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Fat Shaming Tied to Increased Risk of Metabolic Problems

The proportion of US women taking maternity leave has remained about the same for the past two decades, according to a new study. Laws mandating paid leave in four states and an expanding national economy have had no impact on the proportion of working women who take maternity leave, which remains at about 678 per 10,000 births, an economist reports in the American Journal of Public Health. “The US economy has expanded dramatically since the middle of the 1990s,” Jay Zagorsky, from the Ohio State University Center for Human Resource Research in Columbus said. “Since 1994, it’s gone up about 66 percent after adjusting for inflation, and none of those benefits have flowed to women on maternity leave.” The Family and Medical Leave Act entitles employees of companies covered by the law to 12 weeks of unpaid time off during the first 12 months after the birth of a baby or the adoption of a child. But the US Department of Labor estimated in 2015 that only 12 percent of private sector workers have access to paid family leave, Zagorsky writes. He found that men are increasingly taking opportunities for paternity leave, whether paid or unpaid, but the total numbers are still tiny. “There’s a tremendous growth in paternity leave, but we started at such a really low base, like 6,000 men per month, and now we’re up to 22,000,” Zagorsky said. But there are over 300,000 babies born in the US each month, he said, “so we’re up to 22,000 men taking care of newborn children, out of a third of a million each month.” For the study, he analyzed data from a monthly national survey that includes about 60,000 randomly selected households. Based on data for the years 1994 through 2015, he found that about 273,000 new mothers took time off during a typical month, and the rate remained fairly steady over time. Women on maternity leave tended to be older than the average woman who gave birth, as well as more educated, more likely to be married and more likely to be white.

Immigration Raids Putting Babies At Risk?

In the aftermath of an immigration raid, Latina women in the US may be more likely to have low birthweight or premature babies even when they are citizens, a new study suggests. To explore the link between immigration policy and pregnancy outcomes, researchers examined data on babies born before and after U.S. authorities arrested 400 undocumented workers at a kosher slaughterhouse and meatpacking plant in Postville, Iowa, in 2008. At the time, it was the largest single site raid in U.S. history. “The Postville raid caused a great deal of fear and distress for immigrant and U.S.-born Latinos throughout the state of Iowa, including pregnant mothers,” said lead study author Nicole Novak, a researcher at the University of Michigan Population Studies Center in Ann Arbor. “We know that emotional stress can affect pregnant mothers and their infants’ gestation in many ways, including shifting stress hormone balances in ways that affect a developing fetus,” Novak added by email. “Social support networks can help protect against these effects, but after the Postville raid fear isolated people from one another, reducing emotional support and leaving them doubly vulnerable.” For the study, researchers analyzed birth records for 52,344 infants born in Iowa either during the 37 weeks after the raid or in the same 37-week period the previous year. Babies born to Latina mothers after the raid were 24 percent more likely to be underweight than infants born the year before, researchers report online January 23 in the International Journal of Epidemiology. Among foreign-born Latina mothers, 4.5 percent of newborns were underweight before the raid, compared with 5.6 percent afterwards. Among Latina mothers born in the US 5.3 percent of infants were underweight before the raid, compared with 6.4 percent afterwards. Premature births were also more common for Latina
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High-Flow Oxygen May Help Infants With Bronchiolitis

High-flow warm humidified oxygen (HFWHO) does not reduce the amount of time infants with bronchiolitis require oxygen support compared to standard therapy, according to an open-label trial. However, children on HFWHO were less likely to have treatment failure, and most patients who failed standard treatment could be rescued with HFWHO, Dr. Elizabeth Kepreotes of John Hunter Children's Hospital in Newcastle, Australia, and colleagues found. “Standard therapy in most general children’s wards around the world is relatively cold, dry oxygen that is poorly tolerated at flows higher than 2 litres per minute (L/min) via the nose,” Dr. Kepreotes explained in an email to Reuters Health. “High-flow oxygen is warmed and humidified, making it more comfortable and therefore capable of being delivered at higher flows.” While HFWHO has been studied in neonatal and pediatric intensive care units (ICUs), Dr. Kepreotes and her colleagues write, its efficacy and safety have not been studied in randomized controlled trials. In the new study, the researchers randomly assigned 202 children less than 2 years old attending their emergency department for moderate bronchiolitis to receive HFWHO or standard therapy. Time to weaning was 24 hours with standard therapy and 20 hours with HFWHO, which was not a statistically significant difference. Fourteen percent of children on HFWHO had treatment failure, compared to 33% of those on standard therapy (p=0.0016). Children on HFWHO also had a significantly longer time to treatment failure than patients on standard therapy (hazard ratio, 0.3). A similar percentage of children from each group required transfer to the ICU. Four adverse events, including oxygen desaturation and condensation inhalation, occurred in the HFWHO group while there were two cases of oxygen tubing disconnection in the standard therapy group.

Zika Doc Issues Warning

The doctor who first linked the Zika virus to birth defects says Brazil has too quickly forgotten the tragedy of 2,000 babies born with microcephaly and runs the risk of a second wave of infections if the virus mutates. A year after the initial epidemic, public health authorities are reporting very few cases of microcephaly among newborns, a development obstetrician Adriana Melo and other researchers attribute to likely immunity among those already infected by the virus. “We will see sporadic cases, like any virus, but Zika is here to stay,” Mello said at her clinic for expectant mothers in northeastern Brazil, the region hardest hit by the initial wave of Zika in the Americas. After an alarming jump in late 2015 in regional cases of microcephaly, Melo was the first scientist to ask federal researchers to test the amniotic fluid of an expectant mother whose fetus was showing brain problems, providing the first empirical link between the complication and the virus. Microcephaly often signifies arrested brain development. Zika, a viral disease carried by mosquitoes, has spread to more than 60 countries and territories since the outbreak was identified in Brazil in 2015, raising alarm over its ability to cause microcephaly as well as Guillain-Barre syndrome.

More Perivable Infants Survive Without Neurodevelopmental Impairment

Perivable infants are surviving at a higher rate without an increase in the proportion who have neurodevelopmental impairment, a new study suggests. The report addresses concerns that improved survival rates among these infants, born between 22 and 24 weeks’ gestation, were coming at a cost of increased disability. “These findings are important for guiding counseling and decision making with respect to perivable birth,” write Noelle Younge, MD, MHS, a neonatologist at Duke University in Durham, North Carolina, and colleagues from the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. To compare changes in survival and neurodevelopmental impairment, Dr. Younge and colleagues looked at data on 4458 infants from 11 academic tertiary care centers who were born between the gestational ages of 22 weeks 0 days and 24 weeks 6 days between January 1, 2000, and December 31, 2011. Among these infants, 749 (18%) were born at 22 weeks, 1435 (34%) were born at 23 weeks, and 2090 (49%) were born at 24 weeks. The researchers divided the infants by birth year into three epochs: 2000 to 2003 (epoch 1), 2004 to 2007 (epoch 2), and 2008 to 2011 (epoch 3). Birth weight, gestational age, and infant sex distributions were similar across the epochs, although the proportion who were small for gestational age increased over time, whereas the proportion of mothers with an education level less than high school decreased. The overall rate of survival was highest in epoch 3, at 36%, compared with 30% in epoch 1 (P < .001). Moreover, the proportion of infants who survived without neurodevelopmental impairment increased from 16% (217 of 1391) in epoch 1 to 20% (276 of 1348) in epoch 3 (P = .001). In contrast, the proportions of infants who survived with neurodevelopmental impairment did not differ significantly across epochs (15% [207 of 1391] in epoch 1 and 16% [211 of 1348] in epoch 3; P = .29).

Pregnant Opioid Users Need Treatment, Not Jail, Pediatricians Say

Every 25 minutes, a drug-addicted baby is born in the U.S. To try to protect the youngest victims of the nation’s opioid epidemic, Tennessee enacted a law that sent new mothers to jail for substance abuse, while other states employ existing child-abuse laws to punish prenatal drug users and remove their children. But sanctions have backfired, serving only to drive pregnant women away from necessary prenatal care and substance-use treatment, pediatricians say in three new papers. In one, the American Academy of Pediatrics exhorts policymakers to support a public health approach – rather than a criminal justice response - to opioid use in pregnancy. “I don’t think these laws are in the best interests of moms or babies,” Dr Stephen Patrick, lead author of the report, said in an interview. “Opioid-use disorder is a medical problem and not a moral failing.” Patrick is a professor at Vanderbilt University School of Medicine in Nashville, Tennessee, where he treats infants suffering withdrawal from opioids. Instead of jail, he called for improved

perivable infants born at 22 weeks, 23 weeks, and 24 weeks were compared across epochs (15% [207 of 1391] in epoch 1 and 16% [211 of 1391] in epoch 3; P = .29).
access to long-term contraceptives and substance-treatment programs designed to care for pregnant women. About 100 substance-using new mothers went to jail in Tennessee between 2014 and 2016 under a fetal-assault law that's no longer in effect, Patrick said. The law incited so much fear in pregnant addicts that some refused to go to the hospital and gave birth at home, in cars or on the side of the road, he said. Meanwhile, the number of pregnant women who use opioids and the number of babies born with withdrawal symptoms continues to rise. Patrick estimated that as many as 440,000 substance-exposed infants are born in the U.S. every year and asserted: “We’re not going to arrest 440,000.”

**Azithromycin Can Help During Labor**

A dose of azithromycin given to pregnant women during labor protected the mothers and their newborns from infections over eight weeks in a post-hoc analysis of a clinical trial conducted in The Gambia. The maternal mortality rate in The Gambia is one of the highest among all developing countries, and neonatal deaths account for about 40% of all deaths of children younger than 5. Therefore, interventions that target maternal and neonatal morbidity and mortality are “urgently needed,” note Dr Anna Roca from the Medical Research Council. In their original double-blind placebo-controlled trial, they showed that a 2-gram oral dose of azithromycin given to women in labor decreased maternal and neonatal colonization with Staphylococcus aureus, Streptococcus pneumoniae and group B Streptococcus during the neonatal period. The aim of the post-hoc analysis was to see whether azithromycin prophylaxis protected against postpartum infection in the mother and neonatal infection up to eight weeks after delivery. Participants included 829 women (414 received azithromycin and 415 placebo during labor) and their 830 newborns. Results showed that maternal infections were lower in the azithromycin group than the placebo group (3.6% vs 9.2%; relative risk, 0.40; p=0.002), as was the prevalence of mastitis (1.4% vs 5.1%; RR, 0.29; p=0.005) and fever (1.9% vs 5.8%; RR, 0.33; p=0.006). The overall prevalence of infections was also lower in newborns of mothers who received azithromycin during labor (18.1% vs 23.8%; RR, 0.76; p=0.052), as was the prevalence of skin infections (3.1% vs 6.4%; RR, 0.49; p=0.034). “This study is a proof-of-concept and as such, we are yet in an early stage to determine the overall potential impact of the intervention proposed,” Dr Roca said. “Our findings are very encouraging as the trial showed the potential to drastically reduce the occurrence of infection in women and neonates during the first 8 weeks of life.”

**Ohio’s First Fetal Heart Procedure Performed**

A mother and her 29-week-old unborn child are doing well after a team of physicians performed a successful in utero procedure at University Hospitals Rainbow Babies & Children's Hospital (UH Rainbow). Known as fetal aortic valvuloplasty, this is the first heart procedure done before birth in Ohio. This rare approach helps prevent the progression of hypoplastic left heart syndrome (HLHS) in about half of all treated patients. Babies born with HLHS are sometimes referred to as having half a heart, because the left chambers of the heart are too small to pump blood to the body. The minimally invasive procedure may make the baby healthier and more stable at birth and may decrease the number of open-heart surgeries for the child later in life. “Right now, mom and baby are doing well, and we noted improvement in the way the blood flows through the heart prior to mom’s discharge,” says James Strainic, MD, Director, Fetal Heart Program at UH Rainbow. The procedure took place at UH Rainbow through the Congenital Heart Collaborative’s Fetal Heart Program, which offers cardiac interventions for unborn babies with developing HLHS and other critical, congenital heart conditions. The fetal valvuloplasty uses ultrasound guidance and a catheter-based approach to gain access to the fetal heart and to open the aortic valve using a tiny inflated balloon. This increases blood flow through the left ventricle of the heart to help its development. Aimee K. Armstrong, MD, Director of Cardiac Catheterization and Interventional Therapies at Nationwide Children’s Hospital, has performed fetal heart procedures more than a dozen times in her career, but this is her first fetal intervention patient since joining the Congenital Heart Collaborative in 2015. Dr Armstrong built a team of experts from Nationwide Children’s, UH Rainbow and UH MacDonald Women’s hospitals, as part of the Congenital Heart Collaborative. “By performing interventions on the fetal heart, we are able to alter the trajectory of heart and lung disease development before a baby is born with the goal of making the baby’s
heart healthier at birth,” said Dr Armstrong. “We ultimately hope to be able to decrease morbidity and mortality for these babies.” The Congenital Heart Collaborative, formalized two years ago, is a partnership between UH Rainbow Babies & Children's in Cleveland and Nationwide Children's in Columbus, which brings together expert physicians, surgeons and teams to provide world class care for patients and families in Northeast Ohio. With UH Rainbow Babies & Children's and UH MacDonald Women's hospitals both under one roof, Maternal Fetal Medicine specialists and the Congenital Heart Collaborative team can offer the full continuum of care in rare cases like this, for optimal outcomes. When the baby is born, he will receive immediate follow-up care from experts at UH Rainbow and the Congenital Heart Collaborative.

Complete Enteral Feeding System Launched
Medela LLC has received 510(k) clearance from the US Food and Drug Administration (FDA) to market ENFit Low Dose Tip enteral syringes. When used as intended, the ENFit Low Dose Tip can help to deliver accurate doses while reducing the risk of misconnections. This clearance completes Medela’s line of NICU-specific enteral feeding system products, which also includes syringes, syringe pumps, warmers, feeding tubes, and extension sets. “The ENFit products, including the ENFit Low Dose Syringe, were a natural addition to our neonatal enteral feeding system,” said Melissa Gonzales, managing director of Medela LLC for the US market. “As more neonatal intensive care units look to adopt ENFit enteral feeding connectors and ENFit low dose syringes, they will also need dedicated training from their supplier. We’re thrilled to provide the product and the support to our customers.” The ENFit design originated with the Global Enteral Device Supplier Association (GEDSA) to address the issue of misconnections in both intensive care hospital and homecare environments. Specific to enteral feeding, the ENFit Low Dose Tip Syringe was created to improve oral medication accuracy, which is especially necessary for small volume delivery in neonatal intensive care units (NICU). This design helps to improve small-volume enteral drug delivery accuracy by preventing unwanted liquid transfer while connecting and disconnecting from the feeding tube.

NICU Grants Available
Grants are being made available to hospitals to assist NICUs. Brave Beginnings is a program of the Will Rogers Motion Picture Pioneers Foundation that awards grants to hospitals throughout the United States to supply their Neonatal Intensive Care Units with state-of-the-art lifesaving equipment to best support premature lives. Since its inception in 2006, over three million dollars has been granted to 75 hospitals in 39 states, with over one million dollars being awarded last year alone. The imperative need for neonatal equipment was brought to the attention of the foundation when a hospital approached The Will Rogers Institute, a subset of the WRMPPPF that supports research for lung disorders and pulmonary programs and rehabilitation, for a grant to purchase a neonatal ventilator. Inspired by the positive outcome reported by the hospital, a neonatal equipment element was added to the menu of activities for WRI, eventually leading to the establishment of Brave Beginnings. Ten years later, the requests continue to pour in, and Brave Beginnings strives to fulfill every need. “The equipment request ranges from Neopuffs to Transport Incubators with everything in between,” reports Todd Vradenburg, Executive Director of the foundation. “We
have seen an increase in cooling equipment requests over the last two years and the most popular request are Giraffe Omnibeds.” To apply for a grant, non-profit hospitals can find instructions and a link to the online application at BraveBeginnings.org. Hospitals are welcome to apply as many times as they see fit, with a one year waiting period after the receipt of each grant. The application requires hospitals to prioritize the equipment request needed for the NICU and currently does not put a cap on the amount requested. The foundation takes into consideration the need of the requesting hospital, the square mileage served by the hospital, and the hospitals dedication to serve the underprivileged. The program continues to work diligently to understand the importance of funding hospital NICUs’ and the incredible impact that the right equipment can make with the most vulnerable of patients.

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.”

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**Life Adapter Unveiled**

Bunnell Incorporated has announced the US release of the 3.0 mm I.D. LifePort ET tube adapter for use with the Life Pulse High-Frequency Jet Ventilator. The LifePort adapter is the connector that replaces a standard endotracheal tube adapter and allows the Life Pulse HFJV and conventional ventilator to be used in tandem. Since 1988 the Life Pulse HFJV has been used for treating premature infants in acute respiratory failure in hospitals in the US, Canada, and several other countries. The 3.0 mm LifePorts are available in boxes of 10/each. The adapters will also be included in the HFJV Breathing Circuit Kits beginning May 1, 2017. Adapters are available in 2.5, 3.0, 3.5, 4.5 and 5.5 mm sizes. For more information go to www.buml.com.

**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.

**New Chief of Neonatology Named**

Eric Eichenwald, MD has joined The Children’s Hospital of Philadelphia (CHOP) as the new chief of the Division of Neonatology in the Department of Pediatrics, following a national search. Eichenwald joins a premier, comprehensive program staffed by a multidisciplinary team that provides optimal care to more than 4,000 critically ill newborns and infants throughout the CHOP Care Network each year. Physicians and scientists from CHOP’s Division of Neonatology conduct basic and clinical research on many conditions affecting newborns and infants. Eichenwald is also a Professor of Pediatrics, Perelman School of Medicine at the University of Pennsylvania and will hold the Thomas Frederick McNair Scott Endowed Chair at CHOP. He most recently served as chair of Pediatrics and chief of Neonatology at the University of Texas, Houston. He received his medical degree from Harvard Medical School and completed his training in Pediatrics at Children’s Hospital Boston and his training in Neonatology at Harvard Medical School.

**Antenatal Steroids Studied**

Results of a large study support antenatal steroid (ANS) administration in extremely premature babies and the goal should be to give a complete course before delivery, researchers say. The study found that ANS protects against death and neurodevelopmental impairment (NDI) in a dose-dependent fashion in babies born at 22 to 27 weeks gestational age weighing between 401 and 1000 g. The study evaluated 6,121 extreme preemies born at participating sites of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network between 2006 and 2011. They were grouped retrospectively based on ANS exposure: 848 had no ANS exposure, 1,581 had a partial course of ANS, and 3,692 had a complete course. They were followed from birth to about age two. Among all 6,121 infants, 4,284 (70%) survived to 18- to 22-month follow-up. Data on neurodevelopmental outcomes and neonatal morbidities were available for 3,892 (91%). The researchers found significant between-group differences in survival, complications in the neonatal period—including severe intracranial hemorrhage (ICH), bronchopulmonary dysplasia (BPD), and necrotizing enterocolitis (NEC)—and neurodevelopmental outcomes (cerebral palsy, cognitive impairment).

**Thrombocytopenia Called Risk Factor**

Thrombocytopenia is an independent risk factor for failure of patent ductus arteriosus (PDA) closure and more hemodynamically significant PDA in preterm infants, according to new findings from India. The study implies that preterm infants with thrombocytopenia and a patent ductus in the initial days of life need to be followed up closely for a hemodynamically significant PDA. The Postgraduate Institute of Medical Education and Research, Chandigarh, paper noted that a recent review reported a marginal association between thrombocytopenia in the first few days of life and PDA in very preterm infants. However, there have been no prospective studies. To investigate further, within 24 hours of birth the team prospectively enrolled 70 neonates with PDA on echocardiogram. Their gestational age ranged from 24 to almost 34 weeks and they were stratified according to platelet count. The infants underwent echocardiography daily. In the 35 neonates with platelet counts below 150,000/mcl, the time until PDA closure was two days. This was also the case in the 18 with counts of 100,000/mcl to 150,000/mcl. However, in the remaining 17 with counts below 100,000 the corresponding interval was 10 days. Almost all of the neonates in the latter group had thrombocytopenia attributable to mothers with pregnancy-induced hypertension. The researchers conclude that the results suggest that moderate thrombocytopenia is not a risk factor for delayed PDA closure.

**CF Treatment Unveiled**

Digestive Care, Inc. (DCI) and its marketing partner in the US cystic fibrosis community, Chiesi USA, Inc., announced US Food and Drug Administration (FDA) approval for an infant-specific dose of PERTZYE (pancrelipase) in a 4,000 USP lipase units capsule. The new capsule strength will enable guideline-recommended dosing and administration of PERTZYE for infants (up to 12 months) with exocrine pancreatic insufficiency (EPI) due to cystic fibrosis or other conditions. The recommended
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dose of PERTZYE in infants is 4,000 USP lipase units, one capsule, per 120 mL of formula or breast-feeding. The new dose strength approval means that PERTZYE will now be available in three dosing options, providing for improved dosing options from infancy through adulthood. To support administration to infants, the 4,000 lipase units capsule features a reduced microsphere size ranging from 0.8 – 1.4 mm in diameter. This is in contrast to the 8,000 and 16,000 lipase units capsules, which contain microspheres in the range of 0.8 – 2.2 mm in diameter. The largest microspheres in the 4,000 lipase units capsule are approximately 35 percent smaller than the largest microspheres in the 8,000 and 16,000 lipase units capsules.

Accriva Acquired
Werfen and its subsidiary Instrumentation Laboratory (IL) have announced the acquisition of Accriva Diagnostics, a global leader in in vitro diagnostic (IVD) blood testing at the Point-of-Care (POC), including its flagship product portfolio spanning coagulation, platelet aggregation, CO-Oximetry and incision devices. This acquisition will allow IL to establish a market-leading position in hospital-based POC Hemostasis testing, expand its position in POC Critical Care testing, and complement its leadership of the Hemostasis laboratory segment. “Over the course of our 50-year history, we have demonstrated our strong commitment to expanding our IVD business through organic growth, complemented with highly strategic acquisitions,” said Carlos Pascual, CEO at Werfen. “Like our recent acquisition of CA Casyso AG and its Tem subsidiaries, the acquisition of Accriva is exemplary of this commitment, as well as the confidence we have in our future together.” An integral part of Werfen, IL develops and manufactures Hemostasis, Critical Care and Patient Blood Management (PBM) products. Key Accriva product additions to the Company’s portfolio include Hemochron, the gold standard for Activated Clotting Time (ACT) testing, and VerifyNow, the leading system for platelet function analysis, among other leading brands. These products are primarily used at the POC during interventional cardiac and vascular procedures, and in hospital laboratories. “By acquiring Accriva, we are expanding our product offering, expertise, and know-how in Point-of-Care testing, particularly for Hemostasis,” said Ramon Benet, CEO at IL. “The addition of Accriva products to our strong Critical Care, Hemostasis and Patient Blood Management portfolios creates an even more comprehensive and integrated testing solution for hospital acute care settings and laboratories, further impacting positive clinical outcomes and reducing healthcare costs.” Accriva, based in San Diego, California, arose from the merger in 2013 of International Technidyne Corporation (ITC) and Accumetrics. The Accriva product portfolio represents over 40 years of POC leadership and expertise, including product development, manufacturing, marketing and sales. Key brands include Hemochron, VerifyNow, Avoximeter CO-Oximetry systems, and Tenderfoot, Tenderlett and Surgicutt incision devices.

Neonatal Whole Body Cooling is shown to improve outcomes for newborns meeting the requirements for HIE.1,2 Cincinnati Sub-Zero’s Blanketrol® III with it’s “Gradient Technology” and the Kool-Kit® Neonate provide accurate and safe patient temperature management. This system offers the ability to reach and maintain goal temperature as well as provides controlled re-warming for the patient.
Introduction

Preterm birth (PTB) remains a major cause of perinatal morbidity and mortality. Premature birth in the United States accounts for 35% of deaths in the first year of life. The Institute of Medicine’s Committee on Understanding Premature Birth and Assuring Healthy Outcomes estimated the annual economic burden associated with preterm birth in the United States for the year 2015 to be at least $26.2 billion. Medical care services comprised $16.9 billion while maternal delivery costs comprised $1.9 billion. Longer term costs included $611 million for early intervention services and $1.1 billion for special education services. Recently, Kuban, et al studied long-term outcomes of prematurity by analyzing cognitive, behavioral, and neurological parameters in premature children at the age of 10. Of the children, 28% of boys and 21% of girls exhibited moderate to severe impairment of cognitive abilities. Boys had a higher prevalence of impairment than girls in nearly all measures of cognition, were more than twice as likely to have microcephaly (15% in boys, 8% in girls), and require more often assistive devices to ambulate. In contrast, boys and girls had comparable risk of seizure or epilepsy. The committee estimated that lost household and labor market productivity comprised $5.7 billion. While approximately 20% of preterm births are indicated preterm births due to medical or obstetrical complications that jeopardize the health of the mother and/or the fetus, the majority of preterm births are spontaneous preterm births that occur as a result of preterm labor or preterm rupture of fetal membranes.

Potential interventions for reducing the incidence of spontaneous preterm birth can be classified as primary (aimed at all pregnant women), or secondary (aimed at reducing the risk in women with a previous preterm birth). Secondary among such interventions are progesterone prophylaxis and cervical cerclage placement.

A prior history of preterm birth is a major risk factor for preterm birth; however, many women who deliver preterm do not have a history of prior preterm birth. A statistically significant inverse relationship between midtrimester cervical length (CL) and preterm birth has been demonstrated in several studies. The risk for preterm birth associated with a cervical length below the 10th percentile (25mm) at 18 to 24 weeks is between 25% and 30%, and the risk associated with cervical length at or below the 3rd percentile (15mm) is above 50%.

The goal of the study is to assess the usefulness of universal CL screening in reducing the incidence of preterm birth in a large community-based practice.

Materials and Methods

Since 2006, we have instituted a policy of routine cervical length screening via transvaginal ultrasound. Cervical length screening generally begins between 16 and 24 weeks. If the cervix measures more than 35 mm, the exam is repeated every 2 weeks until 32 weeks of gestation. A cervical length of 25 mm to 35 mm is managed with weekly follow-ups. If the cervical length is less than 25 mm, surgical (cerclage), medical (progesterone, tocolytics) or combined therapy is applied.

Statistical analysis

Numerical variables are presented as median (interquartile range [IQR]) and categorical data are presented as a number (percentage). Linear regression was used to assess the relationship between the cervical length, treatment modality and preterm birth. Statistical analysis was performed using IBM SPSS Statistics for Windows (version 20.0; IBM Corporation, Armonk, NY). All statistical tests were 2-sided, and a probability value of <.05 was considered statistically significant. Patients of a different group practice using standard management protocol served as the control group. Preterm birth was defined as a delivery between more than 24 and less than 37 weeks of pregnancy.

Results

A total of 1,319 patients comprised the study group and 2,518 were included into the control group. Patients who delivered at less than 32 weeks were considered extremely premature, while those who delivered in less than 37 weeks were of moderate prematurity (Table 1).

<table>
<thead>
<tr>
<th>Table 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age at birth</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Under 32 weeks</td>
</tr>
<tr>
<td>2.3%</td>
</tr>
<tr>
<td>More than 32 weeks, less than 37 weeks</td>
</tr>
<tr>
<td>4.17%</td>
</tr>
<tr>
<td>Total preterm</td>
</tr>
<tr>
<td>6.47%</td>
</tr>
</tbody>
</table>

*P<0.05

The authors are with Garden Obstetrics and Gynecology, Long Island, NY.
Discussion
Universal cervical length screening has not been universally adopted. The most recent report of the FIGO Working Group on Best Practice in Maternal-Fetal Medicine published in January 2015, recommends that cervical length measurement should be performed in all pregnant patients at 19–23 6/7 weeks of gestation using transvaginal ultrasound. They further recommend that women with a short cervix (<25 mm) diagnosed in the mid-trimester be offered daily vaginal micronized progesterone treatment. However, this approach is far from being universally accepted.

The implementation of a policy of universal second-trimester cervical length assessment remains a contentious topic and is countered by the additional burden it places on the health care system. Alternative strategies, such as using obstetric history to select women who would then undergo screening, have been proposed instead.

ACOG Practice Bulletin on prematurity agrees that transvaginal cervical ultrasonography has been shown to be a reliable and reproducible way to assess the length of the cervix. Unlike the transabdominal approach, transvaginal cervical ultrasonography is not affected by maternal obesity, the position of the cervix, or shadowing from the fetal presenting part. Most authorities agree that cervical screening and progesterone supplementation should be offered to pregnant women with a prior spontaneous preterm birth. However, when it comes to the management of patients without prior history of preterm delivery, opinions differ.

Miller et al. conducted a cohort study of women with a singleton gestation without a history of preterm birth who underwent routine transvaginal second-trimester cervical length screening. According to this study, specificity increases from 62.8% for universal screening to 96.5% with a risk-based approach. They concluded that limiting cervical length screening to women with at least one of the identified risk factors for a short cervix substantially decreases the number of sonograms. However, this strategy results in nearly 40% of women with a short cervix not being ascertained. Arguing against universal screening authors admitted that a risk-based system instead of universal cervical length screening, a reasonably large number of women with a short cervix and a preterm birth will not be identified. In July 2011, a program was implemented, by Son M, Grobman WA, Ayala NK. A universal mid-trimester cervical length screening and treatment with vaginal progesterone to prevent preterm birth: A decision and economic analysis. Am J Obstet Gynecol. 2010; 202 (6): 548. e1-8


References
3. Cahill AG; Odibo AO; Caughhey TB, et al. Universal cervical length screening program, and 17,609 underwent a sonogram after mid-trimester sonogram before the universal cervical length-screening program. Multivariable analysis was used to identify whether the universal cervical length-screening program was associated independently with the frequency of preterm birth. Of 64,207 eligible women, 46,598 underwent their mid-trimester sonogram before the universal cervical length-screening program, and 17,609 underwent a sonogram after implementation of the program. The introduction of the cervical length program was associated with a significant decrease in the frequency of preterm birth at all gestational ages of less than 37 weeks. This reduction in frequency of preterm birth was primarily due to a change in spontaneous preterm births.

Our policy of universal cervical length screening in a large community based practice confirms its effectiveness in reducing preterm births. Our recommendations agree with the ones by Werner, et al who performed a cost-effectiveness analysis of universal cervical length screening. These authors concluded that in low risk pregnancies, universal transvaginal cervical length ultrasound screening appears to be a cost effective strategy. For every 100,000 women screened, $12,119,947 can be potentially saved and 423.9 quality adjusted life years could be gained. When assessing expense for additional sonograms versus the cost of prematurity the multimillion law suits expenses related to prematurity should also be accounted for.
Optimizing clinical care for prematurely born infants is crucial due to the risks faced by this group of highly vulnerable patients, but establishing a standardization of care when it comes to the area of respiratory therapy is still a puzzle due to a lack of research, say the authors of a study out of Australia.

The specific area of study for Calum Roberts and Louise Owen of Royal Women's Hospital in Melbourne, Australia, and colleagues, was pre-term infants with respiratory distress – and comparing continuous positive airway pressure (CPAP) with nasal high-flow therapy.

As is detailed in the study, (Nasal High-Flow Therapy for Primary Respiratory Support in Preterm Infants, published in the September 2016 edition of the New England Journal of Medicine), more and more parents and clinicians are preferring nasal high-flow therapy because of its ease of use.

According to the study authors, other research has established that nasal high-flow is an effective mode of post-extubation support – however, no previous studies have appropriately assessed the efficacy of this therapy as the “primary mode” of respiratory support in this setting.

The research team set out to conduct an international, multicenter, randomized, noninferiority trial in Australia and Norway to test nasal high-flow against CPAP as the primary mode of respiratory support for preterm infants with respiratory distress.

The results show that preterm infants with respiratory distress appeared to do better with CPAP than nasal high-flow therapy, with CPAP showing a lower percentage of treatment failure. However, there were no significant between-group differences in other clinical outcomes, such as rates of intubation, bronchodyplasia, or rates of adverse events.

Caring For Preterm Infants
According to the study, in 2014, there were more than 380,000 preterm births in the US, or approximately 10% of all births that year. These vulnerable patients face a significant risk of respiratory distress syndrome.

“The introduction of endotracheal ventilation has improved the survival rate among preterm infants but is associated with an increased risk of complications such as bronchopulmonary dysplasia. Clinicians aim to use noninvasive respiratory support to minimize the risk of such complications,” the authors wrote.

CPAP is the most widely used device, and has been shown to be an effective alternative to endotracheal ventilation as primary respiratory support for preterm infants. But treatment with heated, humidified, high-flow nasal cannulae (high-flow therapy) is an “increasingly popular means of noninvasive respiratory support,” the authors wrote. “Surveys have shown that approximately two thirds of neonatal intensive care units in the United States and in Australia and New Zealand used high-flow therapy. This approach has several reported advantages over CPAP, including reduced rates of nasal trauma and reduced infant pain scores. Surveys show that it is preferred by parents and nursing staff.

“In a previous randomized trial comparing high-flow therapy with CPAP as respiratory support after extubation in infants born at a gestational age of less than 32 weeks, we found that high-flow therapy was noninferior to CPAP in preventing treatment failure. This finding was consistent with the results of other randomized trials of neonatal respiratory support after extubation. Previous studies comparing high-flow therapy with CPAP as primary support have not shown significant differences in treatment-failure or intubation rates. However, these studies were small, single-center trials, reported interim data, or constituted a substudy of a larger trial.

“The authors of a recent Cochrane Review suggested that additional, adequately powered randomized trials assessing high-flow therapy as primary respiratory support should be undertaken.”

With others recommending more study, the team from the Royal Women’s Hospital in Melbourne, Australia took up the challenge.

The Study
Nine neonatal intensive care units in Australia and Norway participated in the study. The research team assigned 564 preterm infants (gestational age, ≥28 weeks 0 days) with early respiratory distress who had not received surfactant replacement to treatment with either nasal high-flow therapy or nasal CPAP. The primary outcome was treatment failure within 72 hours after randomization. Noninferiority was determined by calculating the absolute difference in the risk of the primary
outcome; the chosen margin of noninferiority was 10 percentage points. Infants in whom high-flow therapy failed could receive rescue CPAP; infants in whom CPAP failed were intubated and mechanically ventilated.

The Results
The trial recruitment ended up having to be stopped early at the “recommendation of the independent data and safety monitoring committee because of a significant difference in the primary outcome between treatment groups,” said the study authors.

Treatment failure occurred in 71 of 278 infants (25.5%) in the high-flow group and in 38 of 286 infants (13.3%) in the CPAP group (risk difference, 12.3 percentage points; 95% confidence interval [CI], 5.8 to 18.7; P < 0.001).

In their analysis of the results, the authors wrote that they “contrast with those of studies of high-flow therapy initiated after extubation, which have consistently shown that the efficacy of high-flow treatment is similar to that of CPAP.” 7-9,16 Unlike the infants in the trials of postextubation high-flow therapy, no infants in our study received surfactant before randomization. 7-9 The higher rate of treatment failure among infants receiving high-flow therapy in our study may reflect its reduced effectiveness in infants with surfactant-deficient lungs. Although high-flow therapy does provide some distending pressure,20-22 the higher, more consistent pressures produced during CPAP may account for the difference in treatment-failure rates that we report.”

However, the authors also found that the rate of intubation within 72 hours did not differ “significantly” between the high-flow and CPAP groups (15.5% and 11.5%, respectively; risk difference, 3.9 percentage points; 95% CI, −1.7 to 9.6; P = 0.17), nor did the rate of adverse events.

“In addition, infants in the high-flow group had a significantly lower rate of nasal trauma,” they wrote.

The calculated total cost of the tertiary hospital stay (in US dollars) per infant did not differ significantly between the CPAP and high-flow groups ($32,036 and $29,785, respectively; P = 0.40).

“We conclude that high-flow treatment results in a significantly higher rate of treatment failure than does CPAP, when used as primary support for preterm infants with respiratory distress.”

References
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While the Optiflow Junior™ System is small in size, our engineers have collaborated with clinicians to create a cannula that is designed to make a big difference to infants and hospital staff. Optiflow Junior™ is a neonatal and pediatric nasal cannula that delivers humidified gases and is specifically designed for:

HIGH PERFORMANCE
- Wide flow range from 0.5 lpm up to 25 lpm to allow for flexibility of treatments
- Humidified to improve tolerance
- Reduced requirement for CPAP & intubation

SAFETY
- Used to reduce the risk of nasal trauma
- 87% average reduction in condensate*

EASE OF USE
- Easy set up, maintenance, care and cycling
- More settled babies = less attendance time

Facilitation of developmental care
- Easier feeding
- Simple Kangaroo Care

*A small cannula designed to make a big difference to clinicians, caregivers, parents and patients. Contact your local F&P representative and book a meeting today.


*Average result found in internal Fisher & Paykel Healthcare testing compared to an F&P RT329 Circuit.
Evaluation of Accuracy of a Pulse Oximeter Designed for Use in the Neonatal Population

Andrea Lampland, MD1; Joyce A. Wahr, MD2; Mark C. Mammel, MD1**

Abstract

Purpose: There is a paucity of Pulse Oximetry accuracy reports in the Neonatal population.

Objective: This prospective, single-center, observational study evaluated the accuracy of the Nonin OEM III Pulse Oximeter Module with the 7000N sensor (Nonin Medical, Inc., Plymouth, Minnesota) in the neonatal intensive care unit (NICU) setting.

Methods: Neonate ages ≤ 30 days old treated in the NICU and having their arterial blood gases (ABGs) analyzed by co-oximetry as part of their care were eligible for the study. ABGs were managed per the routine of the NICU. At the time of a prescribed ABG, the 7000N sensor was applied to the neonate’s foot or palm using adhesive wrap. Readings of the arterial blood oxygen saturation from the co-oximeter (SaO₂) and the OEM III pulse oximeter (SpO₂) were then simultaneously recorded. Accuracy was expressed using mean bias (SpO₂ – SaO₂), precision (SD of the bias) and the root mean square error (RMSE or ARMS).

Results: A total of 231 data pairs were collected from 26 subjects; 176 valid data pairs were included in the analysis. Mean ± SD bias was -0.5% ± 2.74% and ARMS was 2.78%.

Conclusions: The Nonin OEM III with the 7000N sensor is considerably accurate in neonates being treated in the NICU with an ARMS ± 3% for SpO₂ ranges of 70-100%.

Keywords: neonatal, pulse oximetry, co-oximetry, accuracy

Introduction

Pulse oximetry is an optically-based, non-invasive method to estimate arterial blood oxygen saturation (SaO₂). A sensor, which is usually placed on the finger or ear lobe in adults or the foot or palm in infants, passes red and infrared light through perfused tissue. Light absorption changes as arterial blood pressure pulses through the tissue and as the relative amounts of oxygenated and deoxygenated hemoglobin change. Detector located in the sensor measure the change in light absorption, and this allows the SaO₂ to be estimated [1].

Since its introduction in the 1980s, pulse oximetry has been widely adopted to help manage critically ill patients in intensive care units. Today pulse oximetry is routinely used for assessing the respiratory status of hospitalized children because of its non-invasive nature. By providing continuous information about oxygenation status, pulse oximetry greatly reduces the number of required arterial blood draws for blood gas analysis.

Historically, pulse oximetry accuracy and reliability have been verified in controlled laboratory studies on adults under normal perfusion. Also, in the past, the industry standard, which was supported by regulatory agencies such as the United States Food and Drug Administration (FDA), allowed pulse oximeter manufacturers to declare an accuracy range for neonates to be ± 1% of established adult specifications. However, the FDA has since moved toward requiring manufacturers to provide data by obtaining opportunity samples that are drawn during the evaluation and treatment of neonatal patients in the NICU to verify and support accuracy claims in specific patient populations, such as neonates [2]. These clinical studies are now recognized as being more representative of the pulse oximeter's intended use than controlled laboratory studies in adults.

At present, the most widely accepted method of determining the accuracy of a pulse oximeter is by comparing the SpO₂, the oxygen saturation value measured by the pulse oximeter, and the SaO₂, the oxygen saturation measured by a laboratory co-oximeter in extracted arterial blood [3]. A laboratory co-oximeter, which uses multiple wavelengths of light, provides a more specific and accurate measurement of arterial blood oxygen saturation, and is thus considered the gold standard. In the present study, the pulse oximeter was compared to the laboratory co-oximeter to determine the accuracy of the Nonin OEM III Pulse Oximeter Module with the 7000N sensor (Nonin Medical, Inc., Plymouth, MN, USA) in neonates being treated in the neonatal intensive care unit (NICU).

Methods

Device Description

The Nonin OEM III Pulse Oximeter Module is used in a variety of products and is indicated for continuous, non-invasive
phototherapy turned off during data collection. The Institutional Review Board of Children’s Hospitals and Clinics of Minnesota reviewed and approved the study, and parents/guardians of the subject provided written, informed consent to participate in the study.

Neonates have unique physiology and hemodynamics that can influence the signal to noise ratio and can make accuracy of pulse oximetry difficult [6]. The neonatal myocardium is immature at birth, and cardiac output depends in large part on a high heart rate [7]. Increases in systemic vascular resistance can profoundly depress cardiac output and fluid overload is monitoring and display of SpO2 and pulse rate of well or poorly perfused adult, pediatric, and neonatal patients. In adults, the OEM III has a specified accuracy of ± 3% in both normal and low perfusion conditions [4]. The 7000N sensor is a single patient use, flexible sensor for monitoring neonatal patients weighing 2-10 kg. It is intended for use where moderate sensor motion is expected or cross-contamination is a concern.

**Study Overview and Patient Population**

This was a prospective, single-center, observational study to verify the SpO2 accuracy of the OEM III Pulse Oximeter Module with the 7000N sensor in the neonatal population. Neonates ≤ 30 days old who were having their arterial blood gases (ABGs) analyzed by co-oximeter as part of their medical care were eligible for the study. Subjects were excluded if they had evidence of skin breakdown on either hand or foot or had clinical conditions precluding use of the adhesive sensors. Neonates undergoing bilirubin phototherapy had to have

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Result (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (days)</td>
<td>3.2±7.0 (26) (0.37)</td>
</tr>
<tr>
<td>Gestational age (weeks)*</td>
<td>29.7±3.6 (25) (26, 36)</td>
</tr>
<tr>
<td>Male gender</td>
<td>13/26 (50%)</td>
</tr>
<tr>
<td>Race/Ethnicity*</td>
<td></td>
</tr>
<tr>
<td>Black or African American</td>
<td>4/26 (15.4%)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>21/26 (80.8%)</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>2/26 (7.7%)</td>
</tr>
<tr>
<td>Diagnosis*</td>
<td></td>
</tr>
<tr>
<td>Respiratory distress syndrome/hyaline membrane disease</td>
<td>22/26 (84.6%)</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>5/26 (19.3%)</td>
</tr>
<tr>
<td>Prematurity</td>
<td>5/26 (19.3%)</td>
</tr>
<tr>
<td>Diagnosis not provided</td>
<td>3/26 (11.5%)</td>
</tr>
</tbody>
</table>

Data presented as number of observations/number of subjects (%) or mean ± standard deviation (number of observations) (range: minimum, maximum).

*N=25; gestational age was missing for 1 subject

*One subject reported race/ethnicity as Hispanic/Latino and Caucasian

*Most subjects had more than one diagnosis at the time of enrollment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Results (n = 26 subjects, 176 readings)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>1.24 ± 0.66 (143) (0.65, 3.47)</td>
</tr>
<tr>
<td>Phototherapy lights</td>
<td></td>
</tr>
<tr>
<td>On</td>
<td>10/176 (5.7%)</td>
</tr>
<tr>
<td>Off</td>
<td>128/176 (72.7%)</td>
</tr>
<tr>
<td>Not recorded</td>
<td>38/176 (21.6%)</td>
</tr>
<tr>
<td>Sensor placement</td>
<td></td>
</tr>
<tr>
<td>Left hand</td>
<td>24/176 (13.6%)</td>
</tr>
<tr>
<td>Right hand</td>
<td>49/176 (27.8%)</td>
</tr>
<tr>
<td>Left foot</td>
<td>41/176 (23.3%)</td>
</tr>
<tr>
<td>Right foot</td>
<td>23/176 (13.1%)</td>
</tr>
<tr>
<td>Not recorded</td>
<td>39/176 (22.2%)</td>
</tr>
<tr>
<td>Arterial blood gas results</td>
<td></td>
</tr>
<tr>
<td>SaO2 (%)</td>
<td>90.1 ± 6.13 (176) (69, 100)</td>
</tr>
<tr>
<td>pH</td>
<td>7.31 ± 0.07 (176) (6.92, 7.48)</td>
</tr>
<tr>
<td>pCO2 (mmHg)</td>
<td>48.1 ± 10.18 (176) (25, 112)</td>
</tr>
<tr>
<td>pO2 (mmHg)</td>
<td>58.4 ± 27.41 (176) (29, 349)</td>
</tr>
<tr>
<td>HCO3 (mEq/L)</td>
<td>23.6 ± 4.06 (175) (13, 36)</td>
</tr>
<tr>
<td>Base excess (mEq/L)</td>
<td>-1.8 ± 4.09 (174) (-12, 11)</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>37.0 ± 0.01 (131) (37, 37)</td>
</tr>
</tbody>
</table>

Data presented as number of observations/number of subjects (%) or mean ± standard deviation (number of observations) (range: minimum, maximum).

neonatal INTENSIVE CARE Vol. 30 No. 2 • Spring 2017

**Table 1. Subject Baseline Characteristics**

**Table 2. Summary of Arterial Blood Gas Draw Conditions**

**Figure 1.** A scatterplot of the paired SpO2 and SaO2 values, excluding 11 extreme values (see text). The solid black line represents the line of identity. The dashed black lines represent a 2% error from the line of identity. The dashed line is the linear regression line.

**Figure 2.** Bland-Altman plot of the difference (SpO2 - SaO2) plotted against the mean ((SpO2 + SaO2)/2) for each sample, excluding the 11 extreme values (see text). Solid grey line represents the mean bias; dashed gray lines represent the 95% limits of agreement.

**Figure 2.** Bland-Altman plot of the difference (SpO2 - SaO2) plotted against the mean ((SpO2 + SaO2)/2) for each sample, excluding the 11 extreme values (see text). Solid grey line represents the mean bias; dashed gray lines represent the 95% limits of agreement.
motion, and the presence of warming lamps and phototherapy
difficult [9]. Finally, infants and neonates are more prone to
pressure and arterial wave amplitude, detection is even more
arterial waveform difficult; in neonates, with lower resting blood
hypothermia, poor cardiac output) can make detection of the
amplitude due to peripheral vasoconstriction (e.g., hypovolemia,
reduces the “signal” of the arterial pulse [9]. Low pulse wave
120-180 beats per minute, is lower than adults, and often
poorly tolerated [8]. Neonatal systolic arterial blood pressure,
which is typically 50-90 mmHg with a resting heart rate of
120-180 beats per minute, is lower than adults, and often
reduces the “signal” of the arterial pulse [9]. Low pulse wave
amplitude due to peripheral vasoconstriction (e.g., hypovolemia,
hypothermia, poor cardiac output) can make detection of the
arterial waveform difficult; in neonates, with lower resting blood
pressure and arterial wave amplitude, detection is even more
difficult [9]. Finally, infants and neonates are more prone to
motion, and the presence of warming lamps and phototherapy
all create “noise” that may swamp the arterial signal. Thus,
demonstration of the accuracy and reliability of pulse oximetry
monitors in the neonatal clinical setting is critical.

Study Procedures
Arterial blood gases were managed per the routine of the
hospital’s NICU. At the time the prescribed ABG was drawn, the
7000N sensor was applied to the neonate’s foot or palm using
adhesive wrap. The sensor was then connected to an electronic
data capture system (EDCS). The EDCS had a marker capability
to capture the time of ABG so that an accurate comparison could
be made between the co-oximeter SaO2 and the SpO2 determined
by the OEM III with the 7000N sensor. The samples used for the
data analysis were opportunity samples collected as prescribed
by the attending physician.

Statistical Analysis
All data were analyzed using SAS 9.1 (SAS Institute, Inc., Cary,
North Carolina, USA). Continuous variables are presented
as mean or median according to adherence to a Gaussian
distribution and the convention in publication as appropriate
along with standard deviation (SD) and range. Categorical or
discrete variables are presented as a fraction and percentage. All
statistical analyses were performed using the entire sample, with
the following exceptions (if documented): difficulty placing the
sensor, difficulty drawing the blood sample, use of point-of-care
devices instead of a co-oximeter, arterial oxygen saturations
less than < 70%, or unstable SpO2 platesau. The stability of each
SpO2 platesau was determined by reviewing the results before,
during, and after the arterial blood draw. The SD and range of the
SpO2 values were then calculated. Draws with SD or ranges out
of typical range indicates instability and subsequently removed.
Additionally, extreme values that presented both clinically and
statistically warrant further investigation of available data. In
the absence of a clear demonstration that the extreme values
represented an error in recording, miscalculation, equipment
malfunction, or similar circumstance, these values were included
in the analysis.

Accuracy was evaluated by calculating the $A_{BPM}$ value using the
paired arterial oxygen saturation and pulse oximeter oxygen
saturation as per ISO 80601-2-61:2011, which relates to the basic
safety and critical performance of pulse oximeter equipment
that is intended for use on individuals [5]. The two-sided 95%
bias-corrected bootstrap confidence interval is provided for the
$A_{BPM}$ statistic. The mean bias and precision are presented with
their 2-sided 95% confidence intervals. The Pearson correlation
coefficient is also presented. Bland-Altman analyses were
performed for agreement. Additionally, relationships between
bias and subject level characteristics were assessed through
linear regression for continuous variables and analysis of
variance for discrete variables. P-values correspond to Student-t
tests where two groups are compared and slope coefficient in a
linear regression. A value of $p < 0.05$ was considered significant.

Results
Subjects
A total of 29 subjects were consented and enrolled, of which 26
completed the study. Of the three subjects who did not complete
the study, parental consent was withdrawn for one subject prior
to any blood gas sample being drawn, and 2 subjects had their
arterial line removed prior to any ABG being performed. All of
the 26 subjects who completed the study had at least one ABG
drawn. Subject baseline characteristics are presented in Table
1. Subjects ranged from 0 to 37 days old. Gestational age ranged
from 26 to 36 weeks (term gestation is 40 weeks). An equal
number of males and females were represented in the study
population.

Arterial Blood Gas Samples
A total of 231 scheduled ABGs were performed in the 26 study
subjects; however, the ABG data from 15 samples were excluded
because either the analysis was done on a point-of-care machine
or because it was not recorded in the medical record. An
additional 28 ABGs were excluded because the pulse oximeter
was not attached to the subject or the data was not collected.
Of the remaining 188 ABG blood draws, the pulse oximeter data
was excluded in 12 data pair samples drawn during unstable
readings. Therefore, a total of 176 paired data points were
included in the final analysis. Table 2 provides a summary of
the conditions during the ABG draws, including subject weight,
status of phototherapy lights, sensor placement, as well as the
ABG results.

Accuracy Results
Table 3 presents the accuracy statistics, including the mean bias,
precision, $A_{BPM}$, correlation coefficient, linear regression results,
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- Lightweight portability for transport

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and limits of agreement. Ad hoc analysis identified observations where their bias values had extreme t-statistics compared to the remaining data values. There were 11 extreme data pairs out 176 total data pairs (6%). Results are presented with and without these 11 extreme data pairs.

Figure 1 presents the scatter plot of the SpO2 versus the SaO2 values, and Figure 2 presents the Bland-Altman plot of the bias versus the mean. As shown, there is a negligible bias of -0.5%, which was not materially altered with inclusion of the outlier values. Precision was 2.74% and $A_{\text{Bias}}$ was 2.78%.

**Relationships between Bias and Subject Characteristics**

As shown, there is a bias of -0.5%, and was not materially altered with or without inclusion of the extreme values. The accuracy has an approximate $A_{\text{Bias}}$ of 3% which is considered clinical meaningful, based on the accuracy claims in the adult population. The linear regression appeared to be slightly skewed to reporting lower than actual pulse oximetry values above 90% saturation.

Covariate analyses were performed to assess if results could be confounded by subject characteristics and baseline conditions. No significant effects were detected for weight, $pCO_2$, base excess, enrollment age, or presence of photo-therapy light (all $p > 0.1$). There was no discernable effect of placement location or race/ethnicity on the bias or precision. A marginal effect of gestational age at enrollment was detected, but did not reach predetermined statistical significance (an increase in bias of 0.1% per week, $p=0.097$). An effect of $pH$ was detected, where each 0.1 unit decrease in $pH$ resulted in a 1.23% decrease in bias ($p=0.002$; Figure 3). Consistent accuracy was seen on both the foot and the hand ($A_{\text{Bias}} = 2.4$ and 2.8).

**Discussion**

Upon review of the scientific literature regarding pulse oximetry accuracy in neonates, it appears that while pulse oximetry accuracy has been constantly improving, accuracy studies of pulse oximeters involving different manufacturers and in the neonatal population, with their various diagnoses and unique physiology, remain scarce and need to be updated.

The present study demonstrated that the Nonin OEM III Pulse Oximeter Module with the 7000N sensor performed well in neonates being treated in the NICU. The device demonstrated an admissible level of accuracy when compared to the gold standard co-oximeter measurement, with a mean bias of -0.5 ± 2.74. Additionally, the Nonin device, which demonstrated an $A_{\text{Bias}}$ of 2.78% over an SpO2 range of 70-100%, met the FDA standard for pulse oximetry accuracy, which requires the $A_{\text{Bias}}$ to be ≤ 3%.

In an analysis of relationships between bias and subject-level characteristics, no significant effects were detected for weight, $pCO_2$, base excess, enrollment age, gestational age, use of phototherapy, sensor placement location, or race/ethnicity. A slight effect of $pH$ was detected, with each 0.1 unit increase in $pH$ resulting in a 1.23% drop in bias. However, no prior reports of pulse oximetry in adults or infants have found such an association between pH and bias. Furthermore, there is no known physical-chemical rationale that would cause a pH effect on the optical differences between the pulse oximeter and co-oximeter [10]. These data, are likely representing a spurious result given the influence of one extreme data point (Figure 3), and could also be due to unrecognized confounders, such as congenital anomalies or ambient light levels.

Our study had several limitations. First, the data presented here are limited by the constraints of oximetry engineering and human physiology. All oximeters are calibrated on data obtained from humans in a laboratory setting. Although our study included 7 samples with SaO2 between 76 and 79, pulse oximeters are not typically calibrated with extremely low values, and thus true accuracy rates are challenging at low levels of saturation. Bilirubin levels were not measured in this study, and we cannot exclude a potential effect of this common blood chromophore on accuracy [11]. However, the accuracy results represent samples with presence of bilirubin, which could have adversely affected the accuracy.

In conclusion, this study demonstrated a clinically meaningful level of accuracy of the Nonin OEM III pulse oximeter module with the 7000N sensor when tested across a wide range of arterial blood oxygen saturations and physiologic conditions experienced in neonates. Studies such as this are necessary to provide reassurance about the information provided by these vital monitors that are commonly used in the NICU.

**Acknowledgments**

Dr Andrea Lampland, MD is paid to participate in clinical trial steering committee for Discovery Labs Inc. No authors have known conflicts of interest to report. This study was supported by Nonin Medical, Inc., Plymouth, Minnesota, USA.

**References**

11. Ralston AC, Webb RK, Runciman WB. Potential errors in
Table 6. Summary of Accuracy Results by Subject

<table>
<thead>
<tr>
<th>Subject</th>
<th>N</th>
<th>Mean Bias</th>
<th>Precision</th>
<th>Arms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8</td>
<td>-1.9 ± 2.77</td>
<td>2.8(-2.32,2.32)</td>
<td>3.21</td>
</tr>
<tr>
<td>2</td>
<td>16</td>
<td>0.2 ± 3.87</td>
<td>2.9(-1.53,1.53)</td>
<td>2.79</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>-0.9 ± 3.99</td>
<td>4.0(-35.81,35.81)</td>
<td>2.95</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>-0.4 ± 1.82</td>
<td>1.8(-4.51,4.51)</td>
<td>1.53</td>
</tr>
<tr>
<td>5</td>
<td>26</td>
<td>-0.2 ± 3.74</td>
<td>3.7(-1.51,1.51)</td>
<td>3.67</td>
</tr>
<tr>
<td>9</td>
<td>7</td>
<td>0.6 ± 1.03</td>
<td>1.0(-0.95,0.95)</td>
<td>1.15</td>
</tr>
<tr>
<td>14</td>
<td>1</td>
<td>-0.3 ± NA</td>
<td>NA</td>
<td>0.34</td>
</tr>
<tr>
<td>15</td>
<td>1</td>
<td>-0.1 ± NA</td>
<td>NA</td>
<td>0.14</td>
</tr>
<tr>
<td>16</td>
<td>1</td>
<td>0.1 ± NA</td>
<td>NA</td>
<td>0.07</td>
</tr>
<tr>
<td>17</td>
<td>3</td>
<td>-2.7 ± 0.62</td>
<td>0.6(-1.54,1.54)</td>
<td>2.71</td>
</tr>
<tr>
<td>19</td>
<td>15</td>
<td>0.7 ± 1.58</td>
<td>1.6(-0.88,0.88)</td>
<td>1.68</td>
</tr>
<tr>
<td>20</td>
<td>2</td>
<td>-1.2 ± 0.71</td>
<td>0.7(-6.42,6.42)</td>
<td>1.29</td>
</tr>
<tr>
<td>21</td>
<td>6</td>
<td>-1.5 ± 2.72</td>
<td>2.7(-2.86,2.86)</td>
<td>2.88</td>
</tr>
<tr>
<td>22</td>
<td>10</td>
<td>-1.7 ± 2.72</td>
<td>2.7(-1.95,1.95)</td>
<td>3.11</td>
</tr>
<tr>
<td>24</td>
<td>2</td>
<td>2.7 ± 5.06</td>
<td>5.1(-45.47,45.47)</td>
<td>4.51</td>
</tr>
<tr>
<td>25</td>
<td>9</td>
<td>-1.3 ± 2.15</td>
<td>2.1(-1.65,1.65)</td>
<td>2.43</td>
</tr>
<tr>
<td>26</td>
<td>1</td>
<td>-3.6 ± NA</td>
<td>NA</td>
<td>3.57</td>
</tr>
<tr>
<td>27</td>
<td>4</td>
<td>0.6 ± 1.98</td>
<td>2.0(-3.15,3.15)</td>
<td>1.80</td>
</tr>
<tr>
<td>28</td>
<td>2</td>
<td>-1.1 ± 1.08</td>
<td>1.1(-9.71,9.71)</td>
<td>1.34</td>
</tr>
<tr>
<td>29</td>
<td>1</td>
<td>-1.5 ± NA</td>
<td>NA</td>
<td>1.46</td>
</tr>
</tbody>
</table>

*Presented as estimate (95% two-sided confidence interval).

Source: QATR7075.SAS
Impact of Urine on Diapered Skin Health

Suhyoun (Su) Chon, PhD, and Ben Minerath, MS

Summary
Proper hygiene of diapered skin has long been recognized as essential for maintaining healthy baby skin. In particular, the effective removal of urine and feces from baby skin is necessary to maintain an intact skin barrier against external irritants and minimize the incidence of diaper rash. Although the combination of feces and urine causes the most severe skin damage, urine alone is sufficient to trigger skin irritation.

A recent survey on the use of baby wipes revealed that some caregivers do not clean diapered skin if the diaper change involves the presence of urine only. This review describes the impact of urine exposure on baby skin to highlight the importance of good skin hygiene practices for maintaining healthy baby skin. Basic knowledge of urine composition and unique properties of baby skin are first reviewed to describe how urine interacts with and impacts baby skin. Then, potential harmful effects of specific urine constituents and benefits of using appropriately formulated baby wipes are discussed in detail to inform diapering practices that promote healthy baby skin.

Background: Urine and Baby Skin
Newborn bladder function is not mature at birth and continues to develop throughout infancy. The frequency and volume of urination change with increasing bladder maturity and capacity. Detailed metrics on bladder capacity and frequency of urination during infancy are described in Table 1. In general, babies urinate 15-20 times per day with a mean void volume of approximately 60 mL during the first year of life.

<table>
<thead>
<tr>
<th>Age</th>
<th>Bladder Capacity (mL)</th>
<th>Urination Frequency per Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm baby (32 weeks)</td>
<td>12</td>
<td>22-24 times</td>
</tr>
<tr>
<td>Full term baby</td>
<td>50</td>
<td>22-24 times</td>
</tr>
<tr>
<td>1 year old</td>
<td>70</td>
<td>12-15 times</td>
</tr>
<tr>
<td>2 years old (pre-potty trained)</td>
<td>70</td>
<td>12-15 times</td>
</tr>
<tr>
<td>3 years old (post-potty trained)</td>
<td>120</td>
<td>3-7 times</td>
</tr>
</tbody>
</table>


Table 1. Bladder capacity and urination frequency during infancy

The composition and properties of human urine, both in health and disease, have been topics of extensive study. It has long been known that the composition of human urine is primarily water (95%), while the remaining constituents are urea, uric acids, salts (Na, K, Cl, P), and trace amounts of hormones and metabolites (Figure 1). However, advanced analytical technologies have recently been applied to urine analysis, enabling the identification of more than 3000 metabolites in human urine and providing new insights on urine composition and its impact on skin health.

The authors are with Life Sciences, Corporate Research & Engineering, Kimberly-Clark Corporation, Roswell GA, USA.

Figure 1. Composition of human urine.

Although basal skin barrier function of healthy full-term babies seems competent for survival in a terrestrial environment at birth, physical properties of infant skin are quite different from those of adults, as summarized in Table 2. The size (volume and surface area) of corneocytes from baby skin is 20% smaller than those derived from adult skin and the stratum corneum is 30% thinner than in adults. Corneocytes are dead skin cells that normally reside within the outermost layer of the skin, the stratum corneum, and play a key role in the skin’s barrier function. Infant skin has higher surface pH (especially in newborns), lower sebum secretion, and higher transepidermal water loss (TEWL), indicative of diminished barrier properties. However, infant skin continues to mature—especially during the first year of life. For example, acid mantle formation, which plays a pivotal role in barrier augmentation, rapidly develops during the first month after birth. It is clear that the skin microbiome evolves considerably in parallel with skin maturation following birth. Taken together, these intrinsic factors result in baby
having less resilient skin barrier function compared to that of adults.12

Table 2. Different characteristics of baby skin vs. adult skin

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Baby Skin</th>
<th>Adult Skin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epidermis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corneocytes (surface area &amp; volume)</td>
<td>Small</td>
<td>Large</td>
</tr>
<tr>
<td>Stratum Corneum Thickness</td>
<td>Thin</td>
<td>Thick</td>
</tr>
<tr>
<td>Pigmentation</td>
<td>Less</td>
<td>More</td>
</tr>
<tr>
<td>Natural Moisturizing Factor</td>
<td>Less</td>
<td>More</td>
</tr>
<tr>
<td>pH</td>
<td>High (first month)</td>
<td>Low</td>
</tr>
<tr>
<td>Sebum</td>
<td>Less</td>
<td>More</td>
</tr>
<tr>
<td>Transepidermal Water Loss</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Dermis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collagen fiber density</td>
<td>Less</td>
<td>More</td>
</tr>
<tr>
<td>Papillary-to-reticular dermis</td>
<td>Not clear</td>
<td>Clear</td>
</tr>
<tr>
<td>transition</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Modified from Telofski et al., 2012.

In addition to these intrinsic properties, diapered baby skin is frequently exposed to various extrinsic challenges. The main risk factors for diaper dermatitis include: overhydration, mechanical friction, and urine- and fecal-derived skin irritants.2,4,12 In particular, overhydration caused by prolonged urine exposure results in the outermost layers of the skin (stratum corneum) softening and weakening (maceration), thereby making the skin more susceptible to physical damage (i.e., friction) and irritant penetration.2 Warner et al. demonstrated how overhydration disorganized the physical barrier structure of skin using transmission microscopy.16 A simplified illustration describing those changes is provided in Figure 2, which includes: swelling of corneocytes; abnormal formation of large pools of water in intercellular spaces; disrupted intra-corneocyte lipid bilayer structure; and degradation of corneodesmosomes, which are the inter-intra-cellular structures required for corneocyte adhesion.16,17 In addition to these structural changes, clinical data suggest that increased skin pH is positively correlated with skin wetness.19 This correlation was also found in an in vitro skin equivalent culture,19 suggesting that high humidity may disturb acid mantle formation in skin. This is important because acid mantle formation is critical to maintaining intact barrier function. Moreover, increased skin pH is known to promote the growth of harmful microorganisms, including Candida albicans, Staphylococcus aureus, and various streptococci.20 Finally, high humidity has been shown to alter skin microflora.21 Relative to adults, baby skin is more susceptible to the intrusion of pathogens and various irritants due to both intrinsic properties and extrinsic challenges.18,22 Therefore, diaper area cleansing should be effective enough to remove potential irritants but gentle enough to preserve the skin barrier function.

Diapered Area Cleansing Following Urination: Importance and Benefits

Removing Potential Skin Irritants in Urine

Exposure to urine alone contributes less to diapered skin irritation than exposure to feces or urine and feces combined,2,3,15 however, urine components are not benign to skin health. Berg et al. explored the role of urine in the development of diaper dermatitis and found that urine increases the permeability of diapered skin to irritants and can directly irritate skin when exposure is prolonged.4 This harmful effect was not due to overhydration, as the effect of urine exposure was significantly higher than that of water (Table 3), suggesting that certain urine components accelerated skin barrier damage. The underlying mechanism has not been determined, but on possibility is that inorganic salts in urine may cause barrier damage by altering the skin electrolyte balance. Thus, if skin is not properly cleansed at each diaper change, accumulation of excess salts on the skin surface may lead to elevated TEWL, indicative of compromised skin barrier integrity.

Table 3: Skin permeation following water or urine exposure

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Permeation of 3H2O (CPM; Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occlusion only</td>
<td>12,975 ± 5,900</td>
</tr>
<tr>
<td>Water</td>
<td>17,563 ± 5,414</td>
</tr>
<tr>
<td>Baby urine</td>
<td>290,245* ± 24,600</td>
</tr>
</tbody>
</table>

Modified from Berg et al., 19864 *p ≤ 0.05 vs other treatments. Hairless mice were patched with baby urine, water, or dry patches. After 10 days of exposure, the area of skin was excised and placed on a penetration chamber as described by Cooper et al., 1984.21 Permeability of the skin was determined by measuring the penetration of a tracer molecule (3H2O) through the skin.

Except water, urea is the most abundant component (2%) of urine. It has been suggested that urea alone does not trigger significant skin irritation; however, feces is a source of the enzyme urease that produces ammonia from the urea present in urine. Thus, concurrent or subsequent exposure of urine-contaminated skin to feces can cause hydrolysis of urea to ammonia, increasing skin pH and causing skin damage. Thus, prompt removal of urine from the skin should help to maintain the ideal pH of diapered skin.

The composition of the remaining 3% of urine (beyond water and urea) seems to be much more diverse than previously understood. As mentioned previously, Bouatra et al. identified more than 3000 metabolites in human urine in a recent metabolomic study.10 Chemical subclasses and the number of metabolites in each category are described in Table 4. Given that urine is 95% water by weight and hydrophilic in nature, it is surprising that 866 different lipid molecules (hydrophobic) are present in urine. In addition, urine also contains trace amounts of bile acids. Additional research is required to explore the potential effects of these metabolites on diapered skin.10

Eliminating Odor

Residual urine on baby skin often produces unpleasant odors derived from the breakdown of urea to ammonia and other
volatiles. Thus thorough skin cleaning is necessary not only for promoting skin health, but also for preventing the emanation of odors from baby skin.

<table>
<thead>
<tr>
<th>Table 4: Chemical classes in a urine metabolome database</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemical Class</strong></td>
</tr>
<tr>
<td>Aromatic Compounds</td>
</tr>
<tr>
<td>Lipids</td>
</tr>
<tr>
<td>Amino Acids, Peptides, and Analogues</td>
</tr>
<tr>
<td>Aliphatic Acyl Compounds</td>
</tr>
<tr>
<td>Carbohydrates and Carbohydrate Conjugates</td>
</tr>
<tr>
<td>Organic Acids and Derivatives</td>
</tr>
<tr>
<td>Polyketides</td>
</tr>
<tr>
<td>Nucleosides, Nucleotides, and Analogues</td>
</tr>
<tr>
<td>Alkaloids and Derivatives</td>
</tr>
<tr>
<td>Homogeneous Metal Compounds</td>
</tr>
<tr>
<td>Others</td>
</tr>
</tbody>
</table>

Modified from Bouatra et al., 2013.

**Providing Proactive Skin Care Using Appropriately Formulated Baby Wipes**

Proper skin cleansing during diaper changes will not only effectively remove potential irritants, but can also protect skin from subsequent exposures to feces.20 Despite the common perception, many clinical studies have demonstrated that use of premoistened commercial baby wipes is safe and better for maintaining healthy baby skin when compared to cleansing regimens that use only water.24,25,26 Potential benefits of disposable wipe use have been reviewed,27,28 which have identified important skin health attributes as effective removal of skin irritants, balancing physiological skin pH, and applying emollients to protect baby skin from friction and subsequent exposures to urine and/or feces. In discussing the importance of baby wipe formulation development, Cunningham et al. suggested that the ideal composition provides skin care benefits to sensitive baby skin. For example, aqueous solutions used in baby wipes are usually formulated to have a final pH in the range of 4.5-6.5 and provide a buffering capacity to balance skin surface pH, thereby augmenting barrier integrity.20-26 Baby wipe formulations often include emollients such as behenyl alcohol, stearyl alcohol, stearic acid and triglycerides that may promote healthy baby skin by providing lipid-like properties that protect the skin surface from excessive hydration and harmful insults.28 Therefore, baby wipe use after urination should be strongly encouraged, not only for cleansing purposes (removing irritants and preventing bad odor), but also to provide proactive skin care protection in anticipation of subsequent exposures to feces.

**Conclusion**

Prolonged skin exposure to urine and feces is the primary cause of diaper dermatitis. It has been reported that 50% of babies experience this inconvenient skin irritation at some point during the first year of life.7 The incidence and severity of diaper rash can be effectively reduced through consistent use of optimal hygiene practices at each diaper change. Urine exposure can significantly disturb baby's sensitive skin, disorganizing barrier structure of the uppermost skin layer (stratum corneum), and altering skin pH and composition. Potentially harmful effects of residual inorganic salts and other compounds, including those recently identified in the technical literature, cannot be overlooked. Removing sources of odor from baby skin is another obvious benefit in addition to skin health. Thus, thorough skin cleansing using gentle premoistened baby wipes is strongly recommended with each diaper change as part of an optimal skin care regimen.

**Acknowledgement**

We would like to thank Karien Rodriguez for her thoughtful guidance on the paper.

**References**


Cunningham, Corey T., Jeffrey R. Seidling, and Wenzel, S. W.
Introduction
It is well-established that premature birth has severe consequences on both an emotional and financial level. The annual economic impact of premature birth in the United States is estimated at $26.2 billion. In extreme cases, the cost of a single preterm birth can exceed $1 million. On Long Island alone, close to 3,500 infants were born prematurely in 2014 and the overall economic burden of prematurity exceeded $180 million. Preterm birth is a multifactorial problem and no single strategy can eliminate it entirely. Risk factors contributing to preterm birth include: previous pregnancies with an adverse outcome, maternal age, maternal race, genitourinary infection, smoking, multiple gestation births, extremes of body weight, and social disadvantage. Universal cervical length monitoring (CLM) and treatment if indicated (cervical cerclage and/or progesterone therapy) have been shown to decrease the overall rate of prematurity, by approximately 34.8%. If such a screening and treatment protocol were broadly implemented over a particular geographic territory, it could potentially decrease the prevalence of preterm deliveries in that area and the host of costs and complications that accompany such deliveries.

It is important to note that this paper deals exclusively with extreme preterm deliveries defined as birth at or below 32 weeks of pregnancy. We limited our analysis to the Long Island area, therefore the underlying data both for costs of prematurity and the efficacy of the screening and treatment regimen is based upon fairly small datasets without detailed demographic information. This is relevant when including the data for the lifetime costs of cerebral palsy (a potential result of preterm labor), which are based on a national average because local cost data are unavailable.

Finally, our analysis includes only the financial costs of such births to the exclusion of emotional, psychological, and social costs of preterm deliveries.

Materials and Methods
Long Island Vital Statistics Bureau was used to obtain the information on the annual prematurity rate. The total cost of extreme prematurity was calculated using samples of hospital and health care providers bills (part A and B). The total costs of screening and treatment measures for prematurity (cervical length screening, cost of performing cervical cerclages and administering progesterone therapy, etc.) were calculated using the standard fees paid by insurance companies. The difference between those two sums is used to determine financial benefits of the universal screening, if any.

Results
There was a total of 29,907 births on Long Island (Nassau and Suffolk counties) in 2014, out of which 481 were defined as extreme preterm deliveries; 34.8%, or approximately 167 cases of which were considered preventable.

The average cost of transvaginal sonogram (TVS) on Long Island is $82.64. This yields a total expense of $12,357,572 for universal cervical screening. In addition to the cost of universal TVS screening, there will be cases where such screening is followed by treatment, which includes the cost of progesterone therapies and cerclage procedures. Assuming a cost of $4,800 per cerclage procedure (providers, anesthesia, and hospital fees) and a price of $1,000 per progesterone treatment, we find the total cost of the interventions to be $13,497,101.81 (see table 1).

Cost of prevention and treatment of premature birth in Long Island

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Price per unit</th>
<th>Number of Treatments</th>
<th>Total Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progesterone</td>
<td>$1,000.00</td>
<td>196</td>
<td>$196,470.59</td>
</tr>
<tr>
<td>Cerclage</td>
<td>$4,800.00</td>
<td>196</td>
<td>$943,058.82</td>
</tr>
<tr>
<td>TVS Cost</td>
<td>$82.64</td>
<td>149,535 (5 TVS x 29,907 pregnancies)</td>
<td>$12,357,572.40</td>
</tr>
<tr>
<td>Total Cost</td>
<td></td>
<td></td>
<td>$13,497,101.81</td>
</tr>
</tbody>
</table>

We now turn to quantifying the cost savings associated with an early intervention based on a universal regimen of TVS screening. The increased delivery and neonatal costs associated with extreme preterm birth is approximately $69,893.17. See Table 2. If 167 preterm births are avoided as a result of the universal TVS screening, the total savings is $11,672,159.
Table 2

<table>
<thead>
<tr>
<th>Case #</th>
<th>Delivery Week</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27</td>
<td>$78,000.00</td>
</tr>
<tr>
<td>2</td>
<td>26</td>
<td>$112,000.00</td>
</tr>
<tr>
<td>3</td>
<td>31</td>
<td>$89,000.00</td>
</tr>
<tr>
<td>4</td>
<td>26</td>
<td>$134,000.00</td>
</tr>
<tr>
<td>5</td>
<td>32</td>
<td>$16,000.00</td>
</tr>
<tr>
<td>6</td>
<td>27</td>
<td>$46,000.00</td>
</tr>
<tr>
<td>7</td>
<td>29</td>
<td>$52,000.00</td>
</tr>
<tr>
<td>8</td>
<td>31</td>
<td>$62,780.00</td>
</tr>
<tr>
<td>9</td>
<td>29</td>
<td>$89,680.00</td>
</tr>
<tr>
<td>10</td>
<td>29</td>
<td>$42,678.00</td>
</tr>
<tr>
<td>11</td>
<td>25</td>
<td>$92,000.00</td>
</tr>
<tr>
<td>12</td>
<td>28</td>
<td>$66,580.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Average Cost</strong> $73,393.17</td>
</tr>
</tbody>
</table>

There were 319 preterm births between 28 and 31 weeks of pregnancy and 162 prior to 28 weeks of gestation. In the 28-31 week category, there is a 5.4% chance of the neonate developing cerebral palsy, and in the pre-28 week category there was an 8% chance of cerebral palsy. Thus we can determine that there should be approximately 30 cases of Cerebral Palsy on Long Island annually, based on 2014 birth levels. Research has indicated that at least 75% of Cerebral Palsy cases are perinatal in origin, thus 23 cases of Cerebral Palsy on Long Island can be attributed to extreme preterm birth. Assuming a successful rate of intervention of 34.8%, 8 cases of cerebral palsy can be expected to be avoided through the implementation of a universal TVS screening and treatment program. With a lifetime cost of approximately $921,000 per patient, avoiding eight cases annually could result in a net savings of approximately $7,368,000 over the lifetime of the patients. The total system-wide savings resulting the broad implementation of the proposed regimen could be as high as $17,637,358.83.

**Discussion**

The core finding of this analysis is the cost effectiveness of a broad implementation of the proposed screening and treatment regimen of preterm labor in Long Island. According to our calculations, the net overall system-wide savings of implementing the proposed TVS screening and treatment program could be expected to amount to $5,543,057. This number does not include any savings associated with the avoidance of non-extreme preterm deliveries (those occurring between 32 and 38 weeks of pregnancy) or the substantial costs related to long term morbidity, which can include everything from respiratory and learning disabilities to severe physical and cognitive impairment.

While the analysis at hand is limited to the case of the Long Island area, the substantial margin of cost effectiveness strongly suggests that such measures would be cost effective throughout much of the United States. This is all before considering the likely substantial benefits that could accrue relating to all preterm deliveries, which are more prevalent and would likely be prevented by the regimen at a similar rate. While each preterm delivery between 32 and 37 weeks is less costly and the effects of such a delivery less damaging, their prevalence—approximately six times more frequent—would likely have a substantial financial benefit at minimal additional expense. More importantly, this analysis does not consider the wide variety of non-financial harms that result from both long and short-term neonatal morbidity. The financial costs of such morbidity are, likely, quite substantial, but the emotional impact for the life of the child and its family absolutely defies quantification.

**Strengths and Limitations**

The first strength of the present study is the substantial magnitude of the cost savings to be accrued. Even if various factors conspire to elevate the costs and lower the savings, the fact that the net system-wide savings exceeds one third of the overall costs of implementing the regimen create a fairly substantial margin of safety that would likely remain even if the underlying numbers shifted substantially.

The first weakness of the present study is the fairly small data set, both regarding the costs of prematurity and the efficacy of the screening and treatment regimen, upon which the study was based. Furthermore, this data lacks demographic information. The rate of cerebral palsy, even among extreme preterm deliveries, is low enough and the average associated costs high enough, that a slight divergence from the expected number of cerebral palsy cases would have an inordinate impact on the overall cost effectiveness of the regimen. However the margin of cost effectiveness adequately large that even a fairly substantial fluctuation in the number of cases would not threaten the cost effectiveness of the regimen. We must also consider the potential difficulty of convincing women to accede to the procedure and the not insignificant discomfort and inconvenience such a regimen might pose for the patient.

In conclusion, universal implementation of transvaginal ultrasound screening to detect cervical shortening and vaginal cerclage and/or progesterone therapy if needed to avoid extreme preterm delivery is a cost effective strategy on Long Island. The system-wide costs of such screening and treatment are substantially exceeded by the savings accrued by extreme preterm deliveries avoided, even without considering the, likely, substantial savings that would result from the avoided non-extreme preterm deliveries and long term morbidity.

**References**

8. This is reflective of insurance reimbursements to one of the author’s practice
The cost of a 'normal' pregnancy was estimated to be $3,500, which was subtracted from $73,393.17 to yield $69,893.17.


Introduction
World health maternity care standards recommend new mothers nurse their babies within the first hour of birth, with continuous proximity in the early postpartum period to foster natural feeding behaviors and optimal breastfeeding. Unfortunately, this is not always possible. Women with preterm, late-preterm infants or babies in NICU often experience breastfeeding delays, interruptions, or difficulties with subsequent lactation complications, most notably sub-optimal milk production.

Until recently, clinicians did not fully appreciate the complexity of the natural evolution of the maternal-child breastfeeding relationship or the impact of early infant sucking patterns on long term milk production. The purpose of this article is to discuss two evidence-based lactation initiation practices that can help mothers in special circumstances produce more milk more quickly and reach breastmilk volumes similar to women who are breastfeeding healthy term infants.

Lactation Physiology
Animal and human studies consistently indicate mammalian breasts are programmed for milk production in the early days after birth. During pregnancy, alveolar epithelial cells differentiate under the influence of estrogen, progesterone, prolactin, growth hormone and glucocorticoids into milk-secreting lactocytes. Although colostrum is often secreted in small amounts during pregnancy, copious milk production is suppressed by high doses of placental progesterone. After delivery of the placenta, progesterone withdrawal in the presence of high circulating levels of prolactin (~200 ng/mL) triggers secretory activation (also known as lactogenesis II or the process of milk “coming in”). This process occurs approximately 30-40 hours after giving birth. Under the influence of glucocorticoids, tight junctions between the lactocytes close and concentrations of milk components change. Increasing lactose concentrations draw water into the milk compartment of the alveoli causing the onset of significant milk production.

In the first few days after birth before secretory activation occurs, term breastfeeding infants exhibit an irregular, intermittent sucking pattern of rapid sucking bursts of varying lengths followed by long pauses, obtaining very small amounts of colostrum (approximately 15±11 mL per feeding). Many clinicians interpret this erratic sucking pattern as insufficient, indicating baby is sleepy and needs stimulation to awaken and feed more vigorously. However, new evidence (discussed below) suggests this behavior is natural as well as physiologically normal as it primes mothers’ breasts for later optimal milk production. If mothers are unable to breastfeed during this period, they are missing this unique sucking pattern. Once secretory activation begins, milk volumes increase from less than 100 mL per day to approximately 600 mL by day six. In response to the increased milk volume infant sucking changes to a two-phase pattern of rapid sucking prior to milk ejection followed by a slower, deeper sucking pattern for milk expression.

Mimicking Normal Newborn Sucking Pattern with a Breast Pump
Dr. Paula Meier and her team at Rush University Medical Center believed that there was a purpose to this initial irregular sucking pattern that healthy newborns exhibited in the first few days of life. As such, they hypothesized that this unique sucking pattern played a role in the initiation of lactation and the development of adequate milk production.

Since mothers of preterm infants are fully pump-dependent, the first study to investigate the role of the irregular sucking pattern in the initiation of lactation was conducted with moms of babies born less than 34 weeks. This randomized controlled trial by Meier et al compared experimental irregular sucking patterns to a standard bi-phasic pumping pattern (Symphony 2.0) with the goal to assess the influence of the pumping pattern on effectiveness and efficiency of milk removal.

All women in the study (105 completed the study) were randomized into different groups and instructed to pump for 15 minutes, eight times a day, starting with their randomized pumping pattern, either an experimental pattern or the Standard 2.0 program. Once they achieved two consecutive sessions of 20 mL or more, they switched to the Standard 2.0 program for pumping maintenance. At this point, secretory activation was beginning (the milk was “coming in”) and milk production was increasing.

Effectiveness of Initiation Technology
Meier et al reported results of multiple measures taken...
throughout two weeks of comparison. Most notably, on day four, the initiation technology group began to show significant differences in mean daily milk output. Mothers using the initiation technology were, on average, pumping 50% more milk on day four. By day seven, women in the this group had achieved 67% more milk output with significantly higher milk volumes maintained until the study was concluded on day 14.

By day six, women using the initiation program achieved similar average daily milk volumes as women breastfeeding term infants. Of note, women in the initiation technology group achieved and maintained breastmilk volumes significantly higher than volumes reported in previous studies of pump-dependent women.

This trial is an excellent example of insightful research based on observations of real-life phenomena: initial term infant sucking behaviors are natural and purposeful in establishing successful lactation. The results clearly normalize early infant behaviors as non-pathologic and support other research related to skin-to-skin time, prolonged maternal-infant contact and breastfeeding positions that maximize expression of primitive neonatal reflexes and unscheduled breastfeeding.15-18 Furthermore, the results indicate that mothers who miss the experience of breastfeeding can be supported with pumping technology to initiate and build higher milk volumes within the brief period of milk coming to volume.

The Development of Initiation Technology

The study conducted by Meier and colleagues14 led to the development of a breast pump pattern that mimics normal newborn sucking behavior. This Initiation Technology™ was developed for use with the Symphony 2.0™ breast pump and is comprised of a set timed pumping session of 15 minutes that consists of rapid shallow sucking interspersed with several long pauses and shorter bursts of deeper suction cycles. As with normal breastfeeding, once secretory activation was seen to be occurring and milk volumes begin to increase, logic dictated mothers should change to the standard Symphony 2.0 bi-phasic pattern of rapid shallow, sucking for milk ejection followed by slower, deeper cycles for milk expression. The combination of these two patterns will henceforth be referred to as initiation technology, commercially available from Medela, LLC in the Symphony™ PLUS™ breast pump.

Initiation Technology and the Term Infant

Since the publication of the study by Meier and associates,14 two other research studies have been published on the effectiveness of initiation technology with pump dependent mothers who have delivered term and late preterm infants. The first of these studies was reported by Torowitcz and colleagues15 at Children’s Hospital of Philadelphia (CHOP); this descriptive study used initiation technology with mothers of term infants with cardiac anomalies. The second study by Post et al16 described a semi-randomized trial with mothers of term, late-preterm and preterm babies who were unable to initiate early breastfeeding. Although in-depth description of these publications is beyond the scope of this article, both studies report similar findings to those of Meier et al.14 The women who used Initiation Technology™ achieved milk volumes similar to mothers that were breastfeeding healthy term infants. Additionally the time to the onset of secretory activation was faster than mothers who initiated with only the standard bi-phasic breast pump programs.

Early Initiation of Breast Pumping

Support of lactating mothers has changed dramatically in the last 20 years with more and more focus on “bringing nature to the fore”19,20 or helping mothers and babies maximize their natural instincts and reflexes to establish successful lactation. To make this possible, a new mother needs time in the first hour after birth to initiate skin-to-skin contact and introduce her breasts to her baby. As demonstrated so clearly by Colson,17,18,20-23 human infants instinctively respond to facedown, dorsal positioning on their mothers’ abdomen and chest with full body movement towards the breast and nipple, latch and early feeding.

For mothers who can’t have this experience, imitating what should naturally occur seems to help prime maternal breasts for optimal milk volumes and quicker onset of secretory activation. In other words, when a mother can’t breastfeed within the first hour she should be assisted to breast pump as soon as possible.

The 2010 Baby-Friendly USA Guidelines and Evaluation Criteria for Facilities Seeking Baby-Friendly Designation24 and the 2011 Human Milk Banking Association of North America (HMBANA) guidelines25 recommended breast pumping within six hours if a mother wants to breastfeed but hasn’t been able to start. However, more recent studies by Parker and associates26,27 suggest pumping within the first hour, just like breastfeeding in the first hour, is important to lactation success.

Early breast pumping is consistent with World Health Organization recommendations to initiate breastfeeding within 30 minutes to one hour of birth. Both practices provide breast and nipple stimulation, contributing to the cascade of physiologic and hormonal events that stimulate milk production. In 2012, Parker et al26 conducted a randomized pilot study of mothers of very low birth weight infants that suggested pumping within the first hour produces more milk and leads to an earlier onset of secretory activation than pumping one to six hours after delivery. At three weeks, milk volumes of the one-hour pumping group were also higher.

In a 2015 clinical study, Parker and associates27 continued to evaluate the importance by early pumping by comparing outcomes of mothers who initiated pumping within one hour, between one and six hours or after six hours. Study results suggest milk expression within six hours does not positively influence lactation outcomes unless a mother initiates pumping within the first hour following delivery.

Closing Remarks

This article examines initiation support strategies for mothers in special situations from an exemplar of healthy breastfeeding practices. The clinical studies discussed in this article demonstrate these benefits. Since research suggests mothers who are unable to initiate breastfeeding immediately benefit from breast pumping within the first hour and by using initiation technology that imitates early newborn sucking patterns, it would be advantageous to evaluate the cumulative benefit of combining Initiation Technology™ with early pumping on maternal milk volumes. It is clear additional research is needed to confirm clinical practices that can fully support all mothers in meeting their lactation goals.
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References

In 2006, we reported our experience with nuclear transfer from “aged” to “young” oocyte performed at Brookhaven National Laboratory in collaboration with Nassau University Medical Center (B. Petrikovsky and M. Katznelson). The idea of nuclear transfer is to introduce an original maternal DNA into the protoplasm of a younger donor egg. In vitro fertilization has given older women hope, but IVF runs up against a physiological limitation—aging eggs. No one understands exactly what happens to the eggs after several decades in the body, but doctors are convinced that old eggs are the key to age-related infertility. In 2006, we undertook a successful nuclear transfer by removing a nucleus from the “old” egg and transferred it into the donor egg after its own nucleus had been discarded (see Fig 1). Our experience showed that the so-called aging egg protoplasm deteriorates at a higher rate than a nucleus to aging. After the transfer was complete, the new egg containing the original maternal nucleus and donor protoplasm had been inserted into the surrogate mother, resulting in a successful pregnancy. Our limited experience with assessing egg aging suggests that cytoplasm is the most valuable component of the egg, while the nucleus is the most resistant. Most of the research in this area had been conducted overseas, where the political climate appears more favorable. Thus, J. Grifo from NYU, in collaboration with researchers in China, reported a triplet pregnancy after transfer of pronuclei from a patient’s zygotes into zygote cytoplasts donated by a fertile woman. The work was done at Sun Yat University Hospital, Guangzhou, (China). Similar techniques had been recently reported in successful efforts to combat mitochondrial diseases—the so-called three-parent baby. The baby was born in January 2017 in Ukraine and was created via pronuclear transfer. The mother’s egg and a donor’s egg are both fertilized by the father’s sperm. The three-parent IVF procedure for the baby born in Mexico was used because the mom was a carrier for Leigh syndrome. Male fetuses carrying donor mitochondria cannot pass their modified genetics into any children they may have because once a sperm fuses with an egg to form an embryo, the masculine mitochondrion withers and dies leaving the resulting embryo with only mitochondrion from the mother’s egg.

Related research: Collecting and preserving patient’s own ovarian tissue to combat menopause

An ovarian tissue preservation bank had been established in 2000 in collaboration with professor E. Zharov (Russian Federation) with the aim to collect and conserve ovarian tissue collected with the patient’s consent during indicated procedures (cesarean sections 15, minilaparotomies and tubal ligations in 12, gynecological surgeries for benign conditions – 22).

Cryopreservation technique

The ovary is placed in a Petri dish containing 0.9% sterile saline and the cortex is isolated using forceps. When all medullar tissue is removed and the cortex is 2 mm thick, it is cut in 5 x 5 mm pieces. The pieces are then placed in a tube containing 30 ml ice-cold cryoprotectant for 25 min. The fragments of cortex are stored in 1.8-ml cryovials, each containing 1 ml of cryoprotectant and are cryopreserved using a programmable Planner freezer. The following programme was used: 2°C/min to -9°C, 5 min of soaking, then manual seeding, 0.3°C/min to -40°C, 10°C/min to -140°C, where the vials are placed into liquid nitrogen at -196°C. Following freezing, the tubes are sealed in a second plastic holster and stored in two separate nitrogen tanks.

Since our computer-assisted search failed to find an ovarian tissue bank with similar goals, we used an experience of ovarian transplantation program in Denmark with the purpose of preserving ovarian tissue to combat infertility. The ovarian transplantation program started in Denmark in 2000 (800 women have had tissue frozen). For this study, the researchers studied the outcomes of women who had received transplantation between 2003 and June 2014. The average age of the women at the time the tissue was frozen was 29.8 years, and the average age when the first transplant was performed was 33. Out of

Figure 1. Nuclear transfer.
41 women, 32 wished to become pregnant. Ten (31%) were successful and had at least one child (14 children in total); this includes one woman who is in her third trimester of pregnancy. The functional life span of the grafts varied between 1 and 10 years; grafted tissue robustly restored ovarian functions. Three of the 41 women who received an ovarian transplant had a relapse of their cancer: two had a recurrence of their breast cancer at the site of their original tumors, and one Ewing's sarcoma patient had a relapse. The researchers are convinced that none of these relapses appeared to be related to the transplantation of ovarian tissue, and no cancer has developed in the transplanted tissue. As far as we know, this is the largest series of ovarian tissue transplantation performed worldwide, and these findings show that grafted ovarian tissue is effective in restoring ovarian function in a safe manner. In this series of women, the pregnancy rate was about 30%.

Although our patients are still years away from reaching menopause, the authors observed that in addition to enabling women to become pregnant, the restoration of ovarian function is also important for restoring normal levels of circulating sex hormones, which serve many other functions in the body, such as preventing menopausal symptoms, confirming the usefulness of our idea of the ovarian tissue bank.

References
The Successful Accomplishment of Nutritional and Clinical Outcomes Via the Implementation of a Multidisciplinary Nutrition Support Team in the Neonatal Intensive Care Unit

Eurim Jeong¹, Young Hwa Jung¹, Seung Han Shin², Moon Jin Kim³, Hye Jung Bae¹, Yoon Sook Cho¹, Kwi Suk Kim¹, Hyang Sook Kim¹, Jin Soo Moon², Ee-Kyung Kim², Han-Suk Kim³ and Jae Sung Ko⁴

Abstract

Background: Nutritional support is critical for preterm infants in the neonatal intensive care unit (NICU). A multidisciplinary nutritional support team (NST) that focuses on providing optimal and individualized nutrition care could be helpful. We conducted a thorough evaluation of clinical and nutritional outcomes in a tertiary NICU following the implementation of an NST.

Methods: This study used a retrospective approach with historical comparisons. Preterm neonates < 30 weeks gestational age or weighing < 1250 g were enrolled. Clinical and nutritional outcomes were compared before and after the establishment of the NST. Medical records were reviewed, and clinical and nutritional outcomes were compared between the two groups.

Results: In total, 107 patients from the pre-NST period and 122 patients from the post-NST period were included. The cumulative energy delivery during the first week of life improved during the post-NST period (350.17 ± 408.6 kcal/kg, p < 0.001). The cumulative protein and lipid deliveries also significantly increased. The time required to reach full enteral feedings decreased during the post-NST period (6.4 ± 5.8 vs. 4.7 ± 5.1 days, p = 0.016). Changes of Z-score in weight from admission to discharge exhibited more favorable results in the post-NST period (−1.13 ± 0.99 vs. −0.91 ± 0.74, p = 0.055), and the length of ICU stay significantly decreased in the post-NST period (81.7 ± 36.6 vs. 72.2 ± 32.9 days, p = 0.040).

Conclusions: NST intervention in the NICU resulted in significant improvements in the provision of nutrition to preterm infants in the first week of life. There were also favorable clinical outcomes, such as increased weight gain and reduced length of ICU stay. Evaluative data remain sparse in the NICU setting with premature neonatal populations; therefore, the successful outcomes identified in this study may provide support for NST practices.

Background

Multidisciplinary team involvement in providing nutritional support is recommended by the American Society for Parenteral and Enteral Nutrition (ASPSN) and the European Society for Parenteral and Enteral Nutrition (ESPEN) [1, 2]. The team’s main objective is to improve the care of sick patients, and it comprises specialists who focus on the nutritional status and management of patients who require nutritional support [3]. Appropriate nutritional support has been increasingly acknowledged as an integral component of patient management, especially for patients who require intensive care. Pollack et al. [4] reported that critically ill children with associated malnutrition have greater clinical instability and require numerous therapeutic interventions. Previous studies have demonstrated that the involvement of a nutritional support team (NST) in the care of adult patients who required nutritional support was associated with favorable patient safety and cost results [5, 6].

Nutritional support is also essential for preterm infants in the neonatal intensive care unit (NICU). Inadequate nutrient intakes, especially during the first postnatal week, may result in the poor growth of very low birth weight neonates [7]. Despite this, there was an approximately four-day reduction in the NICU stay, and a four-day increase in the length of ICU stay, which are considered significant improvements. The cumulative energy delivery and protein and lipid deliveries increased significantly during the post-NST period, and the time required to reach full enteral feedings decreased. Changes in Z-score in weight from admission to discharge were also more favorable in the post-NST period. The length of ICU stay significantly decreased in the post-NST period, and the cumulative protein and lipid deliveries also increased significantly.

Table 1: Demographics of the study population

<table>
<thead>
<tr>
<th></th>
<th>Pre-NST (n = 107)</th>
<th>Post-NST (n = 122)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA (week)</td>
<td>27 ± 3 ± 2 ± 2</td>
<td>28 ± 2 ± 2 ± 4</td>
<td>0.087</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>895 ± 260</td>
<td>952 ± 266</td>
<td>0.106</td>
</tr>
<tr>
<td>Male</td>
<td>51 (47.7)</td>
<td>50 (41.0)</td>
<td>0.310</td>
</tr>
<tr>
<td>CS</td>
<td>72 (67.3)</td>
<td>73 (59.8)</td>
<td>0.243</td>
</tr>
<tr>
<td>SGA</td>
<td>38 (35.5)</td>
<td>45 (36.9)</td>
<td>0.829</td>
</tr>
<tr>
<td>PROM</td>
<td>47 (43.9)</td>
<td>57 (46.7)</td>
<td>0.672</td>
</tr>
<tr>
<td>CAM</td>
<td>27 (25.2)</td>
<td>58 (47.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Oligohydramnios</td>
<td>21 (19.6)</td>
<td>16 (13.1)</td>
<td>0.182</td>
</tr>
<tr>
<td>PIH</td>
<td>15 (14.0)</td>
<td>16 (13.1)</td>
<td>0.842</td>
</tr>
<tr>
<td>Maternal DM</td>
<td>4 (3.7)</td>
<td>4 (3.3)</td>
<td>1.000</td>
</tr>
<tr>
<td>Prenatal steroids</td>
<td>76 (71.0)</td>
<td>69 (56.6)</td>
<td>0.023</td>
</tr>
<tr>
<td>AS 1 min</td>
<td>3.66 ± 2.06</td>
<td>4.07 ± 1.94</td>
<td>0.129</td>
</tr>
<tr>
<td>AS 5 min</td>
<td>6.02 ± 1.65</td>
<td>6.25 ± 1.75</td>
<td>0.297</td>
</tr>
<tr>
<td>RDS</td>
<td>44 (41.1)</td>
<td>72 (59.0)</td>
<td>0.007</td>
</tr>
<tr>
<td>PDA</td>
<td>81 (75.7)</td>
<td>74 (60.7)</td>
<td>0.015</td>
</tr>
</tbody>
</table>

Abbreviations: GA gestational age, SGA small for gestational age, CS caesarian section, PROM premature rupture of amniotic membrane, CAM chooroamnionitis, PIH pregnancy-induced hypertension, DM diabetes mellitus, AS Apgar score, RDS respiratory distress syndrome, PDA patent ductus arteriosus

Values are presented as means ± SDs or numbers (%)
knowledge, limited studies have investigated the effects of NSTs on preterm populations in a NICU setting.

Neonatal physiology is very different from that of adult and pediatric populations in that the neonate metabolic pathways are immature and nutrient reservoirs are limited [8]. Moreover, preterm neonates who are managed in a NICU are particularly vulnerable to these problems and often present malnutrition and poor growth [9]. As a result of prematurity, many neonates in the NICU cannot tolerate oral or enteral nutrition (EN) immediately after birth; thus, they rely heavily on parenteral nutrition (PN) for the first few weeks, and the goals of nutritional support are to provide adequate nutrition via PN to avoid nutritional deficits in the immediate post-natal period, initiate enteral feeding as soon as possible and sustain efficient EN intake to promote growth. Thus, the implementation of an NST is especially important in the NICU, where special understanding of the neonate’s physiology, nutritional requirements and tolerance levels are required. To date, published studies have seldom illustrated appropriate and comprehensive outcome measures to evaluate NST practices in preterm infants [10].

In this study, we conducted a thorough evaluation of clinical and nutritional outcomes in an NICU associated with the implementation of a multidisciplinary NST that focused on providing optimal, individualized nutrition care.

### Methods

#### Study design and population

This study was approved by the Institutional Review Board of Seoul National University Hospital. This study comprised a retrospective investigation of preterm infants who were admitted to the NICU of Seoul National University Children's Hospital between January 1, 2009, and August 31, 2010 (a period prior to the establishment of the NST) and between January 1, 2012, and August 31, 2013 (a period subsequent to NST establishment). The inclusion criteria included inborn neonates who were less than 30 weeks gestational age at birth or who had birth weights less than 1250 g. Patients diagnosed with a major congenital anomaly or inborn error of metabolism or who expired within 1 week of life were excluded.

The same feeding protocol for the initiation and advance of enteral feedings was applied throughout the entire study period. As soon as there were no contraindications for feeding, such as hemodynamic instability or abnormal abdomen, the infants began enteral feeding. The feeding volume and the rate of advance of the feedings were practiced according to the internal protocol.

Nutritional and clinical data were collected via reviews of the patients’ electronic medical records. The clinical data for the preterm infants included gestational age, birth weight, mode of delivery, length of ICU stay, and other comorbidities. The infants’ weights at admission and discharge were adjusted for gestational age with reference to the Fenton 2013 preterm growth chart [11]. The nutritional data included the daily intake of energy, protein, lipids and glucose during the first 7 days of life, the number of days to the initiation of enteral feeding, the number of days to reach full enteral feeding (>120 ml/kg/day) and the number of days on PN. The amount of energy intake was calculated by adding both non-protein and protein calories. The parenteral intake and the enteral intake were added to determine the total intake per day. Patients who were received more than 80 kcal/kg/day, which is the minimum number of calories required for growth according to ASPEN, on day 7 were reviewed [12].

#### Implementation of the NST

The NST of the Seoul National University Children’s Hospital commenced its work in the NICU in September 2010. Prior to the implementation of the NST, nutrition support was coordinated solely by the attending physician, with intermittent consultation...
with pharmacists. The aim of the NST was to provide high-quality nutritional support through the enhanced coordination of specialists from various fields, including clinical physicians from the pediatric department, pharmacists, dietitians and nurses. Tasks were based on the ASPEN and ESPEN guidelines and included screening for nutritional risk, identifying patients who require nutritional support, providing adequate nutritional management, educating the hospital staff and auditing practices.

Subsequent to the implementation of the NST, meetings were held once per week to evaluate each patient’s clinical course and nutritional requirements. Changes to be made to the parenteral or EN regimens or additional labs to be analyzed were discussed at this meeting. Future medical plans were shared to ensure that all members were aware of patient management issues. In addition, monthly conferences were held to keep team members abreast of updates and to discuss the current nutritional practices.

Parenteral support was initially managed by the NICU physicians; however, patients who required long-term PN were sometimes referred to the NST pharmacists for customized total parenteral nutrition (TPN). Once a PN referral was made, the pharmacists provided individualized TPN regimens via re-consultations or feedback modulation on a daily basis. Enteral support was managed via protocol; however, EN referrals were made to the NST dietitians.

Statistical analysis
For comparisons of categorical variables, such as the morbidity rates between the two groups, chi-squared and Fisher’s exact tests were performed. Continuous variables were compared via independent t-tests. Z-scores were evaluated using paired t-tests. Multivariate linear regression analysis was used to investigate the potential confounding factors related to the length of ICU stay. Stepwise selection was used to enter the variables into the regression model according to the default criteria (i.e., inclusion if p < 0.05 and removal if p > 0.01). A p-value < 0.05 was considered statistically significant. All statistical analyses were performed with IBM SPSS Statistics version 22 software (International Business Machines Corp., New York City, NY, USA).

Results
One hundred seven patients from the pre-NST period and 122 patients from the post-NST period were included in the study. There were no differences in the gestational age at birth (27.8 ± 2 vs. 28.1 ± 2.4 weeks, respectively) or birth weight (895 ± 260 vs. 952 ± 260 g, respectively) between the pre-NST and post-NST groups (Table 1). Maternal history of chorioamnionitis (25.2 vs. 47.9 %, respectively, p = 0.001) and respiratory distress syndrome of the newborn (41.1 vs. 59.0 %, respectively, p = 0.007) were more prevalent in the post-NST group than in the pre-NST group. Prenatal steroid use (71.0 vs. 56.6 %, respectively, p = 0.023) and treated patent ductus arteriosus (75.7 vs. 60.7 %, respectively, p = 0.015) were more prevalent in the post-NST group than in the pre-NST group.

The daily energy intake during the first week of life improved during the post-NST period (days 2–7), as did the protein intake per day (days 4–6) and the lipid intake per day (days 1–7); there was no difference in the glucose intake per day (independent t-test) (Table 2). The cumulative energy delivery during the first week of life increased from 350.2 kcal/kg in the pre-NST period to 408.6 kcal/kg in the post-NST period. The proportion of patients who received a minimum of 80 kcal/kg/day on day 7 increased from 42.1 % in the pre-NST period to 63.1 % in the post-NST period (Table 3).

All of the patients enrolled in the study received glucose and protein within 24 h of admission according to the basic institutional protocol; however, the time of lipid initiation differed on a case-by-case basis. Subsequent to the implementation of the NST, lipids were initiated earlier (3.4 ± 1.5 vs. 1.8 ± 0.8 days, p < 0.001). The initiation of enteral feeding was earlier in the post-NST period compared with the pre-NST period (6.4 ± 5.8 vs. 4.7 ± 5.1 days, p = 0.016). The time to reach full enteral feeding was significantly decreased in the post-NST period (23.5 ± 16.2 vs. 18.8 ± 12.0 days, p = 0.015), and there was an approximately four-day reduction in the duration of PN, which was borderline significant (26.5 ± 22.2 vs. 22.1 ± 14.3 days, p = 0.080). Although there were no differences in the admission Z-scores and discharge Z-scores between the pre- and post-NST periods, there was a borderline significant decrease in the downward change of Z-scores between discharge and admission in the post-NST period (−1.13 ± 0.99 vs. −0.91 ± 0.74, p = 0.055 by paired t-test).

There were no significant differences in the morbidity rate or the mortality rate between the two groups (chi-square test and independent t-test) (Table 4). However, there was a significant reduction in the mean length of ICU stay (81.7 ± 36.6 vs. 72.2 ± 32.9 days, p = 0.040). Because of the discrepancies in the basal characteristics between the two groups, multivariate linear regression was used to adjust the effects of potential confounding factors; it revealed that the involvement of the

<table>
<thead>
<tr>
<th>Table 4 Clinical outcomes of the study population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor</td>
</tr>
<tr>
<td>BPD</td>
</tr>
<tr>
<td>IVH (≥ stage 2)</td>
</tr>
<tr>
<td>PVL</td>
</tr>
<tr>
<td>NEC</td>
</tr>
<tr>
<td>ROP (operation)</td>
</tr>
<tr>
<td>Cholestasis</td>
</tr>
<tr>
<td>Sepsis</td>
</tr>
<tr>
<td>Rickets</td>
</tr>
<tr>
<td>Length of ICU stay (d)</td>
</tr>
<tr>
<td>Mortality (n)</td>
</tr>
</tbody>
</table>

Values are presented as numbers (%) or means ± SDs. Abbreviations: BPD bronchopulmonary dysplasia, IVH intraventricular hemorrhage, PVL periventricular leukomalacia, NEC necrotizing enterocolitis, ROP retinopathy of prematurity.

Table 5 Multivariate analysis of ICU length of stay

<table>
<thead>
<tr>
<th>Factors</th>
<th>Parameter</th>
<th>R² value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>54.831</td>
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<td>0.0</td>
</tr>
<tr>
<td>PDA</td>
<td>22.738</td>
<td>0.154</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>RDS</td>
<td>23.973</td>
<td>0.09</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Pre/Post-NST group</td>
<td>−10.26659</td>
<td>0.017</td>
<td>0.014</td>
</tr>
</tbody>
</table>

Adjusted for NST group (pre-NST =0, post-NST = 1), PDA, RDS, CAM, Steroid use
Abbreviations: CAM chorioamnionitis, RDS respiratory distress syndrome, PDA patent ductus arteriosus
NST independently affected the length of ICU stay \((p = 0.014)\). Moreover, NST involvement was the only factor that contributed to the reduction in the length of ICU stay, as the presence of respiratory distress syndrome and patent ductus arteriosus were related to increases in ICU hospitalization (Table 5).

**Discussion**

NST practices vary according to the hospital setting, the resources available and the patient characteristics. It is widely accepted that NST involvement is associated with many benefits; however, previous studies on this topic are mainly confined to adult populations. Thus, evaluations of the effects of an NST in a NICU setting must include outcomes appropriate to the neonatal population. However, existing data are too limited to fully describe the advantages of a functioning NST in a NICU \([10]\).

Preterm neonates exhibit physiology and tolerance that differ from adult or pediatric populations. Consequently, they require sufficient energy to sustain life, but this energy must be provided through stepwise advancements to minimize the metabolic disorders that may arise \([8, 12]\). In general, it is assumed that poor growth in preterm infants primarily reflects inadequate nutrient intake \([13]\). The ASPEN guideline states that in the presence of adequate protein intake, adequate weight gain occurs at a parenteral energy intake of 80 to 130 kcal/ kg/day, which was more achieved by day 7 after NST implementation in the present study \([12]\). NST intervention reduced the lag time for lipid administration, which enabled more adequate calorie provisions and prevented essential fatty acid deficiencies. Previously, the conventional practice was to withhold lipids in cases of septic conditions, high serum bilirubin levels or pulmonary insufficiency \([8]\). Studies regarding lipid administration have demonstrated conflicting results \([14]\); however, current recommendations state that jaundice and sepsis are not absolute contraindications, and most authors now recommend the early initiation of lipids and the advancement to sufficient amounts when tolerated \([12, 15–18]\). Critical illness induces an increased demand for lipids because of the increased rate of fat oxidation; because children and neonates have limited fat stores, they are susceptible to fatty acid deficiency if they are given a fat-free diet \([18, 20]\).

One of the main functions of a NICU NST that differs from an adult NST is the promotion of appropriate growth \([8, 10]\). Reassessments of whether patients were maintaining normal growth rates and calorie requirements were routinely performed following the NST implementation. One study evaluated the effect of an NST on the growth rates of a neonatal population \([10]\) and indicated that a greater weight gain from birth to discharge was attained following NST implementation. The advantage of the present study is that weight was modified by age using Z-scores, which provide a better assessment of weight change compared to previous studies.

Serious complications resulting from prolonged parenteral access cannot be overlooked. Preterm neonates in a NICU exhibit many risk factors that necessitate long-term parenteral access; thus, the restriction of unnecessary PN use is important. In our study, the mean duration of PN along with the time to reach full enteral feedings was decreased. This difference is likely because of the NST intervention, which included weekly meetings that encouraged active discussions of plans for enteral advancements or various other strategies to improve nutrition access. However, despite the early transition from PN to EN, there were no significant decreases in culture-proven sepsis, rickets or cholestasis.

In the present study, the most notable clinical effect was the reduced mean length of ICU stay by approximately 9 days. Multivariate regression analysis indicated that only the implementation of the NST was significantly and independently associated with a decrease in the length of ICU stay after adjustment for the clinical differences between the two groups. According to previous studies in adult populations, the implementation of early, high-quality nutrition therapy may reduce the length of hospital stay, and several studies also indicate that this approach is cost effective \([5, 21]\).

There are several limitations to the study because it comprises a retrospective analysis with historical comparisons. In the post-NST period, micronutrients, such as trace elements and vitamins, were delivered and monitored more regularly than they were in the pre-NST period; however, comparisons were not possible because of the lack of pre-NST data. Moreover, evaluations of the long-term effects of NST implementation, such as neurodevelopmental outcomes, were not assessed in this study.

**Conclusion**

NST intervention in the NICU resulted in significant improvements in the provision of nutrition to preterm neonatal patients. The general nutritional practices improved following NST implementation, and this improvement correlated with important clinical outcomes, such as weight gain or length of ICU hospitalization. Evaluable data remain sparse in the NICU setting with premature neonatal populations; therefore, the successful outcomes identified in this study may provide support for NST practices.

**Authors’ contributions**

EJ and YHJ conceptualized and designed the study, and wrote the first draft of the manuscripts. SHS conceptualized and designed the study and reviewed and revised the manuscripts. MJK, HJB, YSC extracted the relevant data from the database. KSK, HSK participated in conducting the study and analyzing the data. JSM, E-KK, HSK, JSK conceived of study, participated in coordinating study and revised the manuscript for important intellectual content. All authors read and approved the final version of the manuscript.

**References**


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Comparison of Sodium Ion Levels Between an Arterial Blood Gas Analyzer and an Autoanalyzer in Preterm Infants Admitted to the Neonatal Intensive Care Unit: a Retrospective Study

Hyunho Kim¹, Jin Kyu Kim¹,² and Soo Chul Cho¹,²

Abstract

Background: The difference in sodium ion levels determined with direct and indirect methods often exceeds the permissible limit clinically. Additionally, no previous study has assessed the difference in the sodium ion levels between direct and indirect methods in premature infants. Therefore, the present study aimed to compare sodium ion levels obtained using an arterial blood gas analyzer (ABGA; direct method) and an autoanalyzer (indirect method) to determine whether they are equivalent in premature infants.

Methods: The present retrospective study included 450 preterm infants (weight, <2500 g) who were admitted to the neonatal intensive care unit (NICU) of our hospital between March 2012 and April 2014. We compared sodium ion levels in 1041 samples analyzed using an ABGA (Stat Profile® CCX Series, Nova Biomedical, Waltham, MA) and an autoanalyzer (ADVIA® 2400 Clinical Chemistry System, Siemens, Tarrytown, NY). The data were evaluated using Spearman’s correlation coefficient analysis, Bland-Altman plot, Deming regression analysis, and multivariate logistic regression analysis.

Results: The mean sodium ion levels were 134.6 ± 3.5 mmol/L using the ABGA and 138.8 ± 4.7 mmol/L using the autoanalyzer (P < 0.001). Among the 1041 samples, 957 (91.9 %) showed lower sodium ion levels with the ABGA than with the autoanalyzer and 74 (7.1 %) showed lower sodium ion levels with the autoanalyzer than with the ABGA. The incidence of hyponatremia identified using the ABGA was 51.9 % (541/1041), while the incidence of hyponatremia identified using the autoanalyzer was only 14.0 % (146/1041). The Deming regression analysis of the sodium ion levels between the ABGA and the autoanalyzer yielded the following formula: autoanalyzer Na (mmol/L) = 20.7 + (0.9 × ABGA Na [mmol/L]). In the multivariate logistic regression analysis, low plasma protein level (<4.3 g/dL) was found to be an independent risk factor for a sodium ion level difference of >4 mmol/L between the two methods (odds ratio = 2.870, P < 0.001).

Conclusion: The sodium ion levels determined using the ABGA and the autoanalyzer might not be equivalent in premature infants admitted to the NICU. Therefore, clinicians should be careful when diagnosing sodium ion imbalance in premature infants and providing treatment.

Background

Sodium is an essential electrolyte in the intracellular and extracellular fluids of the body. Metabolism is closely associated with sodium, and an imbalance in the sodium ion levels can result in serious life-threatening conditions [1–3]. In the neonatal intensive care unit (NICU), preterm infants are at high risk for an imbalance in the sodium ion levels because of renal immaturity, renal failure, diuretics use, and fluid management. Therefore, it is very important to frequently determine sodium ion levels in preterm infants.

Direct and indirect ion-sensitive electrodes have been used for electrolyte analysis in recent years. The direct electrode analyzes undiluted whole blood. An arterial blood gas analyzer (ABGA) incorporates a direct electrode. An ABGA is useful method to evaluate baby constantly and requires small amounts of blood. The indirect electrode, incorporated in an automated analyzer, analyzes diluted plasma. It is generally used in central hospital laboratories.

The United States Clinical Laboratory Improvement Amendments (US CLIA) 1988 rules allow for a difference of up to 4 mmol/L in the sodium ion levels [4]. However, the difference in the sodium ion levels between the two types of methods often exceeds the limit clinically. The difference in the sodium ions levels could be caused by a variety of factors, including equipment, transport containers, albumin levels, protein levels, and the patient’s medical condition [5–8]. No previous study has assessed the difference in the sodium ion levels between the direct and indirect methods in premature infants. We hypothesized that sodium ion levels obtained using an autoanalyzer (indirect method) and an ABGA (direct method) are equivalent. The present study aimed to compare sodium ion levels between an autoanalyzer and an ABGA to test this hypothesis.

Methods

The present study included inborn preterm infants (weight, <2500 g) who were admitted to the NICU of Chonbuk National University Hospital between March 2012 and April 2014. We retrospectively analyzed the patient data from the database of the NICU and identified 450 patients who underwent arterial blood collection for electrolyte analysis using both an ABGA and an autoanalyzer.
were diagnosed with hyponatremia, and those with a normal. Patients with a serum sodium ion level <135 mmol/L was considered hyponatremia and hypernatremia according to the indirect method, the sodium ion levels in preterm infants simultaneously determined using the arterial blood gas analyzer was within the acceptable limit defined in the US CLIA 1988 rules. Although the mean difference of 1.0 mmol/L in patients with hyponatremia was within the acceptable limit defined in the US CLIA 1988 rules, it was statistically significant (P < 0.001) (Table 2). The incidence of hyponatremia identified using the ABGA was 51.9 % (541/1041), while the incidence of hyponatremia identified using the autoanalyzer was only 14.0 % (146/1041).

A P-value <0.05 was considered to indicate a statistically significant difference.

### Results

The study analyzed data from 450 infants (1041 samples) admitted to the NICU. The gestational age of the infants was 31.4 ± 3.5 weeks, and the body weight of the infants was 1605.4 ± 513.3 g. The average time of sample collection was 10.0 ± 12.9 days after the admission to the NICU. Samples were collected on admission and every week. The sodium ion levels did not differ between time points of sample collection. The sodium ion levels were 134.6 ± 3.5 mmol/L using the ABGA and 138.8 ± 4.7 mmol/L using the autoanalyzer (Table 1).

The mean difference was 4.2 ± 3.6 mmol/L (P < 0.001), correlation coefficient (R) was 0.682, and adjusted R² was 0.43 with a 95 % confidence interval of 3.96–4.39.

Among the 1041 samples, 957 (91.9 %) showed lower sodium ion levels with the ABGA than with the autoanalyzer and 74 (7.1 %) showed lower sodium ion levels with the autoanalyzer than with the ABGA. A Bland-Altman comparison of sodium ion levels between the ABGA and the autoanalyzer showed that the limits of agreement were −2.8 to 11.1 (Fig. 1). The Deming regression analysis of the sodium ion levels between the ABGA and the autoanalyzer yielded the following formula: autoanalyzer Na (mmol/L) = 20.7 + (0.9 × ABGA Na [mmol/L]) (Fig. 2).

Among the patients with normal sodium ion levels and hypernatremia according to the indirect method, the mean differences in the sodium ion levels between the two methods were 4.2 ± 2.9 and 9.9 ± 3.7 mmol/L, respectively (P < 0.001), exceeding the acceptable limit defined in the US CLIA 1988 rules. Although the mean difference of 1.0 mmol/L in patients with hypernatremia was within the acceptable limit defined in the US CLIA 1988 rules, it was statistically significant (P < 0.001) (Table 2). The incidence of hypernatremia identified using the ABGA was 51.9 % (541/1041), while the incidence of hypernatremia identified using the autoanalyzer was only 14.0 % (146/1041).

### Statistical methods

Means, standard deviations, and coefficients of variation were calculated. A paired t-test was used to compare the sodium ion levels of the ABGA and the autoanalyzer. A Bland-Altman analysis was performed to assess the differences in the sodium ion levels between the ABGA and the autoanalyzer. The factors assessed were gestational age, birth body weight, protein levels, and albumin levels. All statistical analyses were performed using SPSS version 18.0 (IBM Corp., Armonk, NY) and MedCalc Statistical Software version 15.8 (MedCalc Software, Mariakerke, Belgium).

![Fig. 1 Bland-Altman plot of sodium ion levels determined using the arterial blood gas analyzer and autoanalyzer. The horizontal axis shows the mean of the sodium ion level determined using the blood chemistry test and the sodium ion level measured with the ABGA, while the differences in the sodium ion levels between the arterial blood gas analyzer and the autoanalyzer are presented on the Y-axis. Circles indicate low serum protein level (<4.3 g/dL), while triangles indicate high serum protein level (≥4.3 g/dL).](image-url)
In the univariate analysis, a significant association was found between a sodium ion difference of $>4$ mmol/L and the plasma protein level. In the multiple logistic regression analysis, the plasma protein level was identified as an independent risk factor for a sodium ion level difference of $>4$ mmol/L between the methods (odds ratio = 2.870, $P < 0.001$) (Table 3).

**Discussion**

In the present study, we found that the sodium levels in preterm infants simultaneously determined using an ABGA and an autoanalyzer were significantly different.

In correlation analysis, a close relationship was identified in the sodium ion levels between the ABGA and the autoanalyzer ($R^2 = 0.44$). However, the mean difference (4.2 mmol/L) exceeded the limit imposed by the US CLIA 1988 rules (4 mmol/L) [4]. Additionally, the mean difference was highest in patients with hypernatremia (9.9 mmol/L). In multiple logistic regression analysis, the plasma protein level was identified as an independent risk factor for a sodium ion level difference of $>4$ mmol/L between the methods.

The difference in the sodium ion levels between the ABGA and the autoanalyzer might be explained by various factors. Collection and transportation of the samples might have contributed to the difference in the sodium ion levels. However, the heparin syringe used in this study for sample collection for the ABGA includes lyophilized lithium heparin (spray-dried calcium-balanced lithium heparin), and this syringe has been shown to rarely cause bias [5, 9]. The blood collection tube used in this study for sample collection for the autoanalyzer is a microtube containing the clot activator SSTTM Gel. Because the microtube is filled with only 400–600 μL of blood, bias is minimal.

Previous studies have shown that solid elements of blood, including proteins and lipids, can cause a false diagnosis of hyponatremia (pseudohyponatremia) via an electrolyte exclusion effect when an indirect method is used [4, 10, 11]. It is known that younger and smaller infants tend to have low protein levels initially. In the present study, the sodium ion levels determined using the indirect method were higher than those determined using the direct method. Moreover, the difference in the sodium ion levels exceeded 4 mmol/L more often in infants with low plasma protein level (<4.3 g/dL) than in those with high plasma protein level (≥4.3 g/dL). Previous studies in adults showed that the difference in the sodium ion levels between the two methods can be large in patients with hypoalbuminemia and low serum total protein [6, 12].

The sodium ion levels determined using the ABGA and the autoanalyzer were not equivalent in premature infants admitted to the NICU. Therefore, clinicians should be careful when diagnosing sodium ion imbalance and devising treatment. In particular, the difference between the two methods can lead to inaccurate anion gap measurement, resulting in incorrect determination of metabolic status [13]. For correcting inconsistencies for adults with abnormal protein levels, especially for those with multiple myeloma, some hospitals use a compensation equation [14]. However, there was no previous study on the difference in the sodium ion levels between the direct and indirect methods in premature infants, and the critical difference in the neonatal period has not been determined. Our study clarifies the difference in the sodium ion levels between the direct and indirect methods in premature infants. The use of a compensation equation in each hospital is a possible solution to overcome the inconsistency in sodium ion levels assessed using the direct and indirect methods. Additionally, the direct method might be preferable [4, 6]. The direct method is not influenced by the solid components of blood, which could lead to a false result, and does not require dilution of the sample; therefore, the direct method is considered to be more accurate and consistent for the evaluation of sodium ion levels than the indirect method [12].

The main limitation of the present study is its retrospective design. However, the samples analyzed using the ABGA and the autoanalyzer were obtained at the same time points. Another limitation is that the levels of lipid, one of the solid components of blood, were not measured routinely, precluding the analysis of the effect of lipid on the difference in sodium levels determined with the two methods. Despite these limitations, the results can be used for more precise determination of sodium levels in preterm infants, and are therefore important.

**Table 2**

<table>
<thead>
<tr>
<th>Indirect Method (mmol/L)</th>
<th>Sodium concentration (Auto-analyzer – ABGA) Cases (N=1041)</th>
<th>Mean</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;135</td>
<td>146</td>
<td>1.0 ± 2.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>135–145</td>
<td>815</td>
<td>4.2 ± 2.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;145</td>
<td>80</td>
<td>9.9 ± 3.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total</td>
<td>1041</td>
<td>4.2 ± 3.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD

The sodium ion levels determined using the ABGA and the autoanalyzer might not be equivalent in premature infants admitted to the NICU. Although the direct method has been shown to be suitable for assessing sodium ion levels in previous
studies, these studies were performed in adults; therefore, clinicians should be careful when diagnosing sodium ion imbalance in premature infants and providing treatment. Further studies are needed to determine the factors responsible for the inconsistency in the sodium ion levels between the direct and indirect methods.

Authors’ contributions
Study conception and design: JKK. Acquisition of data: HK and JKK. Analysis and interpretation of data: JKK and SCC. Preparation, critical revision: HK and JKK. All authors have read and approved the final version of the manuscript.

References

Table 3 Unadjusted and adjusted odds ratios for the risk of exceeding the upper limit of the sodium ion level (4 mmol/L) according to the protein and albumin levels [15–17]

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases (N = 1041)</th>
<th>Unadjusted</th>
<th>Adjusted</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>OR</td>
<td>95 % CI</td>
</tr>
<tr>
<td>Gestational age (wk)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 34</td>
<td>700</td>
<td>0.914</td>
<td>0.705–1.185</td>
</tr>
<tr>
<td>≥ 34</td>
<td>341</td>
<td>1.000</td>
<td>(Reference)</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1500</td>
<td>442</td>
<td>1.071</td>
<td>0.837–1.370</td>
</tr>
<tr>
<td>≥ 1500</td>
<td>599</td>
<td>1.000</td>
<td>(Reference)</td>
</tr>
<tr>
<td>Protein (g/dL)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>&lt; 4.3</td>
<td>147</td>
<td>2.565</td>
<td>1.779–3.698</td>
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<tr>
<td>≥ 4.3</td>
<td>894</td>
<td>1.000</td>
<td>(Reference)</td>
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<tr>
<td>Albumin (g/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 2.2</td>
<td>1024</td>
<td>0.981</td>
<td>0.435–2.210</td>
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<tr>
<td>≥ 2.2</td>
<td>17</td>
<td>1.000</td>
<td>(Reference)</td>
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<tr>
<td>Sampling day (d)</td>
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<tr>
<td>≤ 7</td>
<td>708</td>
<td>1.360</td>
<td>1.045–1.769</td>
</tr>
<tr>
<td>&gt; 7</td>
<td>333</td>
<td>1.000</td>
<td>(Reference)</td>
</tr>
</tbody>
</table>

OR odds ratio, 95 % CI 95 % confidence interval
Predictors of Neonatal Abstinence Syndrome in Buprenorphine Exposed Newborn: Can Cord Blood Buprenorphine Metabolite Levels Help?

Darshan Shah1, Stacy Brown2, Nick Hagemeier3, Shimin Zheng4, Amy Kyle2, Jason Pryor5, Nilesh Dankhara1 and Piyuesh Singh1

Abstract

Background: Buprenorphine is a semi-synthetic opioid used for the treatment of opioid dependence. Opioid use, including buprenorphine, has been increasing in recent years, in the general population and in pregnant women. Consequently, there has been a rise in frequency of neonatal abstinence syndrome (NAS), associated with buprenorphine use during pregnancy. The purpose of this study was to investigate correlations between buprenorphine and buprenorphine-metabolite concentrations in cord blood and onset of NAS in buprenorphine exposed newborns.

Methods: Nineteen (19) newborns who met inclusion criteria were followed after birth until discharge in a double-blind non-intervention study, after maternal consent. Cord blood and tissue samples were collected and analyzed by liquid chromatography–mass spectrometry (LC–MS) for buprenorphine and metabolites. Simple and multiple logistic regressions were used to examine relationships between buprenorphine and buprenorphine-metabolite concentrations in cord blood and onset of NAS, need for morphine therapy, and length of stay.

Results: Each increase in 5 ng/ml level of norbuprenorphine in cord blood increases odds of requiring treatment by morphine 2.5 times. Each increase in 5 ng/ml of buprenorphine-glucuronide decreases odds of receiving morphine by 57.7%. Along with concentration of buprenorphine metabolites, birth weight and gestational age also play important roles, but not maternal buprenorphine dose.

Conclusions: LC–MS analysis of cord blood concentrations of buprenorphine and metabolites is an effective way to examine drug and metabolite levels in the infant at birth. Cord blood concentrations of the active norbuprenorphine metabolite and the inactive buprenorphine-glucuronide metabolite show promise in predicting necessity of treatment of NAS. These finding have implications in improving patient care and reducing healthcare costs if confirmed in a larger sample.

Background

In recent years, there has been a rise in opioid-related drug use among pregnant women, specifically buprenorphine-containing medications (Eichel and Johannemann 2014). Buprenorphine is Food and Drug Administration (FDA)-approved for detoxification and maintenance therapy for opioid dependence, and is more frequently used in pregnancy than methadone due to better neonatal outcomes (Gugelmann and Nelson 2012; Jones et al. 2010; Prabhakar 2014). Maternal substance use disorder and development of neonatal abstinence syndrome (NAS) poses significant health problems for both woman and newborn with probable long term neurodevelopment adverse outcomes (Burns and Mattick 2007; Kellogg et al. 2011; SAMHSA 2010). From 1995 to 2009, cases of NAS have increased from 0.4 to 4.4 discharges per 1000 live births, representing what many feel is a national public health epidemic (Burns and Mattick 2007; Kellogg et al. 2011; SAMHSA 2010). Despite the rise in numbers for opioid-related NAS, predicting which infants will develop NAS following prenatal opioid exposure remains clinically difficult. Uncertainty of prediction of NAS requires all infants exposed to opioids during pregnancy to stay in the hospital for 5 days, which further increases cost of care. To that end, we investigated the possibility of drug-concentration and metabolite-concentration measurements as a predictor for the development and severity of NAS in exposed infants. In this study, we examine correlates of newborn cord blood buprenorphine and metabolite concentrations and the need to initiate opioid replacement therapy in the newborn, maternal buprenorphine dose, total morphine dose required for withdrawal, the duration of replacement therapy, and the length of neonatal intensive care unit (NICU) stay. Buprenorphine is metabolized by a Phase I oxidation to norbuprenorphine, which is a more potent mu-opioid agonist compared to buprenorphine, and Phase II metabolites include inactive glucuronide forms of buprenorphine and norbuprenorphine, all of which are monitored in our study (Oechsler and Skopp 2010). Additionally, we utilized a unique sample matrix, the newborn cord blood, in order to ensure measurable concentrations of the water-soluble metabolites. This work presents a newer approach for investigating predictors of NAS, and utilizes state-of-the-art analytical technology (LC–MS) with a sample matrix suitable for the quantification of drug metabolites.
Table 1 Sample descriptive statistics (N = 19)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of NICU stay (days)</td>
<td>6.5 (9.2)</td>
</tr>
<tr>
<td>Duration of morphine therapy (days)</td>
<td>5.1 (8.3)</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>38.5 (1.4)</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>2.9 (0.39)</td>
</tr>
<tr>
<td>Maternal daily buprenorphine dose (mg)</td>
<td>11.2 (6.3)</td>
</tr>
<tr>
<td>Buprenorphine concentration (ng/ml)</td>
<td>9.0 (6.7)</td>
</tr>
<tr>
<td>Norbuprenorphine concentration (ng/ml)</td>
<td>13.9 (7.8)</td>
</tr>
<tr>
<td>Buprenorphine-glucuronide concentration (ng/ml)</td>
<td>14.0 (8.2)</td>
</tr>
<tr>
<td>Norbuprenorphine-glucuronide concentration (ng/ml)</td>
<td>23.3 (15.5)</td>
</tr>
</tbody>
</table>

Methods

Clinical sample collection

The protocol for this project was approved by our university’s Institutional Review Board (IRB), and represented a prospective, double-blind, non-interventional study. Women undergoing substance use disorder therapy were identified by history on presentation to the labor and delivery unit. Informed consent was obtained prior to delivery for those who met inclusion criteria for study. Inclusion criteria were gestational age more than 36 weeks, absence of congenital anomaly and no poly substance use. After delivery, cord blood was collected in ETDA–treated tubes and stored in a laboratory freezer (–20 °C) until analysis. Batches of samples were dispatched to the liquid chromatography–mass spectrometry (LC–MS) laboratory for quantification of buprenorphine and related metabolites. Analysts were blinded to maternal medication history. Cord tissue samples were also collected from all neonates and sent to a separate laboratory as per institutional guidelines. All neonates were then followed based on hospital protocol for the development of NAS, diagnosed using the Finnegan scoring system at 4 h intervals by trained nursing staff (Finnegan et al. 1975). Neonates with two Finnegan scores greater than 10, consecutively verified by separate nursing staff members, were transferred to the NICU, and started on morphine treatment. Morphine was started at 0.1 mg/kg every 4 h orally. Infants were weaned on doses of morphine at a rate of 10–20% per day when Finnegan scores were below 7 for 24 h, and based on the infant’s clinical examination at the discretion of attending neonatologist.

Morphine was discontinued when the dose reached less than 0.03 mg/kg per dose. Once weaned from morphine therapy, infants were monitored for 48 h prior to discharge. Results of cord blood metabolite were not available to clinical staff that cared for infants exposed to maternal drugs, but results of cord tissue were available.

Analysis of cord blood samples

Cord blood samples were spiked with deuterium-labeled internal standards purchased from Cerilliant (RoundRock, TX). Samples were subjected to protein precipitation and solid-phase extraction (SPE) using Strata-X Drug B cartridges from Phenomenex (Torrance, CA). Chromatographic separation was carried out using a Phenomenex Kinetex C18 column (1.9 micron, 2.1 × 50 mm), and mass spectrometric detection was achieved using a Shimadzu LCMS–IT–TOP system operating in positive electrospray (ESI) mode (Columbia, MD). The LC–MS method utilized has been previously validated and published (Kyle et al. 2015).

Statistical methods

Patient specific data were entered into a Microsoft Excel spreadsheet, cleaned, and thereafter imported into IBM SPSS Statistics version 20 (Armonk, NY) for analysis. Descriptive statistics were calculated for all variables. Simple logistic regressions were performed to assess the relationship between buprenorphine and metabolite cord blood concentrations and neonatal and maternal characteristics and necessity (yes/no) of morphine therapy. We converted odds ratios (OR) to effect size (ES) to find real associations, rather than p value to assess statistical significance, due to the study’s small sample size. Multiple logistic regressions were conducted for norbuprenorphine and buprenorphine-glucuronide cord blood concentration based on simple logistic regression.

Results

Patient population

A total of 19 women were enrolled for this study. Fifteen women were on Subutex™ (buprenorphine) and 4 were on Suboxone™ (buprenorphine and naloxone). All infants were from gestational age 36–41.2 weeks with mean of 38.5 weeks. Demographics of infants and their course and results from the LC–MS cord blood analysis are presented in Table 1. All women had history of smoking but no poly drug use.

Table 2 Sample descriptive statistics and outcomes of simple logistic regression analyses examining relationships between buprenorphine and metabolite cord blood concentrations and neonate and maternal characteristics, and necessity (yes/no) of morphine replacement therapy* (N = 19)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (SD)</th>
<th>Morphine replacement therapy necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95 % CI)</td>
<td>Effect size</td>
</tr>
<tr>
<td>Duration of NICU stay (days)</td>
<td>6.6 (9.2)</td>
<td>NA</td>
</tr>
<tr>
<td>Duration of morphine therapy (days)</td>
<td>5.1 (8.3)</td>
<td>NA</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>38.5 (1.4)</td>
<td>1.88 (0.12–29.78)</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>2.9 (0.39)</td>
<td>3.10 (0.23–42.65)</td>
</tr>
<tr>
<td>Maternal daily buprenorphine dose (mg)</td>
<td>11.2 (6.3)</td>
<td>1.01 (0.87–1.18)</td>
</tr>
<tr>
<td>Buprenorphine concentration (ng/ml)</td>
<td>9.0 (6.7)</td>
<td>0.97 (0.83–1.12)</td>
</tr>
<tr>
<td>Norbuprenorphine concentration (ng/ml)</td>
<td>13.8 (8.0)</td>
<td>1.92 (0.86–4.16)</td>
</tr>
<tr>
<td>Buprenorphine-glucuronide concentration (ng/ml)</td>
<td>14.0 (8.2)</td>
<td>0.46 (0.20–1.06)</td>
</tr>
<tr>
<td>Norbuprenorphine-glucuronide concentration (ng/ml)</td>
<td>23.3 (15.5)</td>
<td>0.98 (0.92–1.04)</td>
</tr>
</tbody>
</table>

OR odds ratio, 95 % CI 95 % confidence interval around odds ratio

* A statistically significant adjusted odds ratio greater than 1 indicates increased odds of morphine replacement therapy necessity/NICU transfer
neonatal INTENSIVE CARE  Vol. 30 No. 2 • Spring 2017

Table 3  Multiple logistic regression modeling of morphine replacement therapy necessity (yes/no) across norbuprenorphine and buprenorphine-glucuronide cord blood concentration

<table>
<thead>
<tr>
<th>Variable</th>
<th>B coefficient</th>
<th>Standard error</th>
<th>aOR</th>
<th>95% CI</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norbuprenorphine (5 ng/ml)</td>
<td>0.918</td>
<td>0.575</td>
<td>2.504</td>
<td>0.812–7.726</td>
<td>0.507</td>
</tr>
<tr>
<td>Buprenorphine-glucuronide (5 ng/ml)</td>
<td>−0.860</td>
<td>0.448</td>
<td>0.423</td>
<td>0.176–1.019</td>
<td>0.475</td>
</tr>
</tbody>
</table>

aOR adjusted odds ratio, 95% CI 95% confidence interval around odds ratio

Cord blood concentrations and opioid therapy characteristics

Table 2 presents sample descriptive statistics and outcomes of simple logistic regression analyses examining relationships between buprenorphine and metabolite cord blood concentrations and neonatal and maternal characteristics, and necessity (yes/no) of morphine therapy. We converted odds ratios (OR) to effect size due to small sample size. Based on effect size, gestational age (4 weeks), birth weight (kg), norbuprenorphine concentration (5 ng/ml) and buprenorphine-glucuronide concentration (5 ng/ml) were associated with necessity (yes/no) of morphine therapy. Associations were strongest for birth weight (kg) and buprenorphine-glucuronide concentration (5 ng/ml). However, maternal daily buprenorphine dose, buprenorphine concentration (ng/ml) and norbuprenorphine-glucuronide concentration (ng/ml) were not associated with necessity of morphine therapy. For every increase of 1 week in gestational age from 36 to 40 weeks, the odds of necessity of morphine therapy increases 8%. For every increase of one kg in birth weight, the odds of necessity increase 3.1 times. For every increase of 5 ng/ml in norbuprenorphine concentration, the odds of necessity increase 92%. For every increase of 5 ng/ml in buprenorphine-glucuronide concentration, the odds of necessity decrease 54%.

As shown in Table 3, multiple logistic regressions were conducted for norbuprenorphine and buprenorphine-glucuronide concentration in cord blood. Maternal daily buprenorphine dose, cord blood buprenorphine and norbuprenorphine-glucuronide concentration were not included since they were not associated with morphine therapy necessity based on simple logistic regression modeling. Gestational age and birth weight were not selected for the final model since there are correlated. The adjusted odds ratios for norbuprenorphine is 2.504, which indicates that for every increase of 5 ng/ml in norbuprenorphine cord blood concentration the odds of morphine therapy need increases 2.5 times, controlling for buprenorphine-glucuronide. On the other hand, the adjusted OR for buprenorphine-glucuronide is 0.423, which indicates that for every increase of 5 ng/ml in buprenorphine-glucuronide, the odds of necessity decreases 57.7% controlling for norbuprenorphine.

Discussion

Fetal outcomes resulting from maternal opioid exposure depend on multiple variables, resulting in uncertainty of development of NAS in the newborn (Malek and Mattison 2011). Recent literature suggests 22–67% infants present with NAS when prenatally there is a history of buprenorphine intake (Lacroix et al. 2011; Patel et al. 2013; Welle-Strand et al. 2012). In our study, that incidence is 30% (7/19), which is in the range of what has been previously reported. However, the wide range of reported NAS incidence with buprenorphine use is indicative of the unpredictability of this syndrome following maternal use of buprenorphine. One factor that may contribute to this range includes variability in buprenorphine pharmacokinetics associated with CYP3A and CYP2C8, with heightened variation in CYP3A during pregnancy (Elkader and Sproule 2005; Lewis and Dinh 2015). Additionally, CYP2C8 is thought to be highly inducible, whereas the UGT isozymes responsible for Phase II metabolite formation may be less affected by pregnancy, thus implying a higher burden of active drugs with reduced conjugation (Isøherranen and Thummel 2013; Lewis and Dinh 2015). Metabolism within the placenta may also play a significant role in variations in fetal drug exposure to buprenorphine. Conversion of buprenorphine by aromatase (CYP19) to active norbuprenorphine increases with gestational age, thus supporting our results tying birth weight and gestational age to the development of NAS (Fokina et al. 2011), and CYP19 expression in syncytiotrophoblasts has been shown to be subject to genetic variation (Kumar and Mendelson 2011). Another possibility for explaining differences in NAS treatment needs lies in the individual infant’s expression of P-glycoprotein, an efflux transporter present in the placenta. Nekhayeva et al. (2006) demonstrated that this transporter is active against the parent drug, buprenorphine, among other xenobiotics. Finally, the impact of single nucleotide polymorphisms (SNPs) in opioid disposition genes has been investigated to reveal that variants in the OPRM1 118A-G and COMT 155A-G may be linked to lower NAS severity (Wachman et al. 2013).

To our knowledge, this is the largest study to date that has looked at umbilical cord plasma level of buprenorphine and its metabolites, to correlate these quantitative markers with neonatal course in NAS. Previous work by Conchiero and colleagues showed that buprenorphine metabolite concentrations could not predict the development of NAS (n = 5) (Conchiero et al. 2010a, b). Our data, although also limited by a small sample size, suggest that norbuprenorphine and the inactive glucuronide conjugate of buprenorphine can be useful in this respect. These data are in line with evidence presented in a review by Lewis et al., indicating a higher rate of active norbuprenorphine in infants of higher gestational age (Fokina et al. 2011; Lewis and Dinh 2015). Some investigators have suggested sex differences in NAS manifestation, with males showing NAS more often than females; however we were not able to explore this further due to our small sample size (O’Connor et al. 2013). We are in infancy of learning regarding genetic interplay of maternal, placental, and infant’s milieu with regard to maternal ingestion of opioid and resulting fetal effects. We propose that the investigation of metabolites in cord blood may be a practical way to study NAS in the buprenorphine exposed population, as these metabolites represent the end outcome of enzymatic and genetic variability in the maternal-placental-fetal triad.

Results from the MOTHER study (The Maternal Opioid Treatment: Human Experimental Research) show no relationship between maternal buprenorphine dose and the severity of NAS (Jones et al. 2012). Similar results were found in our study. No statistical significance was shown in regards to
maternal buprenorphine dose at the time of delivery or the calculated cumulative dose throughout pregnancy with length of stay or duration of treatment required. Increasing birth weight and gestational age found to be strongly associated with development of NAS which can be explained by more conversion of buprenorphine to norbuprenorphine by aromatase by placental tissue, whose expression increases with gestational age from 16 to 24 km from 27–33 to 34–37 weeks (Fokina et al. 2011). Maternal history at delivery was taken as ‘evidence’ for maternal drug treatment, rather than followed by a confirmatory urine drug test. This discrepancy may have affected our results, as research has shown that ‘history of drug use’ is not the best marker for drug use in pregnancy (Ostrea et al. 2001).

Liquid-chromatography with mass spectrometric detection (LC–MS) has been successfully applied to the study of buprenorphine concentrations in urine, plasma, hair, sweat, and breast milk (Gray and Huestis 2007). Some groups have concentrated on pregnancy specific matrices such as umbilical cord tissue and meconium to quantify in utero exposure to these drugs (Kaciniko et al. 2008a, b; Concherio et al. 2009; Concheiro-Guisan et al. 2009). The LC–MS method used in this study is adapted from these previous studies, all of which were supported by the National Institute on Drug Abuse (NIDA), a trusted source for drug analysis. Our method shows similar limits of quantification for buprenorphine, norbuprenorphine, and the glucuronide conjugates (Kyle et al. 2015). The importance of monitoring buprenorphine metabolites in this study cannot be underestimated. In a 2009 study by Kaciniko et al. (2009), the glucuronidated version of norbuprenorphine was shown to be the primary urinary metabolite for pregnant women in their third trimester, indicating that the ability to measure this metabolite in the cord blood would be key to getting a full picture of neonatal exposure.

Recent study has suggested that cord tissue is equivalent and may be a superior matrix compared to meconium in detecting maternal drug exposure to cocaine, alcohol and amphetamines (Kaciniko et al. 2008a, b). Our hospitals have utilized umbilical cord tissue for screening of maternal drug use as a routine and standard care when there is a history of maternal drugs or clinical suspicion based on maternal history or newborn’s course. Umbilical cord tissue gives only concentration of buprenorphine and norbuprenorphine when present but not buprenorphine-glucuronide and norbuprenorphine-glucuronide metabolite. Umbilical cord plasma is considered a relatively ‘new’ matrix useful for investigating in utero drug exposure, and limited head-to-head comparisons with cord tissue have been initiated (Gray and Huestis 2007) Both cord plasma and cord tissue have the advantage of being immediately available following delivery, and require a non-invasive collection (Gray and Huestis 2007). Our results indicate a false negative rate of 37% using the cord tissue as the analytical matrix to examine the buprenorphine exposure, and of those “negative” samples, 57% tested for norbuprenorphine-glucuronide as the highest opioid marker when the cord blood was analyzed. Only 63% of neonates exposed to maternal buprenorphine in this study had positive cord tissue levels compared to 100% having positive metabolite concentrations in cord blood. Other investigators have shown that the glucuronide conjugates can indeed be quantified in the cord tissue, but the drug concentrations are much lower than in cord blood and meconium, making this a much less sensitive matrix to monitor drug exposure to the neonate (Concheiro et al. 2010a, b). The lower sensitivity for cord tissue in monitoring glucuronide metabolites is likely related to the high water solubility of these conjugates, making them less likely to partition into tissue (Brunton et al. 2011). The institution’s cord tissue assay used in tandem with our study did not monitor for metabolite levels, and therefore, we found that LC–MS analysis of the cord blood with metabolite monitoring was superior to cord stat analysis without metabolite monitoring.

Limitations
A limitation of our study is the small sample size (n = 19). It is unlikely to find significant associations between buprenorphine and buprenorphine-metabolite concentrations in cord blood and the need to initiate morphine replacement therapy in drug-exposed neonates at significance level α = 0.05 given such small sample size. According to statistical theory, p values related to ORs or regression coefficients depend on sample size. Large samples can lead to small p values without resulting in practical significance (e.g., statistical significance does not imply practical significance). On the other hand, small samples can lead to large p values without resulting in practical non-significance (e.g., statistical non-significance does not imply practical non-significance). Therefore, we used effect size (ES) converted from OR, rather than p values related to ORs or regression coefficients to assess the association between the dependent variable and those predictors since ES does not depend on sample size.

Conclusions
In an examination of a small number of neonates with a history of in utero exposure to buprenorphine, we found a trend of an inverse relationship between cord blood concentrations of buprenorphine-glucuronide, and a positive relationship between cord blood concentrations of norbuprenorphine, which can help predict morphine treatment necessity along with birth weight and gestational age. Additionally, we found that glucuronide conjugate metabolite quantification via LC–MS in cord blood samples from these patients is essential in preventing false negative results that appear when only buprenorphine and norbuprenorphine are measured in cord tissue. This has implications for improving patient care along with significant reduction in patient care cost if proven in larger study.

Abbreviations

Authors’ contributions
DS served as the coordinator of the study and the supervising physician on IRB submission, patient consent, sample collection, and data collection. SB developed and validated analytical method used to run cord blood samples and assisted in data interpretation. NH and SZ assisted on the statistical interpretation of the data. AK assisted in analytical method and validation for cord blood sample analysis, analyzed all patient samples, and collated data for statistical analysis. JP recruited patients, collected study samples, led the grant writing initiative for funding acquisition, and assisted in data collation and interpretation. ND and PS recruited patients, collected study
samples, and assisted in data interpretation. DS and SB are the primary authors on the manuscript, and AK, NH, and SZ also contributed to the writing. All authors read and approved the final manuscript.

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