaneous patients.

This study has several limitations. Specifically, we only performed one environmental sampling and neglect screening of patients with perianal swabs to detect the rate of colonized patients. Additional samples might have provided stronger evidence to support our conclu- sion that the CR-KP was spread through cross-infection. Our data is also unable to confirm whether or not the CR-KP strains isolated in the later 3 months of our study are the same as the previous epidemic strain.

Conclusions

In summary, we report that KPC-2-positive K. pneumoniae ST11 and NDM-1-positive K. pneumoniae ST20 are the two main clones that caused neonate infection in our hospital during the study period. During the outbreak, we successfully isolated these two main clones from a radiant warmer and from nurses' hands. The radiant warmer and the nurses' hands may have played an important role in harboring the K. pneumoniae producing KPC-2 or NDM-1 carbapenemases that caused persistent infection within the same ward. Following the emergence of CRE on a ward, Screening and infection control measures must be implemented to block nosocomial transmission. Active and effective infection control measures are indispensable for preventing a subsequent outbreak.

Abbreviations

CRE: Carbapenem -resistant Enterobacteriaceae; CR-KP: Carbapenem resistance -Klebsiella pneumoniae; ESBLs: Extended-spectrum beta-lactamases; KPC-2: K. pneumoniae carbapenemase; MIC: Minimal inhibitory concentration; MLST: Multilocus sequence typing; NDM-1: New Delhi metallo-β-lactamase-1 enzymes; ST: Sequencing type

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Availability of data and materials

All the data on which the conclusions of the manuscript rely is presented in the main paper and additional files 1, 2 and 3.

Authors' contributions

ZS and LC designed the study; YJ and KT performed the experiments; ZR and YW collected the epidemiological data; ZC and XZ collected the microbiological data; LW, LT and WX analyzed the data; YJ wrote the manuscript. All authors read and approved the final manuscript.

Ethics and consent to participate

The study protocol was approved by the Tongji Hospital ethics committee for research in health. Informed written consent was obtained from the parents or legal guardian of the patient before inclusion in the study.

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Neonatal Diffusion Tensor Brain Imaging Predicts Later Motor Outcome In Preterm Neonates With White Matter Abnormalities

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Abstract

Background: White matter (WM) abnormalities associated with prematurity are one of the most important causes of neurological disability that involves spastic motor deficits in preterm newborns. This study aimed to evaluate regional microstructural changes in diffusion tensor imaging (DTI) associated with WM abnormalities.

Methods: We prospectively studied extremely low birth weight (ELBW; <1000 g) preterm infants who were admitted to the Neonatal Intensive Care Unit of Hanyang University Hospital between February 2011 and February 2014. WM abnormalities were assessed with conventional magnetic resonance (MR) imaging and DTI near term-equivalent age before discharge. Region-of-interests (ROIs) measurements were performed to examine the regional distribution of fractional anisotropy (FA) values.

Results: Thirty-two out of 72 ELBW infants underwent conventional MR imaging and DTI at term-equivalent age. Ten of these infants developed WM abnormalities associated with prematurity. Five of ten of those with WM abnormalities developed cerebral palsy (CP). DTI in the WM abnormalities with CP showed a significant reduction of mean FA in the genu of the corpus callosum ($p = 0.022$), the ipsilateral posterior limb of the internal capsule ($p = 0.019$), and the ipsilateral centrum semiovale ($p = 0.012$) compared to normal WM and WM abnormalities without CP. In infants having WM abnormalities with CP, early FA values in neonatal DTI revealed abnormalities of the WM regions prior to the manifestation of hemiparesis.

Conclusions: DTI performed at term equivalent age shows different FA values in WM regions among infants with or without WM abnormalities associated with prematurity and/or CP. Low FA values of ROIs in DTI are related with later development of spastic CP in preterm infants with WM abnormalities.

Keywords: Neonates, Magnetic resonance imaging, Diffusion tensor imaging, Periventricular leukomalacia

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Background

Despite the recent advances in both antenatal and neonatal intensive care, neurodevelopmental outcomes in those born prematurely have improved little over time. Many studies have reported that neurodevelopmental disorders observed in preterm infants comprise motor and cognitive impairment, language delays, behavioral disorders, and psychological problems [1-3].

White matter (WM) abnormalities associated with prematurity are the predominant cause of neurological disabilities in preterm infants. Periventricular foci of necrosis in preterm infants are caused by multifactorial insults including hypoxia-ischemia, infection/inflammation and coagulation disturbance at a particular timing of brain development [4]. Early prediction of motor and cognitive deficits is crucial to recognize patients with WM injury who will benefit from early developmental intervention programs, which offer the possibility of improving the neurological outcomes. Although magnetic resonance imaging (MRI) has provided insight into the underlying WM injury, compared to cranial sonography, structural MRI studies fail to quantitatively measure microstructural abnormalities and predict outcomes during the neonatal period [5].

The diffusion tensor imaging (DTI) of advanced MRI reflects changes in WM connection and myelination by the detection of water anisotropy according to the degree and direction of water molecule permeability in tissues. Fractional anisotropy (FA) is used to measure the directionality obtained in axon bundles as well as myelination. Increasing evidence has suggested that the low FA values in WM association areas are related to negative motor and cognitive functions in preterm infants [6].

Nevertheless, few studies have been conducted to evaluate the correlations between WM connectivity as revealed by DTI and motor neurodevelopment of extremely low birth weight (ELBW; <1000 g) infants with WM abnormalities [7, 8]. Therefore, this study aimed to determine the diffusion tensor characteristics of WM regions associated with motor outcome among preterm infants with or without WM abnormalities and/or cerebral palsy (CP).

Methods

This study is part of a prospective research program on ELBW infants involving short- and long-term postnatal follow-up at the Hanyang Inclusive Clinic for Developmental Disorders in Hanyang University College of Medicine. The 72 ELBW infants (<1000 g) born and admitted to a level 3 Neonatal Intensive

Care Unit at Seoul Hanyang University Hospital of South Korea between February 2011 and February 2014 were eligible for the study. The major exclusion criteria were congenital malformations or chromosomal anomalies. These infants were imaged during natural sleep without sedation using oral chloral hydrate.

Clinical characteristics of study infants

Prenatal and neonatal data were prospectively recorded, including gestational age (GA), birth weight, delivery mode, sex, twin status, Apgar at 5 min, maternal chorioamnionitis, and prenatal steroid use for each infant. Chorioamnionitis was defined by the presence of histologic chorioamnionitis or umbilical cord vasculitis of grade 2 or greater, using the grading system suggested by Salafia et al. [9]. Neonatal outcomes included patent ductus arteriosus, bronchopulmonary dysplasia (BPD), culture-proven sepsis, necrotizing enterocolitis, retinopathy of prematurity, intraventricular hemorrhage (IVH) (grade ≥ III) according to the Papile classification [10], and CP. The diagnosis and severity of BPD were based on the need for supplementary oxygen at 28 days of age and at 36 weeks gestational age [11]. Intraventricular hemorrhage was defined according to Volpe [10], and necrotizing enterocolitis was defined according to Bell et al. [12]. CP was defined as a classification proposed by the Surveillance of CP in Europe (SCPE) collaborative group. Spastic CP was diagnosed if they had at least two of the following criteria: abnormal posture or movement, increased tone, or hyperreflexia [13]. The diagnosis of unilateral or bilateral spastic CP was made by the rehabilitation physician and, when necessary, confirmed by a neuropediatrician at the corrected age of 24 months at follow-up.

All preterm infants who underwent a DTI exam were categorized into the "no WM abnormalities" group, the "WM abnormalities without CP" group, or the "WM abnormalities with CP" group to identify the differences in the clinical characteristics and FA values on DTI according to the regions of interest among these groups. Radiological evaluation was performed by an experienced pediatric neuroradiologist, Y.L., who was blinded to all clinical data. Brain abnormalities were assessed on structural MRI for presence/absence of WM abnormalities and details on co-existing types of lesions.

MRI data analysis (term-equivalent)

Conventional magnetic resonance (MR) images and diffusion tensor images were obtained with a 3.0 T MRI scanner (Philips Real Time Compact Magnet 3.0-Tesla MRI system, Achieva 3.0-Tesla X-series) with a six-channel SENSE head coil operating. Conventional MR images included sagittal and axial T1 spin-echo sequences (400/25/2, TR/TE/signal intensity averages) and axial T2 fast spin-echo (4500/90/3). The Philips Research Imaging Development Environment (PRIDE) Diffusion Registration tool (version 0.4) was used to calculate FAs of the diffusion tensor data after processing of the DT-MRI images. Region-of-interests (ROIs) measurements were performed to examine the regional distribution of FA values in 2-dimensional space. We reconstructed fiber-tracking in 3-dimensional space using PRIDE Fiber Tracking tool (version 4.1) and set 3 ROIs for the motor tract at the ventral part of the pons, the internal capsule and at the centrum semiovale to evaluate fiber connectivity. We didn't include a tractography to analyze quantitatively but performed tractography itself to assess the connectivity and disruption of depicted motor tract.

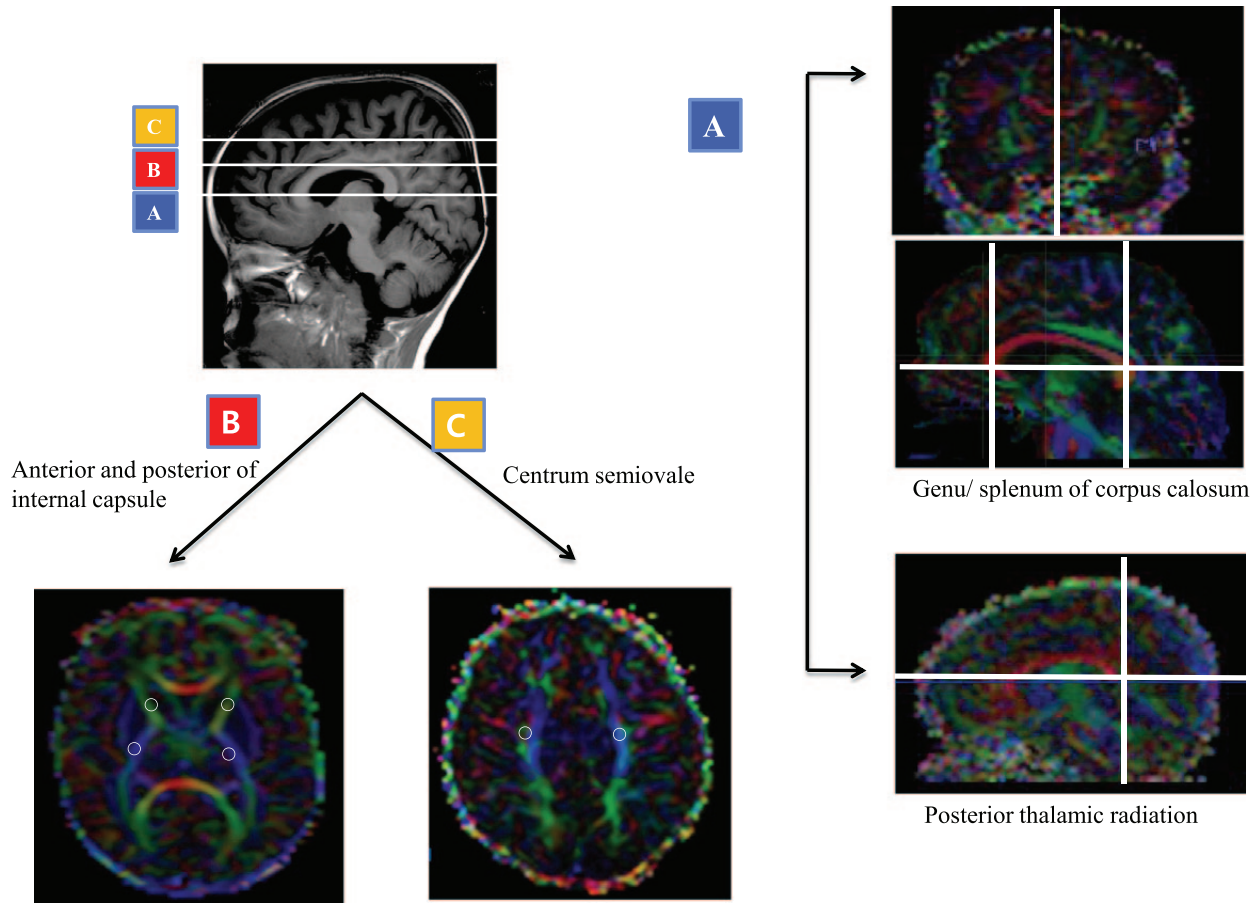

Figure 1. A region-of-interest placement of the white matter tract selected on a representative infant diffusion tensor imaging at near-term age.

Table 1 Clinical characteristic of study infants

	No WM[a] (*N* = 22)	WM[a] without CP (*N* = 5)	WM[a] with CP (*N* = 5)	*P*-value
Gestational age (wk)	26.14 ± 2.44	27.40 ± 2.79	25.00 ± 1.22	0.292
Birth weight (g)	819 ± 133	770 ± 153	738 ± 146	0.441
Cesarean section, *n* (%)	17 (77.2)	5 (100)	5 (100)	0.335
Male gender, *n* (%)	15 (68.2)	2 (40)	2 (40)	0.322
Twin, *n* (%)	7 (31.8)	3 (60)	0 (0)	0.122
Apgar score at 5 min	4.27 ± 1.42	4.60 ± 0.55	5.00 ± 1.22	0.516
Chorioamnionitis, *n* (%)	13 (59.1)	4 (80)	3 (60)	0.678
Prenatal steroid use, *n* (%)	19 (86.4)	4 (80)	4 (80)	0.900
Hospital Days	95.25 ± 22.71	64.80 ± 38.36	70.75 ± 39.94	0.072
Days on ventilation	22.59 ± 15.56	11.60 ± 4.16	32.20 ± 20.12	0.121
PDA, *n* (%)	18 (81.8)	4 (80)	5 (100)	0.606
BPD ≥ moderate, *n* (%)	7 (31.8)	3 (60)	2 (40)	0.497
Sepsis, *n* (%)	10 (45.5)	1 (20)	3 (60)	0.426
NEC, *n* (%)	4 (18.2)	0 (0)	1 (20)	0.575
IP, *n* (%)	3 (13.6)	0 (0)	0 (0)	0.471
ROP ≥ grade 2, *n* (%)	13 (59.1)	3 (60)	1 (20)	0.137
IVH, *n* (%)	8 (36.4)	4 (80)	5 (100)	0.015
IVH, grade III/IV, *n* (%)	2 (9.1)	3 (60)	5 (100)	<0.001
Cerebral palsy, *n* (%)	0	0	5 (100)	<0.001

Data are presented as mean ± SD or number (%)
Abbrevations: *WM[a]* white matter abnormalities, *PDA* patent ductus arteriosus, *BPD* bronchopulmonary dysplasia, *NEC* necrotizing enterocolitis, *IP* intestinal perforation, *ROP* retinopathy of prematurity, *IVH* intraventricular hemorrhage, *PVL* periventricular leukomalacia, *CP* cerebral palsy

Diffusion tensor images were sing a single-shot spinecho planar sequence with a SENSE factor of two and an echo-planar imaging factor of 67 (TR/TE, 13891/55 ms; matrix size, 112 × 112; field-of-view, 224 mm; 90 axial sections; 2.0-mm section thickness). Diffusivities were measured along 15 directions using an electrostatic gradient model (b = 800). Tracking was stopped when the FA in a pixel below 0.18 was reached to prevent streamlines from going into low anisotropy gray matter.

To ensure reliability, consensus on each region of interest placement and measurement was reached by two independent researchers. Tracking was initiated by manually placing a region of interest within anatomically similar regions of the corpus callosum (genu and splenum), anterior internal capsule, posterior internal capsule, posterior thalamic radiation, and centrum semi-ovale (Fig. 1).

Neurodevelopmental assessment

Neurodevelopmental outcomes were assessed at a mean age of 18 ± 3.5 months (range: 15-23 months) with the Bayley Scale for Infant Development-III (BSID-III), which evaluates five distinct scales: cognitive; language, with receptive and expressive communication subtests; motor, with fine and gross motor subtests; socioemotional behavior; and adaptive behavior. The average BSID-III score in healthy infants and children is 100 ± 15.

Statistical analysis

Comparisons between groups were carried out by one-way Analysis of Variance or Kruskal-Wallis tests for comparison of continuous variables. Categorical variables were analyzed by Pearson's chi-square test or Fisher's exact test (both two-sided), as appropriate. To account for multiple comparisons, Bonferroni's correction was considered. All statistical analyses were carried out using SPSS 17.0 (SPSS Inc.). P-values < 0.05 were considered statistically significant. The study was approved by the Hanyang University Hospital Institutional Review Board, and written informed consent was obtained from the patients' parents.

Results

Seventy-two infants with ELBW were admitted during the study period, and 62 infants were included after parental consent was obtained. Eighteen infants were excluded due to instability during the MRI exam with poor results, and two infants were excluded due to insufficient data. Excluding deaths (n = 10) and refusals (n = 10), 32 patients who fulfilled the study criteria were enrolle. During the study period, 32 infants with available DTI data were evaluated for the regional distribution of FA values associated with WM injury with GAs ranging between 23 and 30 weeks and birth weights ranging between 760 and 1740 g. Thirty-two ELBW infants (19 males and 13 females) underwent conventional MRI and DTI at a mean post-menstrual age of 36.5 ± 1.9 weeks. Ten of these infants developed WM abnormalities (bilateral: 4, left side: 6). Five of the ten infants with WM abnormalities (bilateral: 2, left side: 3) developed spastic CP (bilateral: 2, unilateral: 3). The infants enrolled in the DTI analysis were classified into three groups; no WM abnormalities, WM abnormalities without CP, and WM abnormalities with CP. Table 1 shows the clinical characteristics and neonatal outcomes of the groups. The mean gestational age and birth weight were not significantly different among the no WM abnormalities, WM abnormalities without CP, and WM abnormalities with CP groups. The infants in the WM abnormalities with CP group showed a higher occurrence of any grade of IVH and of IVH grade ≥ III (P < 0.001).

FA values of ROIs in the DTI showed that the genu, anterior/posterior limb of the internal capsule, bilateral posterior

Table 2 Fractional anisotropy values of study infants with diffusion tensor imaging

Region-of-interest	No WM[a] (*N* = 22)	WM[a] without CP (*N* = 5)	WM[a] with CP (*N* = 5)	*P*-value
Genu of Corpus Callosum	0.32 ± 0.06	0.30 ± 0.01	0.24 ± 0.02	0.022
				0.020*
Splenum of Corpus Callosum	0.34 ± 0.06	0.33 ± 0.04	0.27 ± 0.04	0.068
Rt. Anterior Internal Capsule	0.31 ± 0.51	0.28 ± 0.07	0.28 ± 0.04	0.345
Lt. Anterior Internal Capsule	0.29 ± 0.03	0.26 ± 0.04	0.26 ± 0.03	0.131
Rt. Posterior Internal Capsule	0.36 ± 0.49	0.32 ± 0.47	0.31 ± 0.07	0.108
Lt. Posterior Internal Capsule	0.36 ± 0.04	0.35 ± 0.01	0.30 ± 0.06	0.019
				0.016*
Rt. Posterior Thalamic Radiation	0.29 ± 0.04	0.25 ± 0.03	0.26 ± 0.08	0.140
Lt. Posterior Thalamic Radiation	0.30 ± 0.04	0.26 ± 0.01	0.28 ± 0.05	0.144
Rt. Centrum Semiovale	0.34 ± 0.04	0.31 ± 0.04	0.31 ± 0.03	0.170
Lt. Centrum Semiovale	0.33 ± 0.05	0.30 ± 0.01	0.26 ± 0.02	0.012
				0.011*

Data are presented as mean ± SD or number (%)
Abbrevations: *WM*[a] white matter abnormalities, *PVL* periventricular leukomalacia, *CP* cerebral palsy, *Lt* left, *Rt* right
* P comparing No PVL group and PVL with CP group in the Bonferroni's correction for multiple comparisons

thalamic radiation, and centrum semiovale were attenuated in the WM abnormalities groups. In addition, DTI parameters in the WM abnormalities with CP showed a significant reduction of mean FA in the genu of the corpus callosum (p = 0.022), the ipsilateral posterior limb of the internal capsule (p = 0.019), and the ipsilateral centrum semiovale (p = 0.012) compared to those in no WM abnormalities group and WM abnormalities without CP group. Although there were no significant differences in the splenum of the corpus callosum between the study groups, the WM abnormalities with CP group had lower FA values compared to the WM abnormalities without CP group (Table 2). In infants with WM abnormalities and CP, patient 1-2 showed successful assessment of bilateral motor fiber tracts, whereas patient 3-4 displaced reduced or disrupted fiber tracts in the left side. Fiber tracts were not delineated in the left side in patient 5 (Fig. 2). The representative axial images on T2 flair image (A) and tractography of motor fibers on DTI (B) are shown in preterm infants with white matter abnormalities without cerebral palsy (Additional file 1).

In infants having WM abnormalities with CP, DTI at discharge revealed abnormalities of FA values in WM regions prior to the manifestation of abnormal motor function and/or impaired cognition. Five children displayed spastic CP (bilateral: 2, unilateral: 3) and/or impaired cognition (four out of five children). The remaining five infants constituted the WM abnormalities without CP group. Four of these five children had normal development without delays of cognitive, motor and language functions as assessed with the BSID-III.

Discussion

This study demonstrated that DTI performed at term equivalent age shows different FA values in WM regions among infants with or without WM abnormalities associated with prematurity and/or CP. The motor outcome of the patients with WM abnormalities associated with prematurity was associated with low FA values in the DTI parameters of the genu of the corpus callosum, the ipsilateral posterior limb of the internal capsule, and the centrum semiovale at discharge in extremely low-birth weight infants.

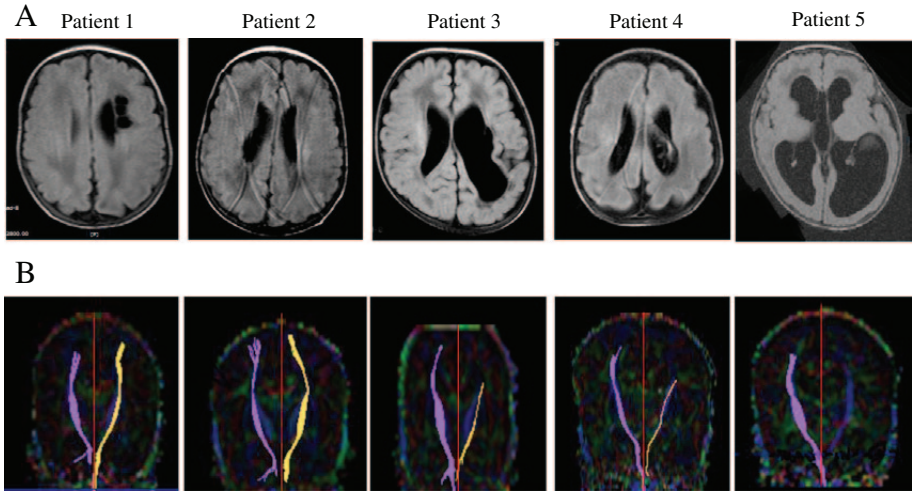

Figure 2. The representative axial images on T2 flair image (a) and tractography of motor fibers on DTI (b) are shown in preterm infants with white matter abnormalities and cerebral palsy.

WM abnormalities associated with prematurity, which is the leading cause of CP, is estimated to occur in 10-15% of very low-birth weight (VLBW; <1500 g) infants and is attributed to the developing brain's vulnerability to hypoxic ischemic events [14]. Follow-up studies reported that 20-40% of children born with VLBW had isolated cognitive deficiencies, even in cases without significant cerebral damage, resulting in impaired language skills, learning, executive functions, or social abilities [15-17]. Few studies have clearly shown that the extent of structural abnormalities, microstructural deviations, and global reductions in brain volumes, both at preterm and term ages, is directly related to the level of neuromotor and neurocognitive performance in childhood [18, 19].

Great progress has been made in the past few decades in the approach to microstructural development with a novel tract-based analysis of DTI data in infants. DTI has good sensitivity and specificity to assess quantitative changes in the various brain microstructures during the developmental stage [20]. Conventional MRI has been limited in the quantitative evaluation of specific WM tracts in the premature brain. While conventional MRI is able to visualize only macroscopic characterization of WM after the myelination, DTI is sensitive to the maturational changes in premyelinating WM prior to the onset of myelination [21, 22]. Although the DTI image analysis of various brain structures in the early developmental phases is challenging in the first 2 years of life, the central regions of the WM are already visible by DTI at birth. Many authors [23-25] have described WM anisotropy and mean diffusivity throughout the development process as a reference with which to characterize the early stages of maturation including the premyelinating state.

Partridge et al. [22] serially examined WM development by DTI in 14 premature infants with no evidence of WM abnormalities by conventional MRI. More significant age-related changes in DTI values were identified in the transverse fiber tracks of the corpus callosum than in other WM pathways. Xueying et al. [26] compared WM maturation patterns in major fiber pathways between 60 preterm infants and 25 term controls with normal MRI and neurologic examinations at term-equivalent age using diffusion parameters, FA, and apparent diffusion coefficients. They showed that the increased FA in the preterm infants at term-equivalent age was significantly different from the decreased FA in the term infants, suggesting that prematurity is an independent factor of accelerated maturation of WM in the extrauterine environment compared to term controls.

However, there have been few DTI studies about the predictive value of abnormal WM lesions prior to the manifestation of hemiparesis in preterm infants with high risk factors. Fundamental questions remain to be addressed to predict long-term developmental outcomes at term-equivalent age, limiting our ability to assess the therapeutic interventions needed during critical periods of development. DTI might add another piece to the puzzle of pathophysiology preceding developmental delay in high-risk preterm infants with WM abnormalities associated with prematurity. The early identification of candidates at risk of developing CP or abnormal WM maturation is helpful in selecting infants for potential therapeutic interventions in order to improve long-term outcomes. In the present study, infants having WM abnormalities in the presence of CP showed a decrease in the FA of diffusion tensor values at term-corrected age, particularly in the regions of the centrum semiovale, the posterior limb of the internal capsule, and the corpus callosum.

Our findings are similar to the results of earlier studies. Murakami et al. [27] examined DTI with fiber tracking for corticospinal tracts in 10 patients with WM abnormalities associated with prematurity during infancy to predict clinical motor functions at the early stage of development as a biomarker. Disturbance to the posterior limb of the internal capsule is especially known to increase vulnerability to hypoxic ischemic injury in infants. De Bruïne et al. [28] confirmed a strong correlation between those low FA values of the posterior limb of the internal capsule at term-equivalent age and subsequent psychomotor delay at the age of 2 years in very preterm infants. Roze et al. [29] determined the association between later development of spastic CP and early perturbation of DTI values. They showed that asymmetries in FA within 4 weeks after birth were predictive of unilateral spastic CP in preterm infants with periventricular hemorrhagic infarction. Rose et al. [30] examined the WM microstructures of six subcortical regions on DTI in 66 VLBW preterm infants at near-term age. They found a relationship between lower mean diffusivity of the thalamus and higher total bilirubin, which is known to be a risk factor of adverse neurodevelopment. Son et al. [31] revealed corticospinal tract disruption prior to clinical manifestations of hemiparetic CP, even though the conventional brain MRI of patients showed no abnormalities. In addition to being a predictor of motor outcomes, several studies suggest a relationship between WM microstructure at term-equivalent age and cognitive outcomes in children and adolescents born very preterm [32, 33]. Perinatal brain damage of WM abnormalities associated with prematurity may impact the normal maturation of cortical grey matter, which reflects the disorganized and disrupted axons. Woodward et al. [14] stressed the importance of cerebral WM connectivity for later neurocognition such as intelligence, language, and executive function. Consistent with data above, our study showed that four of five infants in the PVL with CP group had the expected drop on the Bayley-III cognitive and language scores at 2 years of age, preceded with low FA values in WM t term age. Skranes et al. [6] investigated the relationships between low scores on the Wechsler Intelligence Scale for Children-III test and low FA values in several WM areas in the VLBW group. Although FA analysis of our DTI study was not properly differentiated to the cognitive assessment, early perturbation of DTI values may be associated to later cognitive development in different brain areas.

Conclusions

This study demonstrates low FA values of ROIs in DTI are related with later development of spastic CP in preterm infants with WM abnormalities. A quantitative approach using DTI in specific WM might provide prognostic values for the brain development in preterm infants. The value of DTI in predicting long-term infant neurodevelopmental outcomes should be analyzed in a larger cohort.

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Availability of data and materials
Reproducible materials described in the manuscript, including databases and all relevant raw data, are freely available to any scientist wishing to use them.

Authors' contributions
DK and HP contributed equally to this work. DK and HP carried out the study and drafted the manuscript, SW and HJL participated in its design and performed the analysis of diffusion tensor image. HP and NK collected the data and participated in the statistical analysis. NK and HJL contributed to the clinical assessment. HJL helped to draft the manuscript and revised the final draft. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Consent to publish was obtained from all patients' parents.

Ethics approval and consent to participate
The study was approved by the Hanyang University Hospital Institutional Review Board (No. 200501011003). The informed consent was obtained from the patients' parents, after full explanation of the purpose and nature of all procedures used.

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Estimation of Umbilical Cord Blood Leptin and Insulin Based on Anthropometric Data by Means of Artificial Neural Network Approach: Identifying Key Maternal and Neonatal Factors

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Abstract

Background: Leptin and insulin levels are key factors regulating fetal and neonatal energy homeostasis, development and growth. Both biomarkers are used as predictors of weight gain and obesity during infancy. There are currently no prediction algorithms for cord blood (UCB) hormone levels using Artificial Neural Networks (ANN) that have been directly trained with anthropometric maternal and neonatal data, from neonates exposed to distinct metabolic environments during pregnancy (obese with or without gestational diabetes mellitus or lean women). The aims were: 1) to develop ANN models that simulate leptin and insulin concentrations in UCB based on maternal and neonatal data (ANN perinatal model) or from only maternal data during early gestation (ANN prenatal model); 2) To evaluate the biological relevance of each parameter (maternal and neonatal anthropometric variables).

Methods: We collected maternal and neonatal anthropometric data (n = 49) in normoglycemic healthy lean, obese or obese with gestational diabetes mellitus women, as well as determined UCB leptin and insulin concentrations by ELISA. The ANN perinatal model consisted of an input layer of 12 variables (maternal and neonatal anthropometric and biochemical data from early gestation and at term) while the ANN prenatal model used only 6 variables (maternal anthropometric from early gestation) in the input layer. For both networks, the output layer contained 1 variable to UCB leptin or to UCB insulin concentration.

Results: The best architectures for the ANN perinatal models estimating leptin and insulin were 12-5-1 while for

the ANN prenatal models, 6-5-1 and 6-4-1 were found for leptin and insulin, respectively. ANN models presented an excellent agreement between experimental and simulated values. Interestingly, the use of only prenatal maternal anthropometric data was sufficient to estimate UCB leptin and insulin values. Maternal BMI, weight and age as well as neonatal birth were the most influential parameters for leptin while maternal morbidity was the most significant factor for insulin prediction.

Conclusions: Low error percentage and short computing time makes these ANN models interesting in a translational research setting, to be applied for the prediction of neonatal leptin and insulin values from maternal anthropometric data, and possibly the on-line estimation during pregnancy.

Background

The impact of maternal obesity during pregnancy (maternal overweight/obesity with or without gestational diabetes mellitus) and its association with an increased risk of obesity, as well as reprogramming cardiovascular risk, body composition and cardio-metabolic health in infancy and early adulthood, has been shown in humans and animal models [1-7]. It has been demonstrated that human obesity in children and adults is associated with elevated serum levels of an adipokine, the hormone leptin, reflecting the amount of energy stored in adipose tissue [8, 9]. Leptin was identified as the product of the obesity (ob) gene [10], which is secreted into the circulation by large adipocytes, and has been shown to cross the blood-brain barrier and bind to specific receptors in the hypothalamus to alter the expression of several neuropeptides that regulate neuroendocrine function, energy intake and expenditure leading to a decrease in appetite, reduction of body fat and body weight [11, 12]. The pancreatic hormone insulin also acts in the brain as a negative feedback signal for adipocity. It is also an essential regulator of growth, increasing fat deposition [13] resulting in a greater potential for leptin synthesis by stimulating adipocyte ob gene transcription [14]. As well, leptin also modulates (increases) insulin secretion by pancreatic β cells [15]. Therefore, leptin and insulin control glucose metabolism, acting at the peripheral and central level [16]. During pregnancy, leptin levels regulate fetal development and growth [17, 18] and positively correlate in umbilical cord blood (UCB) with neonatal body weight and fat mass [9]. It has been demonstrated that UCB leptin concentration correlates with insulin levels and anthropometric data (birth weight) only in large for gestational age neonates, but they do not correlate with maternal levels [19-21]. Both leptin and insulin biomarkers are used as predictors of weight gain and obesity during infancy. Indeed, several studies have shown that lower cord blood leptin levels predict an increased weight and length gain, "catch-up" growth, as well as a higher BMI in infancy (2-3 years) [22-24]. Yet, in the first months, decreased cord leptin levels together with gestational diabetes mellitus are

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related to a slower weight gain [25]. For insulin, an inversely relationship was found for weight gain during infancy [26]. Therefore, the prediction of cord blood hormone levels based on anthropometric maternal and neonatal data using mathematical models that take into account the high complexity of this system may be of considerable usefulness. Therefore, Artificial Neural Networks (ANNs) will be used as a system biology approach to simulate cord blood hormone levels.

ANNs [27] have been extensively used for the optimization and modeling of processes, as they are able to represent the non-linear dynamic interaction of complex relationships without any assumptions of the underlying mechanisms [28]. ANNs learn and test the solution of the problem from a data set [29] and provide an interpolation for new data. For the science of medicine, the application of neural networks keeps on expanding [30-32], and now represents a set of methods that have been useful for solving pediatric problems [33, 34], identifying key factors such as in fetal growth [35, 36] and diagnosing neonatal diseases [37].

ANN has the ability to predict data such as measuring biochemical parameters in UCB samples which may be difficult to obtain otherwise. The objectives of the study were therefore: 1) to obtain ANN models (feed-forward) for the prediction of leptin and insulin values in UCB from neonates exposed to distinct metabolic environments during pregnancy (defined as obesity with or without gestational diabetes mellitus or lean women), based on anthropometric maternal and neonatal characteristics (ANN perinatal model) or from only maternal data during early gestation (ANN prenatal model) 2), to examine which parameters, among those analyzed from the mother and neonate, have the most influence on neonatal leptin and insulin values by applying a sensitivity analysis. Essentially, ANN will learn from a database (maternal and neonatal clinical data as well as biochemical experimental data) from a specified problem (maternal metabolic environment) with a known solution (UCB leptin and insulin experimental values for training the model) and then the network, will recreate the system of an inherent complex set of data (testing the model).

Table 1 Maternal and neonatal clinical data

		Mother	
Parameters	Healthy	Obese	Diabetic
N = 49	11	23	15
Maternal age (years)	25.1 (±3.3)	30.3 (±1.1)	35 (±1.2)
Maternal initial weight (kg)	58.3 (±2.1)	74.2 (±2.5)	77.3 (±2.7)
Maternal final weight (kg)	67.9 (±2.6)	85.6 (±3.2)	89.4 (±3.9)
Maternal height (cm)	156.4 (±2.2)	157.1 (±1.3)	157.3 (±1)
Gestational age at delivery, (weeks)	38.8 (±0.2)	38 (±0.4)	39 (±0.3)
Initial Maternal BMI (kg/m^2)	24.3 (±0.4)	30.7 (±0.8)	31.3 (±0.8)
Final Maternal BMI (kg/m^2)	27.7 (±0.5)	34.7 (±1.2)	36 (±1.4)
Parity	1.7 (±0.3)	2.7 (±0.2)	2.6 (±0.3)
Males/Females	5M/6F	7M/8F	11M/11F
Neonatal birth weight (kg)	2.87 (±0.14)	2.88 (±0.09)	3.22 (±0.09)
Neonatal birth body length (cm)	47.9 (±0.6)	47.9 (±0.4)	48.3 (±0.7)
Neonatal head circumference (cm)	34.4 (±0.3)	33.8 (±0.2)	34.7 (±0.3)
Neonatal BMI	12.45 (±0.4)	12.52 (±0.3)	13.88 (±0.4)
5-min APGAR score	9	8.9 (±0.07)	9 (±0.06)

All values are depicted as Mean +/- SEM

Methods

Study subjects

This study was approved by both the Ethics and Research Committees of the Instituto Nacional de Perinatologia "Isidro Espinosa de los Reyes". Venous umbilical cord blood samples were collected from 49 cesarean deliveries. Samples were centrifuged (for 15 min, at 3500 rpm, room temperature), serum was aliquoted and stored at −70 °C until assayed. Hemolyzed or lipemic samples were discarded. Mothers (N = 49) were: lean normoglycemic (initial Body Mass Index, BMI, of 24.3 ± 0.4 kg/m^2, n = 11), obese (initial BMI of 30.9 ± 0.9 kg/m^2, n = 23) and obese with gestational diabetes mellitus (initial BMI of 31.3 ± 0.7 kg/m^2, n = 15). We collected the following information: maternal morbidity (MM), gestational age at delivery (GE), initial and final maternal weight (MWi and MWf), initial and final BMI (MBMi and MBMf), maternal height (MH), maternal age (MA), parity (P), neonatal gender (NG), neonatal birth weight (NW), neonatal body length (NH), neonatal head circumference (NHC), neonatal BMI (NBMI) and 5-min APGAR score. The age range of the participants was 16-43 years. Exclusion criteria were genetic syndromes, chromosomal abnormalities, gross placental abnormalities, infections and substance abuse. The main clinical data are reported in Table 1.

Leptin and Insulin determination by ELISA

Leptin and insulin from umbilical cord blood samples were assayed using commercially available ELISA kits (GenWay, San Diego, CA). The sensitivity of the leptin assay was 0.1 ng/ml; intra-assay and inter-assay coefficients of variations were 4.2 and 6.7 %, respectively. The sensitivity of the insulin assay was 0.3 µU/ml; intra-assay and inter-assay coefficients of variations were 6.3 and 8.5 %, respectively.

Database

We compared neonates and their mothers with distinct metabolic environments during pregnancy (defined as obese, obese with gestational diabetes mellitus or lean women). Fourteen variables were selected from the entire database for 49 subjects. For the ANN models, anthropometric, maternal morbidity (obese, obese with gestational diabetes mellitus or lean women) and biochemical data (umbilical cord blood leptin or insulin) were administered.

ANN learning and testing

Back-propagation (BP) algorithm multiple-layer perceptron (MLP) architecture was trained and tested by the input layer, the hidden layer and the output layer (see Fig. 1). We applied the Log-sigmoid (LOGSIG) and hyperbolic tangential (TANSIG) transfer functions in the hidden layer. Both transfer functions were acceptable however; the hyperbolic tangential performance was slightly superior. According to [38], TANSIG transfer function has a better performance which is in agreement with our result. In the output layer, only the linear transfer function (PURELIN) was employed because the output layer is not normalized. In order to obtain the optimum model, we began in the hidden layer with one neuron until the Root Mean Square Error (RMSE) did not change and the statistical test (slope and intercept [39]) was approved, as well as we avoided over-fitting (for a detailed explanation see Additional file 1) and [40-43].

All calculations were carried out with Matlab mathematical software (Natick, MS, USA) with the Neural Network Toolbox for Matlab [40]. The input layer for the ANN perinatal models consisted of 12 maternal and neonatal variables and the output layer contained one variable for umbilical cord blood leptin or umbilical cord blood insulin concentrations. The variables were: maternal morbidity (MM), gestational age at delivery (GE), initial and final maternal weight (MWi and MWf), initial and final maternal BMI (MBMi and MBMf), maternal height (MH), neonatal gender (NG), neonatal birth weight (NW), neonatal body length (NH), neonatal head circumference (NHC) and neonatal BMI (NBMI) (Table 2). The input layer for the ANN prenatal models (early gestation) contained 6 maternal variables (maternal morbidity (MM), initial maternal weight (MWi), initial maternal BMI (MBMi), maternal height (MH), maternal age (MA) and parity, P) and the output layer had one variable for umbilical cord blood leptin or umbilical cord blood insulin concentrations (Table 2).

In the learning, to change the weights and biases, we applied the Levenberg-Marquardt (LM) algorithm as the learning (training) algorithm allowing to obtain a smaller RMSE [40, 44, 45] (for a detailed explanation see Additional file 1). The RMSE was calculated from the experimental values and network predictions (see Fig. 1a and b).

The experimental database (n = 49) was used to feed the ANN structure. This database (x_i) was randomly divided into: learning (79 %) and validation (21 %). The database was then normalized in the range of 0.1 to 0.9 [46] for the input variables and the output variable was not normalized.

So, the entire input database was scaled to a new value x_i as follows:

$$x_i = 0.8\left(\frac{X_i - X_{\min}}{X_{\max} - X_{\min}}\right) + 0.1 \qquad (1)$$

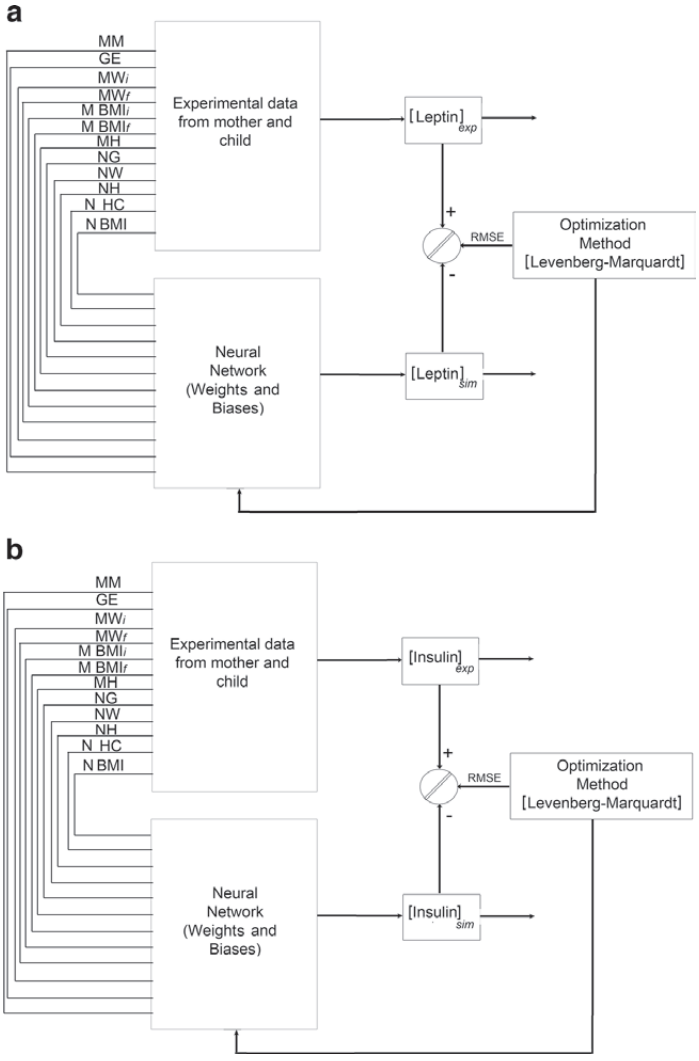

Figure 1. Recurrent network architecture of the ANN perinatal model and the procedure used for learning neural network for the simulation of leptin (a) and insulin (b) concentration in umbilical cord blood (UCB) samples

Statistical test

In order to confirm the best performance of the ANN predictions, a linear regression was carried out to obtain the slope and intercept from the ANN simulations versus the experimental database (learning and validation database), after which we applied a statistical test (slope and intercept, [39, 47]). This last consists in demonstrating that the obtained upper and lower intervals of the slope must be one and the upper and lower intervals of the intercept must be zero, with a 99.8 % confidence level according to the Student t-test.

Results

The main umbilical cord blood leptin and insulin experimental values are reported in Table 3 and are in agreement with the study by [48] (as well as [49-51]). Briefly, obesity exposed neonates had higher UCB leptin levels compared to not exposed neonates and a trend for increased levels in gestational diabetes exposed neonates. Gestational diabetes exposed neonates had the highest values for umbilical cord blood insulin levels than not exposed or obesity exposed neonates.

Proposed ANN perinatal model

The input variables for the ANN perinatal models were 12 (maternal and neonatal) and were presented to the general network, in which the final UCB hormone level prediction corresponded to the output unit: 1 output variable for UCB leptin or insulin concentration. Figure 2 shows the general scheme of such neural network architecture for the prediction of UCB leptin (Fig. 2a) and insulin (Fig. 2b) values from perinatal parameters (as depicted in Fig. 1a and b). 20,000 runs with 100 iterations were applied in each neuron from 1 to 5 neurons in the hidden layer and the final topology was obtained for leptin and insulin predictions. As a result, the best network architecture performance was 12-5-1 for both models: leptin and insulin (Equations [6-11] and the weights and biases are reported in Additional file 1: Tables S1 and S2).

Validation of the ANN perinatal model

Figure 3 depicts the comparison of the experimentally measured ($_{EXP}$) and the predicted ($_{ANN}$) UCB leptin (Fig. 3a) and insulin (Fig. 3b) values for the testing database describing the behavior of the ANN perinatal model using all data available (inputs).

The comparison of ($_{EXP}$) and ($_{ANN}$) data through a linear regression model, ($Leptin_{ANN} = a + b\ Leptin_{EXP}$) and ($Insulin_{ANN} = a + b\ Insulin_{EXP}$), showed regression coefficients of $R^2 > 0.973$ and $R^2 > 0.9873$ for leptin and insulin, respectively.

Upper and lower values of the statistical test (Table 4) indicate

Table 2 List of experimental variables (clinical and biochemical data) analyzed using ANN to obtain umbilical cord blood leptin and insulin values: input and output range conditions studied

Input Variables ($n = 49$)	Range	Output variables	Range
Maternal Morbidity, MM	Healthy, Obese or diabetic	Umbilical cord blood leptin, (ng/ml)	0.17–27 (mean 5.1)
Maternal initial weight, MWi (kg)	49–96 (mean 72)		
Maternal final weight, MWf (kg)	55–117 (mean 83)	Umbilical cord blood insulin, (μU/ml)	0.7–12 (mean 1.9)
Maternal height, MH (cm)	149–173 (mean 157)		
Maternal initial BMI, MBMi (kg/m^2)	22–40 (mean 29.5)		
Maternal final BMI, MBMf (kg/m^2)	24–42 (mean 33.5)		
Gestational age at delivery, GE (weeks) Neonatal gender, NG	37–41 (mean 39)		
Neonatal birth weight, NW (kg)	2.01–4.19 (mean 2.98)		
Neonatal birth body length, NH (cm)	45–54 (mean 48)		
Neonatal head circumference, NHC (cm)	32–37 (mean 34)		
Neonatal BMI, NBMI	10–15 (mean 13)		
Parity, P	1–5 (mean 2.3)		
Maternal age, MA (years)	16–43 (mean 30)		

that the slope included one and the intercept contained zero, with a 99.8 % confidence level for both UCB determinations [39, 47]. These results demonstrated a good correlation between ANN predictions and experimental values.

Sensitivity analysis of the ANN perinatal model

We used an evaluation process based on the neural network weight matrix and the Garson equation [52, 53] to obtain the qualitative significance of the input variables on the predicted UCB leptin and insulin values (for a detailed explanation of Equation [19], see Additional file 1). Figure 4 depicts the relative importance of the calculated input variables showing that all variables had a strong effect on leptin (Fig. 4a) and insulin (Fig. 4b) neonatal values. In addition, the sensitivity analysis showed that maternal BMI (28 %, initial and final BMI), neonatal birth weight (12 %) and maternal weight (11 %) were the most influential factors controlling umbilical cord blood leptin concentration, in contrast with maternal morbidity (healthy, obese or controlled gestational diabetes, 5 %) and neonatal BMI (2 %) that were the less important factors for estimating UCB leptin levels (Fig. 4a).

For UCB insulin concentration, maternal morbidity (healthy, obese or controlled gestational diabetes) appears to be the critical parameter with a relative importance of 18 %, followed by neonatal body length at delivery (12 %), maternal BMI (6-9 %) and less importantly neonatal BMI (5 %) and birth weight (5 %) (Fig. 4b).

Altogether, these results showed that the ANN perinatal models succeeded in predicting the experimental results of UCB leptin and insulin concentration from anthropometric maternal and neonatal values, as well as revealed a good agreement between the experimental data and the predicted values. However, this ANN perinatal models required gestation and at term information in order to predict UCB leptin and insulin concentrations. Therefore, a second ANN model was applied to predict UCB levels using only inputs from early gestation of the same database.

Table 3 Umbilical cord blood hormone concentrations

		Mother	
Parameters	Healthy	Obese	Diabetic
N = 49	11	23	15
Leptin (ng/ml)	3.5 (±1)	6.7 (±1.5)	4.9 (±0.4)
Insulin (μU/ml)	1.3 (±0.4)	1.06 (±0.08)	3.6 (±1)

Proposed ANN prenatal model

The input variables for the ANN prenatal models (early gestation) were 6 maternal and 1 output variable for UCB leptin or insulin concentration. The best neural network architecture obtained for the prediction of UCB leptin was 6-5-1 (Fig. 5a) and for UCB insulin, 6-4-1 (Fig. 5b) (The same Equations [6-11 for leptin and 6-10 for insulin] were utilized in the model but the weights and biases for leptin and insulin simulations are reported in Additional file 1: Tables S3 and S4). The ANN models were able to predict UCB leptin and insulin levels from only anthropometric maternal parameters.

Validation of the ANN prenatal model

Figure 6 depicts the predicted values compared to the experimental values for leptin (Fig. 6a) and insulin (Fig. 6b), showing a good capability of the model to simulate both outputs by describing the behavior of the UCB levels using only maternal anthropometric information from early gestation.

The regression coefficients were $R^2 > 0.963$ and $R^2 > 0.9824$ for leptin and insulin, respectively (Fig. 6). Table 5 depicts intercepts and slopes for the linear regression model of the ANN prenatal models. Therefore, these statistical results guarantee the validity of the ANN prenatal models with a confidence level of 99.8 % for both UCB leptin and insulin [39, 47].

Sensitivity analysis of the ANN prenatal model

The same process used for the ANN perinatal models allowed obtaining the relative importance of the input variables on the simulated UCB leptin (Fig. 7a) and insulin (Fig. 7b) values in the ANN prenatal models. Figure 7a shows that maternal age (27 %) and initial maternal weight (24 %) were the dominant factors for the prediction of UCB leptin in comparison with

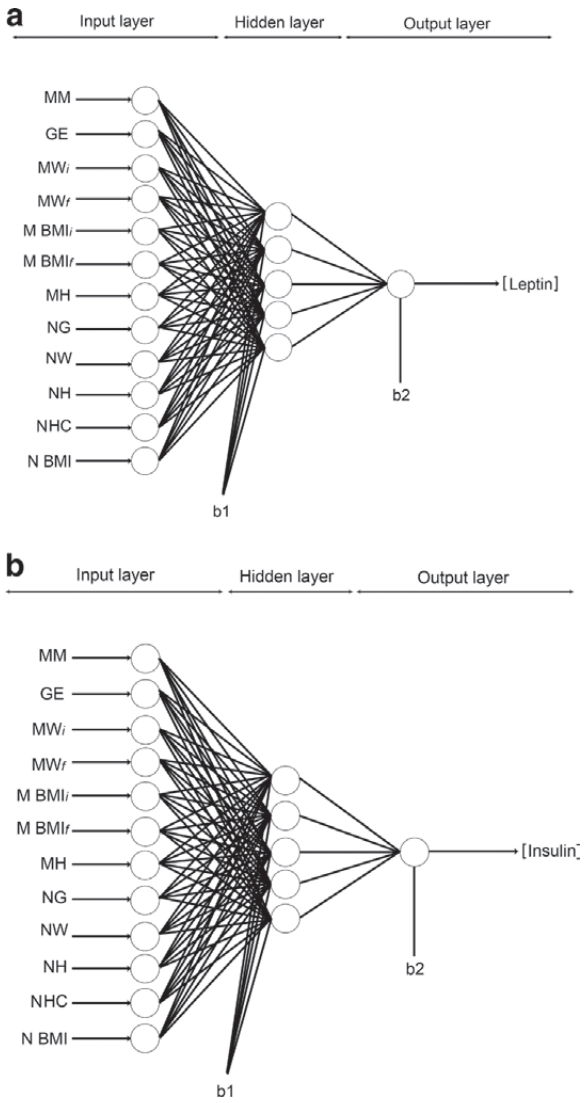

Figure 2. The neural network computational ANN perinatal model for UCB leptin (a) and insulin (b) concentration estimation. The proposed model involved 12 input variables, 5 neurons on hidden layer and 1 output variable.

maternal morbidity (11 %) and parity (8 %), which were the less important parameters. For UCB insulin simulation (Fig. 7b), all maternal characteristics had a strong effect on insulin values but maternal morbidity (31 %) and maternal height (25 %) were the predominant parameters followed by maternal age (11 %) and parity (10 %).

Discussion

Four ANNs models were developed to predict neonatal leptin and insulin concentrations in umbilical cord blood, based on selected experimental conditions (anthropometric and biochemical variables), from gestation and at term data (ANN perinatal models) or only from early gestation data (ANN prenatal models). The neonatal leptin and insulin parameters were successfully simulated by applying in all models, a three layered neural network with 4-5 neurons in the hidden layer, using a back-propagation algorithm that achieved a low average error rate (<3 and <4 %, for the ANN perinatal models and ANN prenatal models, respectively). The results obtained by the ANN perinatal models show a high agreement with experimental results: a good correlation ($R^2 > 0.97$) and small error (RMSE > 0.0012). High level of confidence for the ANN perinatal models was confirmed with the intercept and slope statistical test (99 %).

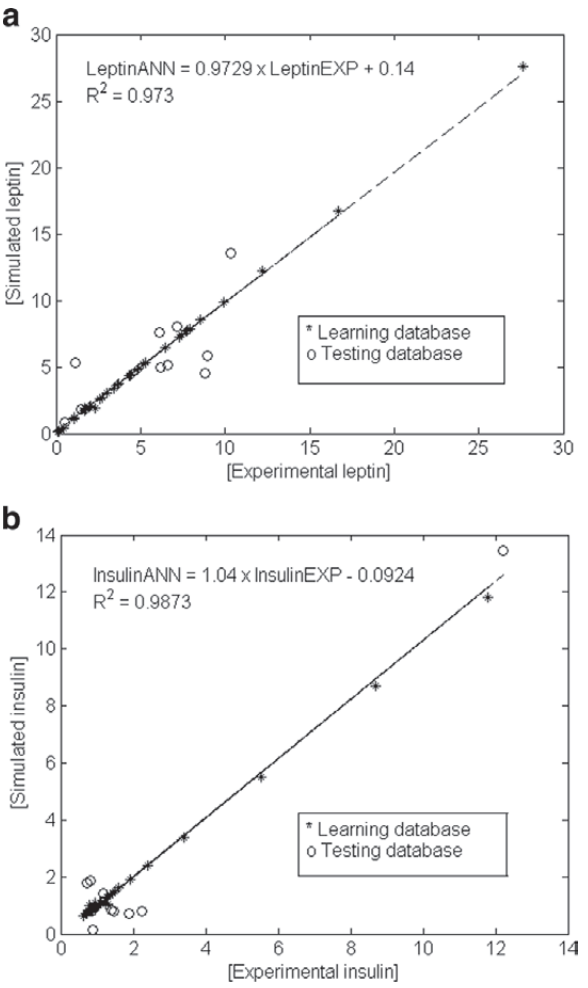

Figure 3. The scatter plot of perinatal experimental (open circles) vs. ANN-predicted values (dark cross) for average UCB leptin (a) and insulin (b). Experimental ($leptin_{EXP}$ and $insulin_{EXP}$) and simulated ($leptin_{ANN}$ and $insulin_{ANN}$) data. Dashed line indicates the fitted simple regression line on scattered points.

Interestingly, the ANN prenatal models, that takes into account only the early gestation information (maternal anthropometric parameters), were also able to estimate leptin and insulin values with a good correlation coefficient ($R^2 > 0.96$ for leptin and $R^2 > 0.98$ for insulin), a small error (RMSE > 0.2) and a confidence level of 99.8 %. These models consider well-known and simple to measure input parameters such as: corporal weight, length and body mass index of the mother at the beginning and/or end of pregnancy, gestational age at delivery, gender, weight, body length and head circumference of the neonate at delivery. Therefore, by means of these ANN models we could be able to obtain any unknown leptin and insulin variables based exclusively in anthropometric data.

ANN was, not only capable of establishing mathematical models estimating neonatal leptin and insulin values in umbilical cord

Table 4 Intercept (a) and slope (b) statistical test to leptin and insulin in the ANN perinatal model

Leptin		Insulin	
a_{lower}	a_{upper}	a_{lower}	a_{upper}
−0.6321	0.9118	−0.3411	0.1564
b_{lower}	b_{upper}	b_{lower}	b_{upper}
0.8624	1.0833	0.9564	1.1156

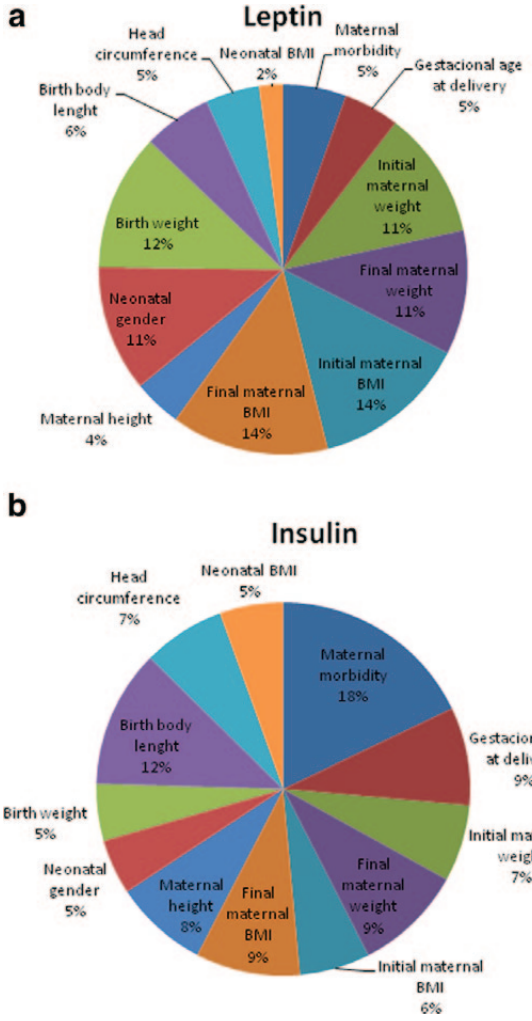

Figure 4. Percentage for the global sensitivity analysis of the 12 input variables in the ANN perinatal model for UCB leptin (a) and Insulin (b) values.

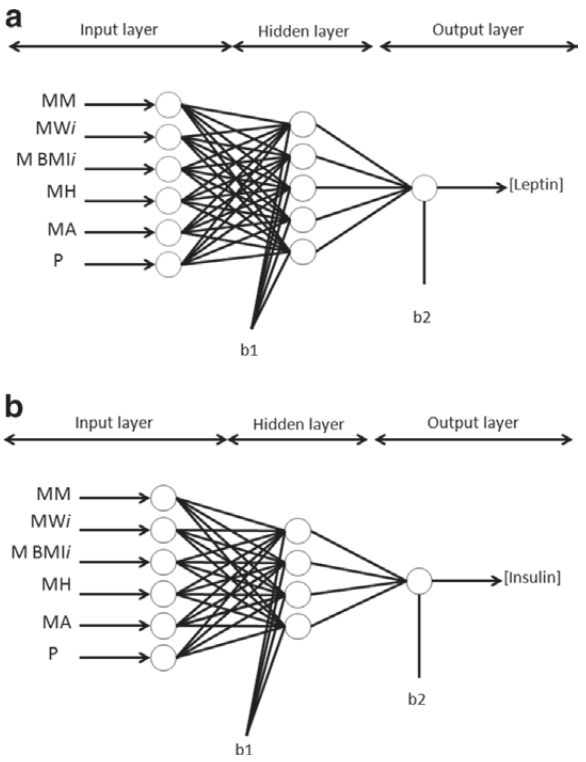

Figure 5. The neural network computational ANN prenatal model for UCB leptin (a) and insulin (b) concentration estimation. The proposed model involved 6 input variables, 5 neurons on hidden layer for leptin or 4 neurons on hidden layer for insulin and 1 output variable.

blood from anthropometric values, but was also able to identify key maternal and neonatal variables, which had mathematically consistent biological relevance for the predicted values. According to the sensitivity analysis of the ANN perinatal models, we found that maternal BMI and neonatal birth weight were the most influential parameters for the prediction of neonatal leptin values, while maternal metabolic health was the principal factor for the simulation of neonatal insulin levels. Interestingly, the sensibility analysis of the ANN prenatal models (taking into account only early gestation maternal anthropometric values) showed maternal age and initial maternal weight had a strong impact on UCB leptin levels, whereas maternal metabolic health was the most important parameter for fetal insulin secretion.

These analyses were capable of confirming a major role of maternal BMI and birth weight for UCB leptin prediction and maternal metabolic health for insulin values. Indeed, it has been shown that UCB leptin concentration correlates with maternal BMI and neonatal birth weight by conventional observational and statistical methods [18-20, 54, 55]. In particular, maternal BMI as a key factor for UCB leptin levels is in agreement with the proposed mechanism for leptin during pregnancy. In fact, the adipose tissue, the placenta and the vascular endothelium of the mother have been demonstrated as sites for regulated leptin production in utero [56, 57] and during pregnancy, leptin has been shown to regulate protein synthesis, growth and immunity [58].

For UCB insulin values, maternal metabolic health (healthy, obese or obese with gestational diabetes mellitus) appears to be the critical parameter, followed by neonatal body length. Indeed, gestational diabetes mellitus exposed neonates had higher umbilical cord blood insulin levels than not exposed neonates [48, 59], which was confirmed by the ANN analysis. The fetal pancreas is the principal source of fetal insulin since maternal insulin does not cross the blood/placental barrier [60]. The fact that insulin is higher in gestational diabetes mellitus offspring may suggest dysregulation of insulin signaling at birth which is compatible with an adaptation for elevated maternal glucose levels [61]. Prediction of UCB insulin levels by neonatal body length is in agreement to insulin's direct anabolic action. This has been proposed to be indirectly mediated via leptin, since UCB leptin levels strongly correlate with UCB insulin values [21]. Also, it has been hypothesized that fetal insulin stimulates fetal adipocyte leptin production [21]. However, UCB leptin levels did not correlate with UCB insulin levels in the offspring of obese women with gestational diabetes mellitus.

Limitations and strengths of the ANN models

It is important to acknowledge the limitations of this study such as the particularly low sample size. However, adaptive learning algorithms like ANN were able to overcome this problem of low sample size due to the training procedure that uses only a part of the database. It is noteworthy to mention that a study from Street and cols used a similar size database for their ANN model in order to identify placental factors for fetal growth [36]. Another limitation of this work is the low test data size. Further simulations with an increased sample size should allow improving the ANN models.

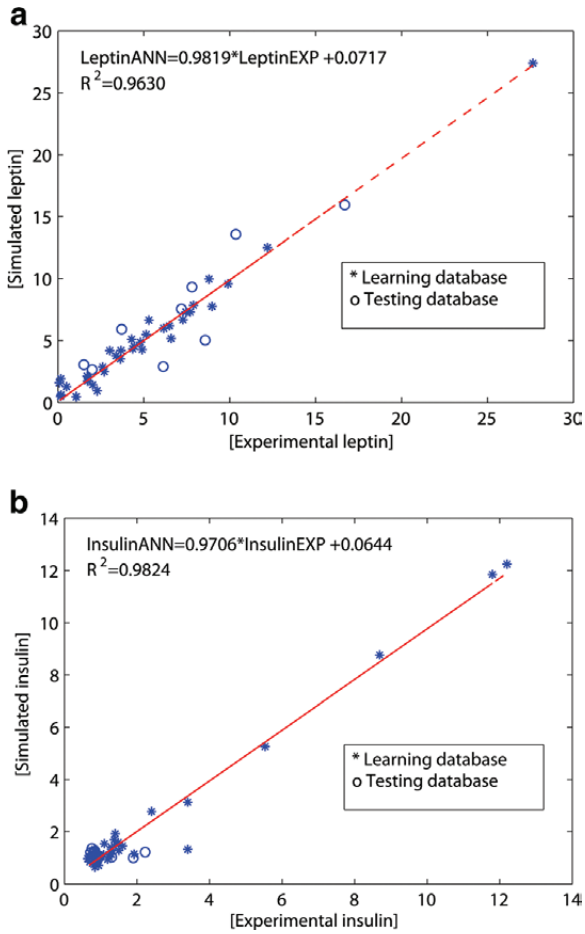

Figure 6. The scatter plot of prenatal experimental (open circles) vs. ANN-predicted values (dark cross) for average UCB leptin (a) and insulin (b). Experimental (leptin $_{EXP}$ and insulin $_{EXP}$) and simulated (leptin $_{ANN}$ and insulin $_{ANN}$) data. Dashed line indicates the fitted simple regression line on scattered points.

In addition, the limits of the modeling are that in order to predict UCB leptin and insulin concentrations, morbidity, anthropometric and biochemical parameters must be placed between the ranges of the input variables (see Table 2). For example, the ANN perinatal model will accurately simulate UCB leptin when applied to mothers with an initial weight (MW_i) comprised between 49-96 kg and an initial BMI ($MBMI_i$) of 22-40 kg/m^2.

One of the strengths of this ANN approach is that the elapsed time to calculate both neonatal parameters is short which can be applied online and that it represents the dynamic interactions of complex relationships. These characteristics suggest a possible translational utility of these ANN models.

Insulin and leptin cord blood levels have been used as predictor of postnatal growth and weight gain in infancy. So, the establishment of ANN prenatal models that predicts these values from maternal anthropometric variables during gestation, without the need for cord blood samples, could be helpful to prognosticate infant growth and permit the possibility of conducting interventions.

For example, it is tempting to speculate that infants from obese mothers that had the highest cord leptin values will probably have the worst of all weight gain but the highest BMI in infancy, since higher cord blood leptin and gestational diabetes are

Table 5 Intercept (a) and slope (b) statistical test to leptin and insulin in the ANN prenatal model

Leptin		Insulin	
a_{lower}	a_{upper}	a_{lower}	a_{upper}
0.8508	1.1131	0.8838	1.0574
b_{lower}	b_{upper}	b_{lower}	b_{upper}
−0.8453	0.9886	−0.2069	0.3357

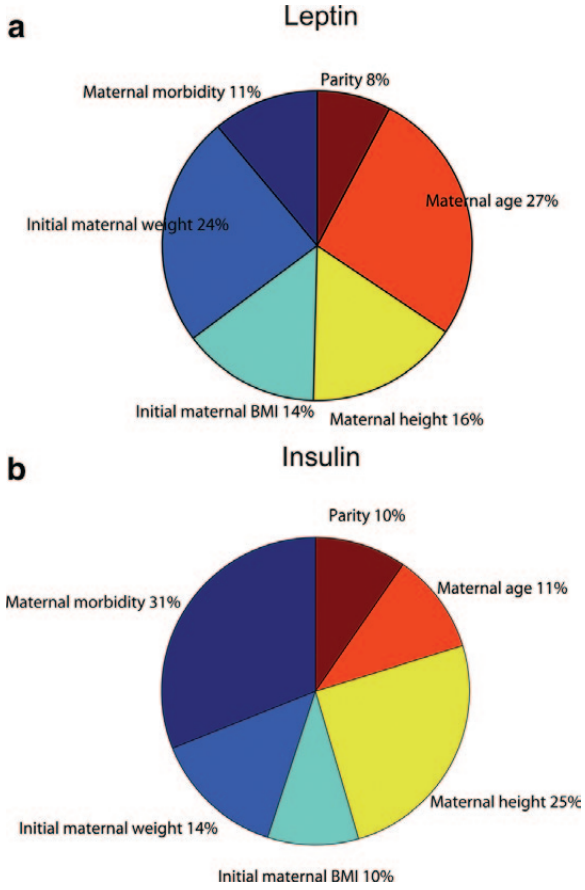

Figure 7. Percentage for the global sensitivity analysis of the 6 input variables in the ANN prenatal model for UCB leptin (a) and Insulin (b) values.

related to a slower weight gain and an increased BMI at 2-3 years [23, 24]. The use of these ANN models could make easy to follow growth and perhaps estimate the risk of obesity and diabetes in these children.

Conclusions

Low error percentage and short computing time makes this ANN models attractive to be applied for the prediction of UCB leptin and insulin values from maternal and neonatal anthropometric data, and possibly the on-line estimation during pregnancy, birth and infancy. In particular, the prediction of these hormone values in UCB may be of great interest to prognosticate infant growth and permit the possibility of conducting interventions before incurring costly and time-consuming events, such as neonatal morbidity. Moreover, the fact that the ANN prenatal model, based merely on early gestation anthropometric maternal information, was able to confidently simulate UCB leptin and insulin levels, make these particular models an interesting application for following the impact of maternal anthropometrics and metabolic health on these hormone UCB values and to predict leptin and insulin values at birth from early gestation.

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Improving Vascular Access Outcomes for Hospitalized Pediatric Patients: A Comparison of Catheters

Chris Campbell

When it comes to pediatric patients, using the least-invasive treatment possible is paramount for medical professionals. However, sometimes not enough information exists about the benefits of a certain type of device for some hospitals to switch from the procedures they currently have in place.

Case in point: Extended dwell/midline peripheral intravenous catheters, known as EPIVs. The Kosair Children's Hospital in Louisville, KY has achieved "positive results" from its use of EPIVs with pediatric patients, according to a retrospective review by the University of Lousiville.

A team of UL researchers conducted the review to document those positive results because EPIVs are not widely used in pediatric hospitals. What are widely used, according to the review, are peripherally inserted central catheters, known as PICCs.

The overall goal was to find more stable peripheral access for pediatric patients. According to the published review, "Despite the potential benefits and low risks, EPIVs to date have not been widely used in pediatric populations…Although vascular access team members reported observing positive outcomes with EPIVs, the team determined there was a need for a more systematic evaluation. The overall goal of this evaluation was to determine whether the vascular access decision tree had been successfully implemented with regard to EPIVs and PICC lines."

The research team reported that it was important to provide a more detailed evaluation because vascular access is often required for pediatric patients.

"Maintenance and preservation of vascular access is an important patient safety and quality concern. In our 263-bed full-service free-standing children's hospital, and in most other hospitals,[1] more than 90% of pediatric patients have some type of vascular access device placed while in the hospital."

"This evaluation is the first to compare the use and outcomes of EPIVs compared with PICC lines in a pediatric inpatient population."

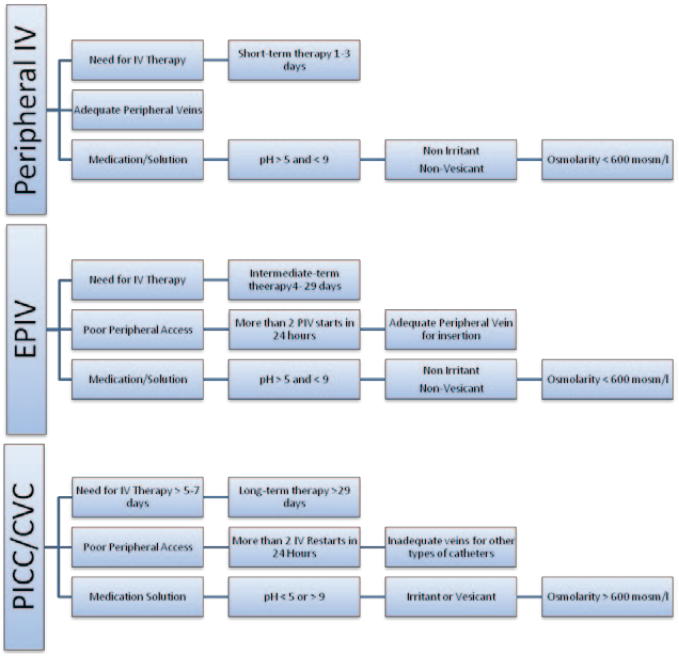

Figure 1. Catheter Selection Criteria

Background

Short peripheral intravenous (PIV) catheters are described by the UL researchers as usually the first choice for obtaining vascular access, and appropriate for short-term, nonvesicant therapies.

"Although PIVs are relatively easy to place, they typically have short dwell times, particularly in neonates,[2] and require frequent replacement as a result of infiltration, leakage, occlusion, or dislodgement.[3] These limitations can lead to multiple attempts at reinsertion, causing patient pain and anxiety."

PICCs are a less invasive means of gaining access to central vessels for long-term venous access or infusion of caustic agents, according to the authors, but "there is greater risk of bloodstream infection with central venous catheters, including PICC lines, compared with peripheral lines.[4,5] Therefore, reduction of the use of PICC lines is a goal."

The EPIVs alternative is more commonly used with adults, and considered "effective in delivering fluids and medications, and in allowing daily blood draws with a very low rate of infection or

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phlebitis.[5-7] Appropriate use of these catheters in place of PICC lines has also resulted in a decrease in central

line-associated bloodstream infection.[5] EPIV catheters are shorter than PICC lines or central catheters, and may dwell in a peripheral vein for up to 29 days,[8-10] although in 1 study of 140 midline catheters, some were in place as long as 49 days without incident, prompting O'Grady et al[7] to recommend that extended dwell/midline catheters be replaced only when there is a specific indication. In children, EPIVs may be inserted in the upper or lower extremities or scalp.[7,11] EPIVs can often be inserted without sedation and do not require fluoroscopy for placement, thus avoiding exposure to radiation. Despite the potential benefits and low risks, EPIVs to date have not been widely used in pediatric populations. Similar to other institutions,[12] the use of EPIVs in our pediatric hospital began in the neonatal intensive care unit with positive results."

The staff developed a "venuous access decision tree" in order to guide clinicians in determining the safest and most appropriate venous access device for patients. In 2013, vascular access nurses initiated placing EPIVs in other pediatric patient populations, according to the authors.

The EPIVs were originally considered a bridge between PIVs and PICCs for patients requiring reliable, noncentral access, however their was successfully expanded to include placement when venous access for longer periods of time was required, for infusing noncaustic agents such as pain medication or sedation, and in ventilated patients with respiratory syncytial virus or bronchiolitis who needed venous access for sedation drips.

"Because EPIV lines can be used in children of all ages and in any area of the hospital they have provided a dependable venous access and a safe alternative to PICC line placement," the authors wrote.

Results

The UL evaluation looked at patient data from 2013-2015 at Kosair. Findings indicated that the venous access decision tree was adhered to with regard to EPIVs and PICC lines. EPIV insertion only employed 1.9F and 3F catheters, only nonvesicant fluids were administered via EPIVs, and the course of treatment with EPIVs was limited to 30 days or fewer with the average dwell time of 9 days.

"About half of those patients with an EPIV during the evaluation period completed their course of treatment without complications," the authors wrote.

Conclusions

"EPIVs were most beneficial in younger patients admitted to the children's hospital with a medical diagnosis, because 79% of patients who had an EPIV placed were aged 5 years or younger and the EPIV was used for infusion of antibiotics and other medications," the authors wrote. "The EPIV added an alternative device to a PICC line that does not require radiography for placement in younger patients. However, maintenance of EPIVs in the younger population was noted to be more difficult than with older patients due to movement of extremities. Therefore, strategic placement and securement of the line are key factors in the maintenance of EPIVs in younger patients. The optimum placement is the antecubital area for older children and the scalp for infants. EPIVs are a successful alternative to PICCs or PIVs for children in an inpatient acute-care facility who have good or limited venous access and who need 30 days or fewer of nonvesicant intravenous therapy. The venous access decision tree provided useful guidance in determining the appropriate venous access device for pediatric patients and the decision tree has been adhered to by the vascular access team."

The authors recommend more research to test the application of the venous access decision tree in a randomized clinical trial.

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