

neonatal INTENSIVE CARE

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The Journal of Perinatology-Neonatology



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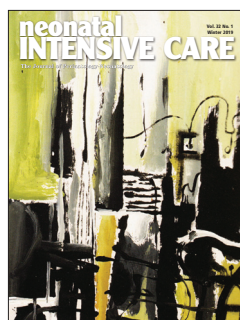
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Philadelphia, PA

David J. Hoffman, MD
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Penn State College of Medicine
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The Reading Hospital and Medical Center
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Newborn Intensive Care Unit
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Chang-Ryul Kim, MD
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College of Medicine
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Neurophysiology
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Philadelphia, PA

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The University of Chicago
Chicago, IL

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Pediatrics
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Meram Medical Faculty
Necmettin Erbakan University
Konya, Turkey

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Chief, Neonatology Division
Wake Forest University School of Medicine
Winston-Salem, NC

Lisa Pappas, RRT-NPS
Respiratory Clinical Coordinator NICU
University of Utah Hospital
Salt Lake City, UT

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University of Pavia, Italy

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Los Angeles, CA

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NY

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Neonatology and Neonatal Research
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Royal University Hospital
University of Saskatchewan
Saskatoon, Saskatchewan, Canada

Istvan Seri, MD, PhD
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Head, USC Division of Neonatal Medicine
University of Southern California,
Los Angeles, CA

Tushar A. Shah, MD, MPH
Division of Neonatology
Cincinnati Children's Hospital Medical
Center
Cincinnati, OH

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& Special Care Nursery Charge Therapist
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Emergency Response Team (NOHET)
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Valencia, Spain

Dharmapuri Vidyasagar, MD
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Chicago, IL

Dräger Continues Its Commitment to Education

In recognition of Respiratory Care Week and the vital role that respiratory therapists (RT) play in positive patient outcomes, Dräger donated 33 Babylog VN500 Ventilators to RT schools throughout the US. This marks the fourth year of Dräger's RT school donation program, which began in 2014. Healthcare organizations have a growing need for qualified respiratory therapists (RT) to care for patients suffering from conditions and diseases that impact cardiopulmonary function. According to the U.S. Department of Labor, employment of respiratory therapists is projected to grow 23 percent through 2026, much faster than the average for all occupations. Respiratory therapy (RT) schools are challenged with educating this next generation of professionals on the latest techniques and technologies so they are prepared to meet the demands of today's healthcare environment. "We want our RT program graduates to be fully prepared for the challenges they will face in patient care settings, and for healthcare organizations to recognize our school for its commitment to exceptional education," said Monica Schibig, MA, RRT-NPS, CPFT, respiratory therapy program director, University of Missouri at Columbia. "In order to meet these goals, we must provide students the opportunity to train on advanced technologies. We are thankful to Dräger for its ventilator donation and the company's ongoing commitment to the RT profession." One specific area of care where RTs have a significant impact is the neonatal intensive care unit

(NICU) caring for newborns suffering from respiratory issues. However, a recent survey of ventilation practices in the NICU found RTs in the U.S. need greater education and experience with volume-targeted ventilation (VTV), which can reduce the risk for lung injury in preterm babies. In a recent survey of U.S. neonatologists, only 39 percent of respondents used VTV as a primary mode of ventilation, with 62 percent citing lack of understanding or lack of training/experience as their main barriers to using this new standard of care. "We have long been committed to the RT profession and recognize that in order to enhance respiratory care delivery at the bedside, we need to support education and training of new RTs well before they receive their diplomas," said Edwin Coombs, MA, RRT-NPS, ACCS, FAARC, director of marketing, Intensive Care, Dräger. "We hope that this latest donation of Babylog VN500 Ventilators will help RT students gain valuable knowledge and experience on advanced ventilation techniques to support positive outcomes in the NICU."

No reason to delay BCG vaccine in low birthweight preterm babies

A systematic literature review and meta-analysis has confirmed that there is no reason to delay administration of bacillus Calmette-Guerin (BCG) vaccination for preterm and/or low birthweight infants. The evidence supports BCG vaccination within 7 days of birth in clinically stable infants born preterm (after <30 weeks' gestational age) and/or of low birthweight (weighing >1.5 kg), the authors say. In a report in JAMA Pediatrics, Dr Shiraz Badurdeen from the Newborn Research Center, The Royal Women's Hospital, Victoria, Australia and colleagues note that BCG vaccine, the only approved vaccine for prevention of tuberculosis (TB), is typically given soon after birth to infants born at term. However, for the 15 million infants born preterm and 20 million born with low birthweight each year, administration is commonly delayed due to uncertainty about safety and immunogenicity. To investigate further, the researchers identified 40 studies relevant studies that included infants born at 26 to 37 weeks' gestational age and/or weighing 0.69 to 2.5 kg at birth. The BCG vaccine was administered at or before 7 days of life in 10,568 clinically stable infants who were preterm and/or had low birthweight. In 4,310 infants, vaccination was delayed and given at varying times between 8 days and 12

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Phone: 310-443-4109

Fax: 310-443-4110

E-mail: s.gold4@verizon.net

Web: www.nicmag.ca

Publisher/Editor in Chief

Steve Goldstein

Managing Editor

Christopher Hiscox

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months after birth. Most of the studies involved healthy neonates born at more than 30 weeks' gestational age or weighing more than 1.5 kg and reported no increased risk of adverse reactions or infant death after BCG vaccination within 7 days of birth compared with BCG vaccination at later points, the authors say. There were no differences between early and delayed BCG vaccination for scar formation (relative risk, 1.01; 95% confidence interval 0.95 to 1.07) or tuberculin skin test (TST) conversion (RR, 0.97; 95% CI, 0.84 to 1.13). None of the studies evaluated protective efficacy comparing early versus late BCG.

"Clinicians have traditionally delayed administering the BCG vaccination in infants born premature or small because of uncertainty about safety and the ability to generate a protective vaccine response," Dr Badurdeen commented. "We systematically reviewed all studies dating back to the 1950's, and found that BCG vaccination within 7 days of birth of healthy preterm or low-birthweight infants was in fact safe. Early vaccination also generated similar vaccine responses to delayed vaccination, but there was little data on protective immunity or the risk of developing tuberculosis." Dr Badurdeen added: "Our independent study strongly supports the most recent World Health Organization advice of early BCG vaccination in healthy infants born preterm or with low-birthweight, and details the evidence both for safety and for the response to vaccination. Policymakers and clinicians around the world should assess their local rates of BCG vaccine uptake, and strongly consider updating policies and local systems to ensure BCG vaccination is not unnecessarily delayed in this vulnerable group."

AAP Updates Screening Policy for ROP

Premature infants require regular screening for retinopathy of prematurity (ROP), according to an updated policy statement from the American Academy of Pediatrics (AAP). The statement, which was published online November 26 in Pediatrics, revises a 2013 statement on screening of preterm infants for ROP, a developmental disorder of the eye and a leading cause of blindness in childhood. Walter M. Fierston, MD, FAAP, FAAP, from the AAP Section on Ophthalmology, and colleagues highlight the need for experienced ophthalmologists to perform carefully timed examinations of at-risk infants. The examinations should be performed on the basis of the infant's gestational age at birth and subsequent disease presence and severity. "The goal of an effective ROP screening program is to identify infants who could benefit from treatment and make appropriate recommendations on the timing of future screening and treatment interventions," they write. "Because undiagnosed or treatment-delayed ROP can lead to permanent blindness, it is important that all infants who are at risk be screened in a timely fashion, recognizing that not all infants require treatment." Like the previous statement, the updated version recommends retinal screening examinations using binocular indirect ophthalmoscopy for infants with a birth weight of 1500 g or less or a gestational age of 30 weeks or less, and also for certain at-risk infants with a birth weight from 1500 g to 2000 g. The updated statement includes new recommendations that address various issues, such as the use of remote photographic screening for ROP. In this process, an examining ophthalmologist in a neonatal care unit conducts digital photo screening for ROP, then forwards the images to a remotely located ophthalmologist who has experience in ROP. That ophthalmologist then provides expert interpretation. The statement also recommends that "indirect ophthalmoscopy be performed at least once by a qualified ophthalmologist before treatment or termination of acute-phase

screening of ROP for infants at risk for ROP." The authors write that ophthalmologists should consider using intravitreal injection of anti-vascular endothelial growth factor (VEGF) agents to treat aggressive posterior ROP. They discuss recent data that support the promise of these agents in this setting. For example, in infants with stage 3+ ROP, studies have shown that intravitreal injection of bevacizumab (Avastin, Genentech) is effective and may lead to significantly better structural results for zone I disease than is possible with laser ablation. However, ophthalmologists should be aware that, compared with conventional laser peripheral retinal ablative treatment, anti-VEGF treatment tends to be associated with much later recurrence of ROP. The statement highlights the importance of interprofessional care in the management of infants with ROP. For example, it recommends that neonatology and ophthalmology services in each neonatal intensive care unit establish specific criteria (such as infant birth weight and gestational age) that will automatically trigger screening for ROP. Interprofessional collaboration is also important with regard to the transition of care of infants. "The transferring or discharging pediatrician, after consultation with the examining ophthalmologist, has the responsibility for communicating to the receiving physician what eye examinations are needed and their required timing," the statement concludes. The authors caution that infants who have had ROP are at increased risk of developing unrelated visual disorders, such as strabismus, amblyopia, high refractive errors, cataracts, and glaucoma. Therefore, infants who have had ROP require ophthalmologic follow-up for these potential problems within 4 to 6 months after discharge from the neonatal intensive care unit.

Reassuring Data on Triplets

A large retrospective study provides reassuring data on neonatal outcomes of very preterm and very low birth weight triplets. "Our results identified that, when matched by country of birth, gestational age and sex, the outcomes of preterm triplets were similar to those of singletons, meaning that their risk of mortality and illnesses common to preterm neonates are similar," Dr Prakesh Shah of Mount Sinai Hospital, part of Sinai Health System, in Toronto, Canada. "The literature on this topic of outcome of triplets vs. singletons is marred by small, single-center studies and some showing that the outcomes are worse and some showing they are similar," Dr Shah explained. He and his colleagues compared neonatal outcomes of more than 6,000 triplets born between 24 to 32 weeks' gestation or weighing 500 to 1,499 g at birth with that of three times as many singletons from 11 high-income countries. "This is the largest set of premature triplets studied in the world," Dr Shah said. The results showed no difference in the primary outcome (a composite of mortality or severe neonatal morbidity [severe neurologic injury, treated retinopathy of prematurity, and bronchopulmonary dysplasia] between triplets and singletons (23.4% vs. 24.0%). The odds ratio was 0.91 in a model adjusted for maternal hypertension and birth weight z-score and 1.00 in a model adjusted for these factors plus cesarean birth and antenatal steroid use. There were also no significant between-group differences in rates of severe neonatal morbidities. The results were also similar for a subsample of 1,648 triplets and 4,944 matched singletons born at 24 to 28 weeks' gestation. "Our findings from a large cohort of neonates can be used to provide reassuring results for families and care providers that although triplets do incur strain to already resource-limited neonatal units, their outcomes are similar to those of singletons," the authors conclude.

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Indication

INOMAX is indicated to improve oxygenation and reduce the need for extracorporeal membrane oxygenation in term and near-term (>34 weeks gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension in conjunction with ventilatory support and other appropriate agents.

Important Safety Information

- INOMAX is contraindicated in the treatment of neonates dependent on right-to-left shunting of blood.
- Abrupt discontinuation of INOMAX may lead to increasing pulmonary artery pressure and worsening oxygenation.
- Methemoglobinemia and NO₂ levels are dose dependent. Nitric oxide donor compounds may have an additive effect with INOMAX on the risk of developing methemoglobinemia. Nitrogen dioxide may cause airway inflammation and damage to lung tissues.

- In patients with pre-existing left ventricular dysfunction, INOMAX may increase pulmonary capillary wedge pressure leading to pulmonary edema.
- Monitor for PaO₂, inspired NO₂, and methemoglobin during INOMAX administration.
- INOMAX must be administered using a calibrated INomax DSIR® Nitric Oxide Delivery System operated by trained personnel. Only validated ventilator systems should be used in conjunction with INOMAX.
- The most common adverse reaction is hypotension.

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^{*}INomax Total Care is included at no extra cost to contracted INOMAX customers.

[†]Emergency deliveries of various components are often made within 4 to 6 hours but may take up to 24 hours, depending on hospital location and/or circumstances.

Reference: 1. Data on file. Hampton, NJ: Mallinckrodt Pharmaceuticals.



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Brief Summary of Prescribing Information

INDICATIONS AND USAGE

Treatment of Hypoxic Respiratory Failure

INOMax® is indicated to improve oxygenation and reduce the need for extracorporeal membrane oxygenation in term and near-term (>34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension in conjunction with ventilator support and other appropriate agents.

CONTRAINDICATIONS

INOMax is contraindicated in neonates dependent on right-to-left shunting of blood.

WARNINGS AND PRECAUTIONS

Rebound Pulmonary Hypertension Syndrome following Abrupt Discontinuation

Wean from INOMax. Abrupt discontinuation of INOMax may lead to worsening oxygenation and increasing pulmonary artery pressure, i.e., Rebound Pulmonary Hypertension Syndrome. Signs and symptoms of Rebound Pulmonary Hypertension Syndrome include hypoxemia, systemic hypotension, bradycardia, and decreased cardiac output. If Rebound Pulmonary Hypertension occurs, reinstate INOMax therapy immediately.

Hypoxemia from Methemoglobinemia

Nitric oxide combines with hemoglobin to form methemoglobin, which does not transport oxygen. Methemoglobin levels increase with the dose of INOMax; it can take 8 hours or more before steady-state methemoglobin levels are attained. Monitor methemoglobin and adjust the dose of INOMax to optimize oxygenation.

If methemoglobin levels do not resolve with decrease in dose or discontinuation of INOMax, additional therapy may be warranted to treat methemoglobinemia.

Airway Injury from Nitrogen Dioxide

Nitrogen dioxide (NO₂) forms in gas mixtures containing NO and O₂. Nitrogen dioxide may cause airway inflammation and damage to lung tissues.

If there is an unexpected change in NO₂ concentration, or if the NO₂ concentration reaches 3 ppm when measured in the breathing circuit, then the delivery system should be assessed in accordance with the Nitric Oxide Delivery System O&M Manual troubleshooting section, and the NO₂ analyzer should be recalibrated. The dose of INOMax and/or FiO₂ should be adjusted as appropriate.

Worsening Heart Failure

Patients with left ventricular dysfunction treated with INOMax may experience pulmonary edema, increased pulmonary capillary wedge pressure, worsening of left ventricular dysfunction, systemic hypotension, bradycardia and cardiac arrest. Discontinue INOMax while providing symptomatic care.

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from the clinical studies does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Controlled studies have included 325 patients on INOMax doses of 5 to 80 ppm and 251 patients on placebo. Total mortality in the pooled trials was 11% on placebo and 9% on INOMax, a result adequate to exclude INOMax mortality being more than 40% worse than placebo.

In both the NINOS and CINRGI studies, the duration of hospitalization was similar in INOMax and placebo-treated groups.

From all controlled studies, at least 6 months of follow-up is available for 278 patients who received INOMax and 212 patients who received placebo. Among these patients, there was no evidence of an adverse effect of treatment on the need for rehospitalization, special medical services, pulmonary disease, or neurological sequelae.

In the NINOS study, treatment groups were similar with respect to the incidence and severity of intracranial hemorrhage, Grade IV hemorrhage, periventricular leukomalacia, cerebral infarction, seizures requiring anticonvulsant therapy, pulmonary hemorrhage, or gastrointestinal hemorrhage.

In CINRGI, the only adverse reaction (>2% higher incidence on INOMax than on placebo) was hypotension (14% vs. 11%).

Based upon post-marketing experience, accidental exposure to nitric oxide for inhalation in hospital staff has been associated with chest discomfort, dizziness, dry throat, dyspnea, and headache.

DRUG INTERACTIONS

Nitric Oxide Donor Agents

Nitric oxide donor agents such as prilocaine, sodium nitroprusside and nitroglycerine may increase the risk of developing methemoglobinemia.

OVERDOSAGE

Overdosage with INOMax is manifest by elevations in methemoglobin and pulmonary toxicities associated with inspired NO₂. Elevated NO₂ may cause acute lung injury. Elevations in methemoglobin reduce the oxygen delivery capacity of the circulation. In clinical studies, NO₂ levels >3 ppm or methemoglobin levels >7% were treated by reducing the dose of, or discontinuing, INOMax.

Methemoglobinemia that does not resolve after reduction or discontinuation of therapy can be treated with intravenous vitamin C, intravenous methylene blue, or blood transfusion, based upon the clinical situation.

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NICU Staff Honoured

In honor of Prematurity Awareness Month (November), Chiesi USA, Inc., a Cary-based specialty pharmaceutical company, saluted NICU staff for their commitment to the families of babies born too soon in a video that shares stories of the people impacted by premature birth. The video provides a first-hand account of reality in the Neonatal Intensive Care Unit (NICU), from the worry and fear families experience, to the exceptional care provided by NICU staff. "NICU staff work tirelessly every day to serve the most fragile patients. The compassionate care they provide to families not only helps them through their time in the NICU, but also builds relationships that last a lifetime," said Josh Franklin, Senior Vice President of Marketing and Corporate Development, Chiesi. "We're honored to share their stories of strength and resilience through this video, and we hope it helps to raise awareness about prematurity and the important role of the NICU staff in hospitals across the country." The video showcases candid interviews with NICU families who share stories of the challenges they overcame and the care received while in the hospital. They also offer hope to other families experiencing preterm birth. "Having a baby in the NICU is such a rollercoaster of emotions," said Karen Reeder, who delivered a 2-pound, 11-ounce baby girl at 31 weeks. "Every day is filled with worry, fear, and uncertainty. But the constant love and support, in addition to the education provided by the NICU staff, really made a difference in helping our family navigate the difficult times. Two years later, the nurses who helped us along our NICU journey are now some of our closest friends." Equally important is to share the loss that is very real. In the video, mom Moline Pandiyan talks about her son Niko who never made it home from the NICU. "We spent 164 days in the NICU with Niko, and during that time, our family forged unbreakable relationships with the NICU team, which includes the doctors, nurses, respiratory therapists, social workers, therapists, receptionists, and so many others," said Pandiyan. "Each one left an important mark on our family's heart for the way they took care of Niko and how they mourned with us when we lost him. They were his family and continue to be a part of our lives." In the United States, more than 380,000 babies are born premature

each year. That's about one in 10 babies born too soon, according to March of Dimes. During Prematurity Awareness Month, Chiesi hopes this video will help raise awareness for preterm birth and the important work being done in NICUs across the country.

Endotracheal-Suctioning Curb Tied to Respiratory Problems in Some Newborns

Avoidance of routine endotracheal suctioning of meconium-stained nonvigorous newborns, as recommended in recent guidelines, may be associated with a higher risk of respiratory problems, according to Texas-based researchers. Previously, nonvigorous newborns born through meconium-stained amniotic fluid (MSAF) "were routinely intubated and suctioned below the vocal cords to prevent perinatal aspiration of meconium," Dr Arpitha Chiruvolu of Baylor University Medical Center, in Dallas, and colleagues note in Pediatrics. Guidelines from the Neonatal Resuscitation Program now suggest that positive-pressure ventilation should be used instead, the team adds. To investigate, the team examined data on 130 nonvigorous neonates born a year before implementation of the new guidelines and on 101 infants born in the year after they went into effect. Maternal and other characteristics were similar between these groups. Endotracheal suctioning was performed in 70% of the pre-implementation group compared to only 2% of those born after the change in management. However, significantly more infants in the post-implementation group were admitted to the neonatal intensive care unit (NICU) than had been the case before the change (40% vs. 22%; odds ratio, 2.2). There were similar findings for need of oxygen therapy (37% vs. 19%; OR, 2.5), mechanical ventilation (19% vs. 9%; OR, 2.6) and surfactant therapy (10% vs. 2%; OR, 5.8). There were no differences in the incidences of other outcomes, including meconium-aspiration syndrome and hypoxic-ischemic encephalopathy. Given these findings and the fact that the new recommendations were "not based on large randomized controlled trials performed in the developed world," the researchers call for such trials "to look into the safety and efficacy of this practice change." Dr Marie Blomberg, a professor in the division of children's and women's health at Linköping University, in Sweden, likened the

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choice to that between plague and cholera. “This change in clinical practice, avoiding a large number of intubations, did not increase the number of infants with the severe complication of meconium aspiration syndrome,” she said. “On the other hand, the authors found a higher proportion of newborns admitted to the NICU for respiratory issues, more infants who needed oxygen therapy and mechanical ventilation, in the group treated with positive-pressure ventilation.” “This study,” she concluded, “elucidates the ongoing challenge in clinical care, to figure out what risks are in a sense acceptable to take and which are not.”

Beta-Blockers in Pregnancy Not Associated With Congenital Malformations

First-trimester use of beta-blockers was not associated with a substantial increase in the risk for congenital malformations in offspring, in a recent international study. As many as 1% of pregnancies are exposed to beta-blockers during the first trimester. Beta-blockers cross the placenta and have shown possible teratogenic effects in some animal studies, but their association with the risk for human congenital malformations remains controversial. Led by Dr Brian T. Bateman from Brigham and Women's Hospital and Harvard Medical School in Boston, the research team used data from national health registries in the five Nordic countries and the Medicaid database in the US to examine the association between first-trimester exposure to beta-blockers in utero and congenital malformations. They restricted their analysis to pregnancies with a diagnosis of hypertension that ended in a live birth. The study included 3577 women in the Nordic group (19.1% exposed to beta-blockers) and 14,900 in the U.S. Medicaid group (11.2% exposed to beta-blockers). The relative risks of congenital malformations overall, cardiac defects, and cleft lip or palate were nominally increased in both cohorts, but all 95% confidence intervals (CI) included 1.0, according to the *Annals of Internal Medicine* online report. “The upper bound of the 95% CI suggests an excess risk per 1000 persons exposed to beta-blockers in the first trimester of no more than 12.6 for congenital malformations overall, 8.4 for cardiac malformations, 3.0 for cleft lip or palate, and 4.0 for CNS malformations after adjustment for confounding factors, including maternal hypertension,” the researchers note. Results were similar when the analyses pooled data from both cohorts.

In a separate analysis, the point estimates for overall malformations appeared to be similar among women exposed to beta-blockers and those exposed to calcium-channel blockers, but the confidence intervals were wide. “In the setting of small numbers of outcomes, our study cannot exclude an increase in the relative risk for the less common malformation types, cleft lip or palate and CNS malformations,” the authors conclude. “However, the point estimates from our analysis suggest a more modest increase in the relative risk for these malformations than earlier publications have reported. The potential risks to the fetus must be balanced against the risks to the mother associated with untreated hypertension.”

Neonatal Abstinence Syndrome a Risk With Kratom Use in Pregnancy

There is a risk for neonatal abstinence syndrome (NAS) in women who use kratom during pregnancy to self-treat opioid withdrawal symptoms, doctors caution in a new report. Kratom is an herbal supplement widely available on the Internet and in retail outlets as a powder, tea and capsule. Its use is increasing in the U.S. with marketing campaigns touting it as a nonopioid remedy for opioid withdrawal. However, the US Food and

Drug Administration (FDA) recently warned that compounds in kratom act like prescription-strength opioids. In their paper, Dr Whitney Eldridge and colleagues at St. Joseph Women's Hospital in Tampa, Florida, describe the case of an infant with NAS born to a mother who used kratom tea daily throughout her pregnancy to help with sleep and opioid withdrawal symptoms. The mother had a seven-year history of oxycodone use but had successfully completed rehab for the addiction. Her last oxycodone use was two years before delivery and her urine was negative for drugs on admission for delivery. The infant was born at term and roomed with the mother after an uncomplicated cesarean delivery. At 33 hours of age, the baby showed signs “concerning” for opioid withdrawal including jitteriness, excessive sucking, facial excoriations and irritability. When the baby's father disclosed the mother's use of kratom daily during pregnancy, the infant was diagnosed with NAS and transferred to the neonatal ICU for further evaluation and management. In the neonatal intensive-care unit, the baby's Finnegan NAS scores were elevated, ranging from 9 to 14. The baby was started on morphine (0.03 mg/kg every three hours per protocol) and his Finnegan scores dropped significantly (range, 2 to 3). However, the infant appeared to be overly sedated without respiratory depression but with sinus bradycardia. The infant remained sedated despite rapid weaning from morphine. Other etiologies of bradycardia and lethargy were ruled out. Completely off morphine (on day 3 of life), the infant again developed signs of withdrawal and his Finnegan scores climbed. He was then trialed on clonidine (1 mcg/kg every three hours). His Finnegan scores improved, but he again developed sinus bradycardia. Clonidine was discontinued on the fifth day of life. The infant improved over the next few days and was discharged. Dr Eldridge and colleagues note in their paper that kratom use in pregnancy and its effects on the developing fetus and newborn are “largely unknown. Only a few case reports of NAS due to maternal Kratom use are reported internationally. There is a lack of literature to help guide the pediatrician in management of NAS in the kratom-exposed infant.” With the current opioid epidemic and increasing incidence of opioid use among pregnant women, cases of NAS due to maternal kratom use are likely to increase “as mothers look to what they believe to be nonopioid alternatives for opioid dependence,” they point out. “As highlighted by our case, it is important for pediatricians to be aware of nonprescription self-treatments for opioid withdrawal. Because Kratom is not reported on urine drug screens, pediatricians need to ask specifically about nonprescription uses during pregnancy when taking histories from mothers with opioid dependence to better care for their newborns,” they conclude.

Severe Neurodevelopmental Delays Follow Preterm Isolated Cerebellar Hemorrhage

Preterm cerebellar hemorrhage in the absence of supratentorial injury is commonly associated with severe neurodevelopmental delays, according to a systematic review. “Early injury to the developing cerebellum has bigger consequences on neurodevelopmental outcome than most of us might have thought,” Dr Jeroen Dudink from Wilhelmina Children's Hospital and University Medical Center Utrecht in The Netherlands said. “Therefore, it is important to assess the cerebellar integrity in high-risk infants (such as preterm babies).” Earlier studies and reviews evaluating the neurodevelopmental sequelae of neonatal cerebellar hemorrhage have not consistently described the presence of concomitant supratentorial injury, which can also have a negative effect on neurodevelopment.

Dr Dudink and colleagues evaluated the relationship between neonatal cerebellar hemorrhage in preterm infants (<32 weeks' gestational age) in the absence of supratentorial injury and neurodevelopmental outcomes at 12 months or older, with a focus on cognitive, motor, language, and behavioral outcomes. Their review included 8 studies with 185 preterm infants, 128 of whom had isolated cerebellar hemorrhage. Among these infants, 38% had severe cognitive delay, 39% had severe motor delay, 41% had severe language impairment, and 38% had severe behavioral impairment.

The incidence of severe developmental impairment in at least one of these four domains was 43% to 75%, according to the report. Outcomes were worst among infants with vermis involvement: 80% developed cognitive impairment, compared with 19% of infants with unilateral cerebellar bleeding; 73% versus 18%, respectively, had severe motor impairment; 86% versus 12%, respectively, had severe language impairment; and 87% versus 0%, respectively, had severe behavioral impairment. Larger bleeds were also associated with worse outcomes than were punctate cerebellar hemorrhages. Compared with preterm infants without cerebellar hemorrhage or supratentorial

injury, infants with isolated cerebellar hemorrhage had 4.7 times higher odds of severe cognitive impairment, 4.3-fold higher odds of motor impairment, 4.6-fold higher odds of language impairment, and 21.3-fold higher odds of behavioral impairment.

Maternal Intellectual Disability Boosts Odds of Newborn Discharge to Protective Services

Newborns of women with intellectual or developmental disability (IDD) are more than 30 times as likely to be discharged to child protective services than are newborns of women without IDD, researchers from Canada report. About 1% of women have

an IDD, and studies suggest that 40% to 60% of women with IDD lose custody of their children at some point, the team notes.

"This issue is complicated by the long history of stigma related to sexuality and pregnancy in women with IDD," Dr Hilary K. Brown of the University of Toronto Scarborough said. "The reality is that, with increased community integration of persons with IDD, their childbearing rates are increasing. Services must be developed that are tailored to their needs." "We know from other research that maternal-infant separations have negative

consequences for both mothers and babies because they disrupt maternal-infant bonding and breastfeeding," she said. "Prior studies have shown that women who experience such separations are at increased risk for mental health problems and even suicide, and their children have higher rates of developmental problems." Dr Brown's team used linked databases to estimate and compare the risk of discharge to child protective services directly from the birth hospitalization in newborns of women with IDDs versus without IDDs and evaluated risk factors for discharge to child protective services among newborns of women with IDDs. Their analysis included 3,845 live births to women with IDDs and more than 379,000 live

births to women without IDDs. The rate of discharge to child protective services directly from birth hospitalization was 32.8-fold higher in newborns of women with IDDs (5.7%) than in newborns of women without IDDs (0.2%), a significant difference. The relative risk was lower after adjusting for baseline sociodemographic, health, service and perinatal characteristics, but remained significantly increased. In multivariable analysis, psychotic disorders, social assistance receipt, failure to receive an ultrasound by 20 weeks, and receipt of <4 prenatal visits by 36 weeks were independently associated with an increased risk of discharge to child protective services

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among newborns of women with IDD. The rate of sustained maternal-infant separation was also significantly higher in women with IDDs (4.9%) than in women without IDDs (0.1%) and was independently associated with psychotic disorders, social assistance receipt, failure to receive an ultrasound by 20 weeks and neonatal morbidity. "One in 20 women with IDD are separated from their infants at birth," Dr Brown said. "When separations do happen, services should be in place that support the mental health of women with IDD." "At the same time, 19 out of 20 women with IDD go home with their babies," she said. "This means that services should be in place for these women to support breastfeeding, infant care, and parenting."

Myo-Inositol Doesn't Prevent Severe Retinopathy of Prematurity

Myo-inositol does not reduce the risk of type 1 retinopathy of prematurity (ROP) in infants born before 28 weeks' gestational age, according to new findings. The

randomized clinical trial was terminated early because infants given myo-inositol were significantly more likely to develop type 1 ROP than those on placebo, and their mortality risk was also higher. "Based on the study's findings, myo-inositol is not recommended for use as a supplemental medicine for premature infants," Dr Dale L. Phelps of the University of Rochester, in New York, said. Trials done in the late 1980s and early 1990s found myo-inositol, a sugar alcohol naturally found in babies' blood, reduced ROP risk and improved survival

when used as a surfactant component in infants with respiratory distress syndrome, Dr. Phelps and colleagues write. "Use of antenatal steroids and exogenous surfactants has since reduced respiratory morbidity from respiratory distress syndrome; however, ROP remains a serious sequela among survivors of extremely preterm birth," they note. The authors randomized 638 infants across the U.S. to receive 40 mg/kg of myo-inositol every 12 hours, intravenously at first and then during feeding, for up to 10 weeks. The study's primary outcome was type 1 ROP (meaning it met criteria for surgical intervention) or death before ROP outcome could be assessed. Death or type 1 ROP occurred in 29% of the infants given myo-inositol versus 21% of those on placebo (adjusted relative risk, 1.41; $P=0.01$). In the myo-inositol

group, 18% died of any cause before 55 weeks' postmenstrual age, compared to 11% of the placebo group (adjusted risk difference, 1.66; $P=0.007$). Serious adverse events that occurred within the seven days after an infant's last dose included necrotizing enterocolitis, in 6% of the myo-inositol group versus 4% of the placebo group; poor perfusion or hypotension (7% vs. 4%); intraventricular hemorrhage (10% vs. 9%); systemic infection (16% vs. 11%); and respiratory distress (15% vs. 13%). The authors had planned to enroll 1,760 infants, but the data and safety monitoring committee recommended terminating the study due to the increase in all-cause deaths among infants on myo-inositol.

Maternal Tdap Vaccination and Neonatal Immunity, Timing Key

Maternal immunization with tetanus, diphtheria, and acellular pertussis (Tdap) vaccine early in the third trimester results in higher pertussis antibody concentrations in neonates compared

with earlier or later immunization during pregnancy, according to a study. "Pertussis toxin antibody concentrations at birth were sufficiently high in infants born to Tdap-immunized mothers that, even allowing for the natural decay of maternal antibodies, most infants would have had substantial antibody levels until initiation of the primary vaccine series, thus reducing their risk of pertussis-related mortality and morbidity," write lead author C. Mary Healy, MD, from the Baylor College of Medicine, Houston, Texas, and colleagues. Previous studies of pertussis

immunity in infants, including a recent report examining a 2016 pertussis outbreak in California, have demonstrated that timing of maternal immunization is integral to decreasing the risk for pertussis infection in neonates.

The Advisory Committee on Immunization Practices recommends vaccinating pregnant women with Tdap as early as possible between 27 and 36 weeks' gestation during every pregnancy to prevent neonatal infection, but the optimal timing in that window has been unclear.

In the current prospective observational study, Healy and colleagues evaluated data from 626 mother-infant pairs at a

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tertiary referral center between December 2013 and March 2014. Infants were eligible if there was clear record of their mother being vaccinated during pregnancy or not being vaccinated. Among these, 312 women received a Tdap vaccine between weeks 27 through 36 (mean 31.2 weeks) and 314 were not vaccinated. The authors found that the geometric mean concentration (GMC) of pertussis toxin antibodies in cord blood in the Tdap-exposed group was 47.3 IU/mL (95% CI, 42.1 - 53.2) compared with 12.9 IU/mL (95% CI, 11.7 - 14.3) in the Tdap-unexposed group, resulting in a ratio of 3.6 (95% CI, 3.1 - 4.2; $P < .001$). The ratio remained significant even after controlling for factors such as maternal age, ethnicity, and gestational age at delivery. Further, the neonatal pertussis antibody increased sequentially each week when Tdap vaccine was administered during 27 through 29 weeks of gestation, reached its peak when administered at week 30 (GMC 57.3 IU/mL; 95% CI, 44.0 - 74.6), and declined thereafter. Although the optimal antibody level required to confer protective immunity in infants is not clear, the researchers found that Tdap-exposed infants had antibody levels well above those considered to be protective until the standard infant immunization series began. The authors acknowledge study limitations such as the fact that all data were collected from a single center and the observational nature of the study does not allow for a cause-and-effect interpretation of the findings. "This study demonstrated that, following US immunization recommendations and in accordance with current understanding of the kinetics of placental transfer, optimal time to administer Tdap vaccine to maximize pertussis toxin antibodies at birth may be early in the third trimester, with the window of 27 through 30 weeks of gestation yielding the highest cord blood levels," conclude Healy and colleagues.

Venezuelan Hospital Encourages 'Kangaroo' Baby Care to Spare Incubators

Venezuela's largest maternity hospital is asking mothers to care for non-critical premature babies with skin-to-skin contact known as "kangaroo care" rather than in incubators, as wards struggle with a lack of equipment. At the Concepcion Palacios Hospital, doctors held tutorials to show nurses and mothers how to hold newborns against their bare chests inside a pouch or cloth wrap. Researchers have identified kangaroo care - which has gained adherence in countries including the United States, Norway and Finland - as a way of lowering infant mortality and improving developmental outcomes for premature and underweight babies. In Venezuela, where public hospitals face shortages of basic medicine and the flight of nurses and doctors abroad after five years of economic crisis, kangaroo care can also provide a way to reduce pressure on scarce resources. A senior doctor at Concepcion Palacios, speaking anonymously, said the hospital lacked almost all material needed to treat patients, such as water, disinfectant, hospital beds, and useable cubicles.

Venezuela's Information Ministry did not respond to a request to comment about the lack of equipment in hospitals. According to the last statistics released by Venezuela's Health Ministry, infant mortality, or death of children aged under two, climbed 30 percent to 11,466 cases in 2016 from the year before. The report cited neonatal sepsis, pneumonia, respiratory distress syndrome, and prematurity as the main causes. Lide Diaz, the 'Kangaroo Mama' program's coordinator at Concepcion Palacios, said the new focus on skin-to-skin care ensured incubators were available for babies considered to be critical condition. "We take the baby out of the incubator...and place it here," said Diaz,

gesturing to her chest. Concepcion Palacios is the only public hospital in Venezuela with a kangaroo program, as others are not able to provide the year of necessary follow-up care, Diaz said. The program's rooms are well-maintained, with pictures of kangaroos on the walls. The United Nations children's agency (UNICEF) has provided the hospital with technical assistance and medical equipment to evaluate babies' health. "The kangaroo method saves the lives of premature babies...and for that reason we support the program at the Concepcion Palacios Hospital," UNICEF said in a September press release.

Heliox Boosts Endurance in Adult Survivors of Very Preterm Birth

Mechanical constraints to ventilation play a role in the limited exercise endurance seen in adult survivors of very preterm birth, new research shows. Breathing heliox, a mixture of helium and oxygen, improved time to exhaustion in adult survivors of very preterm birth, Dr Joseph W. Duke of Northern Arizona University in Flagstaff and colleagues found, while it did not affect endurance in controls. "Adult survivors of preterm birth have a clearly obstructed airflow pattern and when we reduce some of their airflow resistance they can exercise longer," Dr Duke said. Up to 15% of births are preterm, but not everyone born preterm develops lung problems, Dr. Duke noted. While adult survivors of very preterm birth have worse pulmonary function and aerobic endurance than term-born individuals, the etiology of these differences remains unclear, but could involve "impaired pulmonary gas exchange efficiency, mechanical ventilatory constraints and/or dyspnoea," he and his colleagues note. Dr Duke and his team previously showed that adult survivors of very preterm birth have expiratory flow limitation during exercise. In the new study, they tested whether breathing heliox - in which the nitrogen in normal ambient air is replaced with helium - would improve time to exhaustion (TTE). They enrolled 19 adults who had been born at least eight weeks premature, regardless of whether or not they had bronchopulmonary dysplasia, and 16 controls. TTE improved significantly in PRET when they breathed heliox compared to normal air, the researchers found, but breathing heliox did not affect TTE in controls. While there are some similarities between adult survivors of very preterm birth and people with mild COPD or asthma, Dr Duke noted, the etiology of their lung obstruction is likely to be entirely different. "The real issue here is that these preterm born individuals, there's not really enough of their physiology that is known, particularly with the respiratory system," he said. "The survival rate of people born premature continues to rise because neonatal medicine has been getting so good at keeping them alive," he added. "This problem isn't going to be a problem that goes away any time soon, thankfully."

Use of *B. infantis* EVC001 in the NICU for Pathogen Defense Through Improved Nutrient Availability

Tracy Shafizadeh, PhD

Infant Gut Dysbiosis

There are many reasons that an infant may need care in a NICU setting, including preterm birth, developmental abnormalities, or traumatic birth events. One common condition across patients in the NICU is gut dysbiosis, which is defined as an overabundance of pathogenic bacteria in the gut microbiome. The organisms that comprise the infant gut are initially acquired at birth and are largely determined by birth mode and diet.^{1,2} Gut microbes are passed from mother to infant during vaginal delivery, and human milk selectively promotes the growth of beneficial gut microbes, specifically *Bifidobacterium longum* subsp. *infantis* (*B. infantis*), creating a highly functional and protective gut microbiome in the newborn. However, antibiotic use and C-section delivery can disrupt this mom-to-baby transfer of *B. infantis*, allowing for potentially pathogenic bacteria present on surrounding surfaces of a hospital environment to colonize the infant gut.

Maximizing Nutrient Availability from Human Milk

As mentioned previously, infant diet is a major driver of the early gut microbiome composition. Human milk is not only the optimal nutrition source for the newborn, but also contains unique carbohydrates, called human milk oligosaccharides (HMO), that are indigestible by the infant and instead serve as food for the infant gut microbiome. *B. infantis* is the only bacterium capable of complete digestion and utilization of HMO and is therefore the predominant species typically found in the breastfed infant gut.³ The products of HMO metabolism by *B. infantis* are lactate and acetate, molecules that are not only fuel for the developing colonocytes, but also signaling molecules that participate in much of the immune and metabolic programming events taking place in the first 100 days of life.^{4,5} However, in the absence of *B. infantis*, HMO are not fully utilized, and instead the vast majority are excreted in the infant stool.⁶ *B. infantis* is particularly

important for infants in the NICU who receive costly donor milk, as the absence of this organism leads to up to 15% loss of the milk nutrients through fecal excretion of HMO, in addition to the loss of the important functional end products, lactate and acetate. Restoring *B. infantis* colonization of the infant gut through probiotic use has been clinically demonstrated in breastfed infants and led to near complete digestion and utilization of HMO in the infant gut.⁶ Additionally, restoration of *B. infantis* to the infant gut led to significant improvement in stool quality, thought to be largely attributed to the reduction in HMO excretion.⁷

Reduction in fecal pH was accompanied by a dominance of B. infantis in the infant microbiome, along with a 93% reduction in the abundance of pathogenic bacteria including E. coli, C. difficile, Klebsiella pneumoniae and Streptococcus pneumoniae.

Defense Against Pathogen Colonization

Recent studies have linked the pH of infant stool to the composition of the infant gut microbiome, and infants colonized by *B. infantis* exhibited a more acidic pH compared to those who lack this bacterium.⁸ This pH differential can be explained by the metabolism of HMO by *B. infantis*, and the subsequent generation of the acidic metabolic end products, lactate and acetate. In recent clinical studies, probiotic use of *B. infantis* EVC001 (Evivo®) was shown to reduce the fecal pH of breastfed infants to levels observed in infants naturally colonized by this bacterium.⁶ This reduction in fecal pH was accompanied by a dominance of *B. infantis* in the infant microbiome, along with a 93% reduction in the abundance of pathogenic bacteria including *E. coli*, *C. difficile*, *Klebsiella pneumoniae*, and *Streptococcus pneumoniae*, and an 85% reduction in pathogen associated virulence factors.⁹ Interestingly, a recent study by Brooks *et al.* demonstrates that the NICU room environment can serve as a reservoir of bacteria for the early colonization of the newborn gut microbiome.¹⁰ Analysis of fecal samples from preterm infants in the NICU, along with sinks and surfaces from the same room, showed that the infants were commonly colonized by nosocomial antibiotic-resistant pathogens also found on surfaces of the hospital. This provides a possible mechanism of how infants in the same NICU are often colonized by the same strains, even if their stay in the NICU is separated by years. It also

B. infantis is particularly important for infants in the NICU who receive costly donor milk, as the absence of this organism leads to up to 15% loss of the milk nutrients through fecal excretion of HMO.

Tracy Shafizadeh is a nutritional scientist and the Director of Scientific Communications at Evolve BioSystems.

establishes that the HMO in mother's milk, in conjunction with *B. infantis*, provides an important natural defense mechanism against pathogen colonization in the newborn infant at a time when their own immune system has still not yet developed.

It is well documented that infants in the NICU often experience gut dysbiosis. However, utilization of an infant specific probiotic, such as Evivo® (*B. infantis* EVC001) has now been clinically shown to restore the natural colonization of this protective bacterium to the infant gut, and provide both optimal nutrient availability from human milk, along with a mechanism against pathogen colonization in the hospital environment.

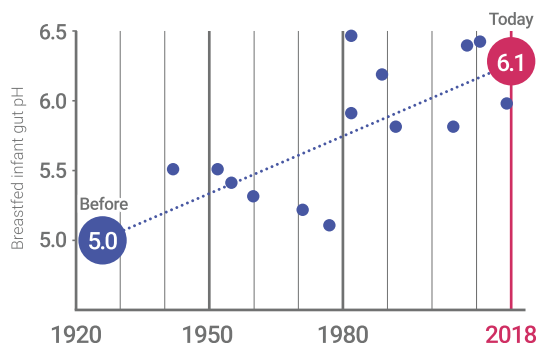
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The Fourth Trimester: Caring for NICU Mothers When They Need It Most

Maria Sienkiewicz Lennon, RN, MSN, CNM, IBCLC

Introduction

Most everyone is familiar with the fact that a term 40-week pregnancy is divided into three trimesters, each lasting about three months, with the third trimester concluding at birth. After a spontaneous vaginal delivery and discharge from the hospital, the next contact a new mother has with her doctor or midwife is usually at the six-week postpartum visit. At that time, most women are deemed healthy, ready to resume physical and sexual activity, and return to work if desired. At this critical time in a woman's life, as she is recovering from childbirth, transitioning into her role as a mother and learning to feed and care for her newborn, she is expected to know how to handle the many challenges of postpartum and navigate the healthcare system, for the most part all by herself.¹

However, there is another trimester, the fourth trimester. This is a lesser known term; definitions of what it is and how long it lasts vary. Some say it refers to the infant's adjustment to extrauterine life and others say it's the time it takes for the mother's body to return to its pre-pregnancy state after giving birth. Some say it lasts six weeks, some say three months and other sources say the fourth trimester lasts 12 months.

Although there are some discrepancies in the definition, most experts agree that the fourth trimester is a period of transition for both infants and mothers. The newborn infant needs as womb-like an environment as possible, and contact with his mother to acclimate to the extrauterine world. Mothers are recovering from childbirth, adjusting to physical, psychological and social changes, and transitioning to motherhood.

The fourth trimester perspective views the mother and infant as deeply interconnected, behaviorally and physiologically. Care must focus on the mother-infant dyad as a single unit, even when they are physically separated.¹⁹

The Problem

In addition to adapting to multiple physical, social, and psychological changes, new mothers are having to deal with sleep deprivation, overwhelming fatigue, pain, breastfeeding

difficulties, increased stress, hormonal and mood changes, body image issues and often lack of sexual desire. Women may also have pre-existing health conditions such as diabetes or hypertension, and social situations such as financial issues, substance use or abuse, intimate partner violence or other concerns. In the weeks after childbirth, women's healthcare is fragmented between maternal and child healthcare providers, and the postpartum visit is still six weeks away. Over 60% of maternal deaths occur in the postpartum period; 65% occur within the first week after birth.²⁰ Currently, up to 40% of women do not keep their six weeks postpartum appointment.¹

In addition, 23% of employed women return to work within 10 days postpartum, and an additional 22% return to work between 10 days and 40 days.⁶ Is it any wonder that more women die in the United States from pregnancy-related complications than in any other developed country?⁷ The US is the only industrialized nation with a rising maternal mortality rate, and between 2000 and 2014, there was a 26% increase in the number of women dying in the perinatal period.⁸

What the New Mother Needs from Caregivers

New mothers' needs do not disappear the moment the baby is born. In many ways, their needs increase as they begin the evolution into motherhood. Physically, they must heal from childbirth; some mothers must heal from major abdominal surgery after having a Cesarean birth. Most all new mothers must deal with shifting hormones, lack of sleep, painful breasts, increased stress, hemorrhoids, etc. Some mothers had pregnancy complications or currently have coexisting chronic health conditions, that still require close monitoring and follow-up.¹

"Mothers need just as much attention as a newborn, because they too have just been born."

— On the 4th Trimester Project's Facebook Page.

Maria Sienkiewicz Lennon has been caring for mothers and infants as a perinatal nurse for over 35 years. She became a board-certified lactation consultant in 1985, the first year the certification exam was given. As a Certified Nurse Midwife, Maria most recently worked in a full-scope practice on the Navajo Nation in northeast Arizona. Maria is an independent perinatal education consultant for Medela LLC.

Cultures around the world have long been aware of the increased needs of newly postpartum women, and provide additional care and support in the weeks after birth. Traditionally, the mother and baby couplet is nurtured and cared for by family and friends for 30 or 40 days, until the mother's convalescence is up and she is confidently able to care for her infant alone.²⁰

In practice, clinicians and providers need to shift from previous practices of assessing and treating mothers and infants as separate individuals to considering them as mutually regulating dyads. In other words, the needs of one half of the dyad affects the needs and responses of the other half.¹⁹

The American College of Obstetricians and Gynecologists (ACOG) issued new recommendations for postpartum care including scheduling a visit with a maternal care provider within the first three weeks after childbirth, rather than waiting the routine six weeks. A comprehensive postpartum visit should be scheduled to assess physical, psychological, emotional and social issues no later than twelve weeks after birth.¹

Education about the postpartum experience should begin early in pregnancy. For a few minutes of each prenatal visit, the provider can address postpartum issues, discuss who the mother identifies as her helpers, and develop a postpartum care plan. In high risk antenatal units, clinicians can also help prepare the mother and her family for the upcoming transition from pregnancy to childbirth and then on to parenthood.

For the Mother Whose Baby is in the NICU

The mother whose baby is in the NICU, has all the same needs of any mother who has just given birth, just multiplied several times over. NICUs are rarely experienced in caring for mothers, but with the paradigm shift in postpartum care, they have a responsibility to assist mothers in navigating the transition from pregnancy to parenthood. The mother of a NICU baby is dealing with being separated from her baby, sometimes with the NICU being many miles away from her home.

NICU staff should be aware of the mothers' needs since much of the fourth trimester is spent while their babies are patients in the NICU. Postpartum care is a process, not just a singular visit. Each woman is unique with individualized needs and her postpartum health care plan should be designed as such.¹

Caring for Mothers Physically: Postpartum care is still necessary after birth, and mothers are still at risk of suffering complications. All the risks of pregnancy-related deaths, like hemorrhage, preeclampsia and infections still exist after women are discharged from the hospital, and new threats such as postpartum depression, stress disorders and substance abuse may arise.

When a baby is hospitalized in the NICU, a mother may need to travel long distances just to be in close proximity to her newborn. She may then have to walk a long distance from the car to get to the NICU. Whatever can be done to ease her trip will aid in her physical healing and reduce stress.

In order to heal physically, mothers need nutrition, hydration and rest. A calm and soothing environment where mothers can grab a bite to eat, connect with other parents, and rest when tired will be conducive to mothers' well-being.

Caring for Mothers Emotionally: Postpartum depression (PPD) is the most common mental health complication of childbirth. The CDC estimates that 15% of all mothers experience symptoms that meet the criteria for the diagnosis of postpartum depression.⁴ The NICU experience increases the number of stressors a mother faces in the immediate postnatal period. Some of the stressors include strain on relationships,

financial burdens, family issues, concern about the survival of the infant, distressing sights and sounds of the NICU, lack of understanding and communication issues, to name just a few. It's no wonder that mothers of infants in the NICU are 40% more at risk for developing PPD than mothers of healthy term infants, and have rates of postpartum depression rates ranging from 28%–70%.¹⁶

Wanting to decrease stress on mothers and improve outcomes, a family-minded care model which opened last year in Vancouver, British Columbia aims to bridge the gap between mothers and their newborns post-birth.¹² The Teck Acute Care Centre at BC Children's Hospital and BC Women's Hospitals in Vancouver, British Columbia in Canada is the first hospital in North America that has a NICU that offers single room care where mothers can stay with their infants while receiving routine postpartum care - throughout their baby's hospital stay.¹⁵ They can remain with their NICU infants immediately after birth and never have to be separated.

Breastfeeding/Breastpumping Considerations: Most postpartum mothers who have infants in the NICU have been educated as to the superiority of mother's own milk for improved infant outcomes. Whether feeding directly at the breast or using an electric breast pump to extract milk from the breasts, mothers need proper instruction, the right equipment and continued support and encouragement from the NICU staff in order to produce optimal volumes of milk throughout the infant's NICU stay.¹¹

Establishment of Milk Supply: The first couple of weeks after birth are the most critical for initiating and establishing an adequate milk supply. Parker and colleagues have demonstrated that expressing breast milk within one hour of birth positively impacts future milk volume.¹³ Mothers should begin double pumping using an evidence-based, hospital grade (multi-user) breast pump. The Symphony PLUS[®] with Initiation Technology[™] incorporates the sucking pattern utilized by healthy-term infants during the first two days after birth and has been shown to improve initial milk volumes.^{10,14,17} Nurses and other NICU staff are responsible for using evidence-based practices to guide and support mothers' use of their own milk for their babies throughout the NICU stay.^{5,11}

Troubleshooting problems early in the process can help mothers overcome difficulties so they can continue breastfeeding or pumping and meet their breastfeeding goals. Once the new postpartum care paradigm is put into practice and the first postpartum visit is made within three weeks of birth, breastfeeding problems can be identified much sooner and difficulties corrected before the milk supply is compromised or early weaning occurs.

Conclusion

There is much work to be done in order to redefine and optimize care for all postpartum women. The good news is that the work has already begun and the ACOG Committee Opinion, Optimizing Postpartum Care, is a great start. The Academy of Breastfeeding Medicine, the American College of Nurse-Midwives, the National Association of Nurse Practitioners in Women's Health, the Society for Academic Specialists in General Obstetrics and Gynecology, and the Society for Maternal-Fetal Medicine endorse this document. If each organization puts the principles of postpartum care into practice, the stage will be

set for improved long-term health and well-being in the care of women.

Resources for Parents and Professionals

The Fourth Trimester Project: To improve care, the Fourth Trimester Project is bringing together mothers, health care providers, and other stakeholders to explore what families need most from birth to 12 weeks postpartum. To stay updated on the latest work, follow the 4th Trimester on Facebook (<https://www.facebook.com/4thTrimesterProject/>) and subscribe (<https://www.mombaby.org/subscribe-to-email-updates/>) to the newsletter.

The project has many resources helpful to parents and OB Care providers.

The American College of Obstetricians and Gynecologists:

Committee Opinion #736: Optimizing Postpartum Care <https://www.acog.org/Clinical-Guidance-and-Publications/Committee-Opinions/Committee-on-Obstetric-Practice/Optimizing-Postpartum-Care?IsMobileSet=false>.

Other helpful resources:

www.acog.org/More-Info/OptimizingPostpartumCare.

Apps for phone

LactMed: FREE. LactMed, part of the National Library of Medicine's (NLM) Toxicology Data Network (TOXNET®), is a database of drugs and dietary supplements that may affect breastfeeding. It includes information on the levels of such substances in breast milk, and possible adverse effects. Suggested therapeutic alternatives are provided.

Preterm Growth Tracker: FREE. Preterm Growth Tracker is designed to help parents and medical professionals track the growth of preterm infants. Uses the Fenton 2013 Growth Charts.

My Medela: FREE. Easily log your breastfeeding and pumping sessions, keep tabs on your baby's height, weight, sleep, and diaper changes. Data can be exported and printed to share with others. Gives breastfeeding tips and educational information.

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Bruises at Birth and Use of Prophylactic Phototherapy in Extreme Premature Infants

Shabih Manzar, MD, FAAP

Extreme premature infants are at risk of getting skin bruises due to their fragility. Slight pressure and mere handling during delivery may lead to bruises. The presence of blood under the skin is a potential source of bilirubin. To decrease the risk of kernicterus from hyperbilirubinemia healthcare providers use prophylactic phototherapy (pPTx) soon after birth in these babies.

Skin bruises go through stages. The blood under the skin has the potential to produce bilirubin during red cell degeneration (Figure 1).

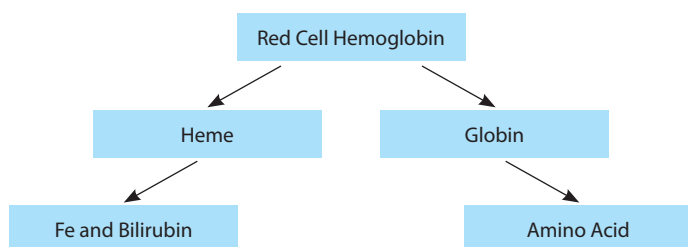


Figure 1

The bilirubin under the skin can be chemically changed by using photon energy. Phototherapy by isomerization (structural and configurational) and oxidation converts the non-soluble potential toxic bilirubin to more soluble non-toxic chemicals that are excreted from the body. But the question is: do skin bruises have enough bilirubin for the pPTx to act upon?

There are clear guidelines for treatment of hyperbilirubinemia in infants born at or greater than 35 weeks.¹ However, similar literature is lacking for small premature infants. A recent article from a multi-center study presented the treatment option of phototherapy in infant born less than 35 weeks of gestation.² In the article the treatment level of bilirubin given for less than 28 weeks of gestational age was 5-6 mg/dl. This poses the second question: should prophylactic phototherapy be initiated without obtaining the exact level of bilirubin? It is interesting to note that in the same article there is a mention of an option of pPTX in less than 26 weeks gestation but no rationale was given with respect to skin bruising.

The other argument against pPTx could be that the exact time taken by heme to convert into bilirubin in vivo may be variable and it is difficult to predict the exact bilirubin level. Also phototherapy has potential to cause increase in transepidermal water loss (TEWL) and temperature instability in extreme premature infants that could be detrimental to these fragile babies. These arguments pose a question mark on the use of pPTX in these high risk premature babies.

About 33 years back, Curtis-Cohen et al³ studied the use of pPTx in a randomized fashion in premature infants and they concluded that the clinical course of hyperbilirubinemia is not altered by using pPTx. A recent Cochrane review concluded that pPTX helps to maintain a lower serum bilirubin and may affect the rate of exchange transfusion and risk of neurodevelopmental outcome however no change in mortality was reported.⁴

Basing on these reasons and studies presented above, we conclude and suggest that the routine use of pPTx should be viewed critically and it should be reserved in infants who have significant other risk factors for development of hyperbilirubinemia.

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Shabih Manzar is with the Neonatal Intensive Care Unit at St. Elizabeth Hospital, Christus Southeast Texas Health System, 2830 Calder St, Beaumont, TX 77702. Email: shabihman@hotmail.com

Music in the NICU: An Evidence-Based Healthcare Practice with Proven Benefits

Michael R Detmer, MME, MT-BC (NICU-MT)

While there is nearly 30 years of published research demonstrating the positive impact of music on preterm infants in the neonatal intensive care unit (NICU), including shorter hospital stays, a more positive behavior state, improved physiological status, better feeding skills and fewer re-hospitalizations (Standley, 2012), healthcare providers and parents of patients still have many questions about the why, what, when and how related to NICU music therapy interventions.

Milestones in Infant Auditory Development

In order for an infant’s auditory system to properly develop, including fine-tuning of the cochlear hair cells and appropriate formation of neural pathways, he or she must be exposed to meaningful auditory stimuli either in utero, or in the NICU environment in the case of pre-term infants.

Infant Age	Milestones
24-25 Weeks	Begin to respond to vibroacoustic stimuli
28 Weeks	Hearing structures including appropriate neural pathways, in place and operational, allowing consistent response to vibroacoustic stimuli
29 Weeks	Has a moderate hearing range, including the natural singing range for most females
32 Weeks	In utero learning – thus memory – of sounds, such as music and the mother’s voice, have been demonstrated
40 Weeks	Discrimination for what they like to hear, with their mother’s voice being the favorite, especially in a higher pitched, singsong style

Infants that are deprived of meaningful sounds during auditory development are at risk for inhibited brain maturation, and ultimately inhibited speech and language acquisition.

The Role of the NICU Music Therapist

Research has shown that age-appropriate sensory stimuli, such as carefully selected music, can significantly benefit the clinical and neurodevelopmental outcomes of premature infants in the NICU (Standley, 2012; Standley & Walworth, 2010). The role of a

Michael Detmer is a music therapist and adjunct faculty member at University of Louisville and Norton Women’s and Children’s Hospital, Louisville, Kentucky. USA. Michael and Dräger worked in collaboration to develop this article as part of Dräger’s continuing efforts to advance neonatal care through the sharing of insights, knowledge and best practices within the neonatal community.

“Among preterm infants receiving multimodal neurologic enhancement interventions for 15-20 minutes twice a week, baby girls went home 21.3 days sooner, and boys 16.8 days sooner, compared to those who did not receive the therapy.”
– Walworth, Standley, Robertson, Smith, Swedberg, & Peyton, 2012

board-certified music therapist (MT-BC) with specialized NICU therapy (NICU-MT) training is to enhance these outcomes.

While over 50 percent of the top US children’s hospitals engage the services of board-certified music therapists with their NICU-MT specialization (Standley, 2014), there are many misconceptions about the field of music therapy — it is far more than a musician strumming a guitar or a nurse pressing “play” on a Pandora playlist.

In order for NICU music therapy to optimize the developmental outcomes of pre-term infants it must be delivered as an intentional, individualized intervention by a highly skilled, credentialed professional with extensive knowledge on the developmental care of these infants. Furthermore, music therapy should be utilized in close coordination with other members of the interdisciplinary team including speech language pathologists, occupational therapists, and physical therapists.

NICU music therapy uses specialized, research-based interventions that impact patient outcomes. Therefore a board-certified NICU music therapist with extensive experience working with pre-term infants must be the one to develop and manage the program. But that doesn’t mean that other NICU staff and parents do not have a role. Rather, they can be invaluable in extending the benefits of music.

We know from the speech and language development literature that babies learn to speak sooner and have higher language development scores the more they are exposed to language and the more words they hear, particularly from the voice of a parent. Infants will attend longer to a parent’s voice, especially singing, than a stranger’s voice because it is familiar and more rewarding to them.

In my first interactions with parents, over 95 percent tell me they are not good singers and don't want to harm their babies by singing to them. But we know from research that it is less about the quality of the voice and more about the familiarity and exposure. I frequently have to remind parents of that — singing to your baby is critical for his/her language development and opportunities for bonding, and he/she will attend to you for longer periods of time and respond better to your voice than a stranger's voice. They not only like your voice, but they *require* it for optimal speech and language development.

“The Pacifier Activated Lullaby® (PAL) intervention has resulted in shorter hospital stays, as well as increased volume intake, feeding rates, number of oral feeds per day, and shorter duration of gavage feedings.”

— Chorna, Slaughter, Wang, Stark, & Maitre, 2014

Regardless of who is providing the music — a music therapist, nurse or parent — it must be infant-directed. The singer must be able to read the cues of the infant and respond in the moment to optimize the interaction and the infant's response. For example, if an infant becomes more interactive during music, the singer could raise his/her eyebrows or sing a little faster. On the other hand, if the infant shows signs of stress, the singer could reduce the complexity of the music by beginning humming the song rather than singing the words.

Music Therapy Protocols

There are two primary protocols that we use in the field of NICU music therapy. One called “multimodal neurologic enhancement,” is a 22-step progression that systematically introduces stimuli to the infant, first sound (ie, live lullaby singing), then touch (ie, stroking of the infant from the top of the body down and from the middle of the body out), and lastly rocking. The goal of the intervention is to help preterm babies, who have immature sensory systems, learn to tolerate layering of sound, touch and movement in an attempt to decrease stress, which impacts sleep and neurodevelopment. We have been performing this protocol for more than two decades and have seen remarkable results.

“PAL® has also had an effect on infants admitted to the NICU for in-utero drug exposure including significantly decreased withdrawal symptoms as measured by the Finnegan Scoring Tool.”

— Detmer, DeLoach, Forbes, & Gossom, 2017

The other protocol uses the Pacifier Activated Lullaby® (PAL). This is a FDA-approved medical device featuring a pressure sensor that fits into the back of a pacifier. When the baby sucks on the pacifier the device plays lullaby music for 10 seconds. The music then stops unless the infant sucks on the pacifier again within the 10-second timeframe. The device allows the therapist to change the duration of the reinforcement (music) period, and the suck settings including the strength and the number of

Evidence-Based Recorded Music Guidelines For Premature Infants In The NICU*

Eligibility Criteria

- At least 28 postmenstrual weeks
- Daily nursing approval

Music Characteristics

- During initial presentation and for very premature infants, music should be as simple and non-alerting as possible.
- Soothing, constant, stable, and relatively unchanging:
 - » Voice alone or voice with one instrument
 - » Light rhythmic emphasis and slow tempo
 - » Constant rhythm and volume
 - » Melodies in a higher vocal range, which infants hear best
 - » Female (mother preferred) or child vocalists
 - » In the native language of the family
- Least alerting music for premature infants include:
 - » Three chords or less
 - » Major chords
 - » Lullaby style (repetitious: no separate melody for chorus/bridge)
 - » Played slowly and softly
- Various selections should be used to promote learning and avoid infant fatigue.
- Live, infant-directed singing (interactive and responsive to the infant) is recommended and more effective than recorded singing if it adheres to the characteristics mentioned earlier.

When to Play

- When awake or at the beginning of sleep
- During kangaroo care
- Immediately after painful/stressful procedures
- Audio recordings should not be left unattended in the high-risk infant.

When to Stop

- If infant exhibits frequent/continuous signs of overstimulation (eg, squirming, arched back, grimacing, increased heart rate, irregular breathing patterns, change in skin color, crying, splay finger, hiccoughing)
- During painful/stressful procedures

Duration and Frequency

- Maximum of four hours per day, alternating between 30 minutes of music and 30 minutes of no music

Volume

- 65–75 dB, scale C (measured at ear, not source)
- Music should be played with background noise not exceeding 50 dB.

Presentation

- Place speakers on each side of infant's head or feet so sound stimuli are received binaurally (*Note: the speakers don't necessarily have to be independent speakers, the sound just needs to be presented binaurally*).
- Music equipment must be tested to ensure it does not create electrical interference with medical equipment such as cardiac monitors and ventilators and is resistant (if used in the isolette) against high temperatures (36C) and humidity (75 percent) levels.

Contraindications

- Musical toys and mobiles because of the highly repetitive nature of the sole music selection usually available with these toys, the inability to adjust sound levels, and the lack of research on their use
- Radio, white noise, or nature sounds
- Earmuffs
- Headphones on the infant or directly on the mother's abdomen while pregnant
- Music played free field in an open bay because the volume is difficult to manage for each infant and it may not be appropriate because of the gestational age for those subjected

Least Alerting Songs

For a list of the least alerting songs for babies in the NICU, refer to *Detmer, M. R. & Whelan, M. L. (2017) Music in the NICU: The role of nurses in neuroprotection. Neonatal Network, 36(4). 213-217.

sucks per burst required by the infant to activate the music. We commonly use this intervention starting with infants around 34 weeks when they are just learning how, or preparing, to breast or bottle-feed. The pacifier can help them establish the strength, oral motor control, and suck-swallow-breathe coordination required for successful oral feeding.

Evidence-Based Guidelines for Music Therapy in the NICU

In my role as a board-certified music therapist, NICU nurses and other therapists often ask me for guidelines on using music in the care of premature infants, including the contraindications. When I began pulling together all of the music therapy and developmental literature, I realized there was no one single set of step-by-step guidelines that can serve as a resource for clinicians. I decided to use the current literature to fill this void and developed a set of evidence-based guidelines for the use of music with premature infants. These guidelines were published in the July/August 2017 issue of the journal *Neonatal Network*.

In reviewing the guidelines (see sidebar) it becomes clear why music therapy is such a complex field. It is no simple task. It requires a keen eye for clinical decision-making and control over multiple elements of music, including tempo, rhythm, volume, harmony and style.

While infant-directed singing that is applied within established guidelines and protocols can improve outcomes for NICU babies, research and clinical observations have shown that misguided efforts on music or other sound in the NICU can cause more harm than good, including infant overstimulation, stress, increased heart and respiration rates and sleep disturbances.

In my research I found some clinicians make emotionally-based rather than evidence-based decisions on music for NICU patients. For example, one study found nearly half of NICU nurses said they prefer the use of classical music for their patients. As an adult that seems to make sense because we think of classical music as calming. But in reality, classical music is very inconsistent, with volume and tempo changes and multiple instruments, which research has shown can over stimulate preterm babies.

Other therapists have attempted to mimic womb sounds with instruments such as a whooshing drum or ocean disc (both which contain beads that roll around) in the belief that the preterm infant will be soothed by the familiar sounds of the womb. What they don't take into consideration is that while infants can hear at 26-27 weeks gestation, they don't remember sound before 32 weeks and it is likely not until 34-35 weeks that they remember sounds consistently. So a baby born at 30 weeks has no memory of womb sounds. Furthermore, research has shown that preterm infants prefer and are most stable with predictable, consistent and rhythmic auditory stimuli, and there is no way to create rhythm with a whooshing drum or ocean disc. Finally, this lacks language input, which we know is critical for development.

Presenting the Case for a NICU Music Therapy Program

In today's healthcare environment, where health systems and hospitals are trying to deliver better patient outcomes at a lower cost, NICU music therapy is a natural fit. Studies have shown that NICU music therapy interventions facilitated by board-

Studies have shown that NICU music therapy interventions facilitated by board-certified music therapists contribute to shorter hospital stays for premature infants among many other developmental and medical benefits.

— Standley, 2012

certified music therapists contribute to shorter hospital stays for premature infants among many other developmental and medical benefits (Standley, 2012). Shorter length of stay drives savings for healthcare organizations, and increases revenue generation since it frees up beds for additional patients.

With music therapy we are essentially wiring the brain of preterm infants so that they work more like a typically developing term infant's brain. As a result, we see acquisition of important developmental milestones sooner than those who did not receive the therapy. This has the potential to minimize the number of therapeutic interventions needed for the child long-term (eg, speech therapy), further reducing healthcare costs.

Additional Resources

Below are resources for healthcare staff and parents of preterm infants seeking additional information on music therapy in the NICU:

- *The National Institute for Infant & Child Medical Music Therapy*: offers a registry of all trained NICU music therapists by city: <http://www.music.fsu.edu/NICU-MT>
- *Music Therapy with Premature Infants: Research and Developmental Interventions, 2nd ed.*, by Jayne M Standley and Darcy Walworth: this handbook discusses prematurity, medical/developmental assessments, NICU care procedures, and infant growth and maturation goals and the NICU music therapy procedures to facilitate these goals. While it is aimed toward medical professionals, it is valuable for parents as well.
- *Bright Start Music: A Developmental Program for Music Therapists, Parents, and Teachers of Young Children* by Darcy Walworth: This is a research- and developmentally-based music curriculum aligned with the Centers for Disease Control & Prevention (CDC) developmental milestones. This book and CD walks parents and therapists through age-based milestones in child development and presents musical activities designed to support developmental milestones.

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Should There be a Non-Compete Clause for Neonatologists?

Shabih Manzar, MD

The field of neonatology is a service-based discipline. However, since the introduction of the managed care, it has become a business model of practice. Historically, the physician practicing neonatal medicine leaves a practice and can work at another without any legal implications. But in recent years, the language of most of the employment contracts has changed. The introduction of non-compete clauses has become standard.¹ At one end the company has to protect their business competition, while at the other end the physician has a distinct patient population and need in the community.

This article highlights the points from a physician's perspective as described earlier.² The problems with non-compete clauses are two-fold. First, the verbiage is very legal and second it usually favors the company. In Example 1, as noted very clearly that all items are in favor of the company. The clauses c, d and e are understandable standard business—protecting strategies but item a and b leave the physician with no choice. He/she can't provide any services in the area (medical, consultation, staff), and can't own, manage, operate or control, thus can't open a practice. The two options are: wait for the period (2 years) or move out of the area of practice. It is not easy to secure jobs right away after losing one. Also, once physically and emotionally invested in a community, it is very difficult to move out, especially when kids are in schools and the housing market is tight. Also the geographic restriction is overkill, limiting the physician to work close by.

Example 1

Employee and Company agrees that without Company's prior permission he or she will not during the term of this agreement and for a period of two years of employment will engage in

- a) Any services including medical, consultation or staffing
- b) Own, manages, operate, control a business or enterprise in competition with the company
- c) Solicit or attempt to induce patients, hospitals, clinics, insurances contracted with the company.
- d) Diverts or attempt to divert any business from Company
- e) Attempt or solicit any person employed or contracted by the company
- f) Engage in specialty practice within a geographic restriction of 30 mile radius from the place of employment

As indicated in the dossier by the American Medical Association,³ there has to be a balance between protecting healthcare companies and physician interests. The language of non-compete clauses should be structured in such a way that protects both parties. A buy-out option should be provided.⁴ The purpose of this write-up is to address the issue of non-compete in healthcare employment contracts pertaining to practicing neonatologists with the hope to spark some discussion so that a favorable solution is sought.

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- 4 <https://www.ama-assn.org/sites/default/files/media-browser/public/omss/a17-omss-employment-presentation.pdf>

Shabih Manzar is with the Neonatal Intensive Care Unit at St. Elizabeth Hospital, Christus Southeast Texas Health System, 2830 Calder St, Beaumont, TX 77702. Email: shabihman@hotmail.com

The Extended Dwell Peripheral Intravenous Catheter Is an Alternative Method of NICU Intravenous Access

Kimberlee B Chenoweth, DNP; Jia-Wen Guo, PhD, RN; Belinda Chan, MD

Abstract

Background: Establishing vascular access is a common neonatal intensive care unit procedure. The extended dwell peripheral intravenous (EPIV) catheter is a 6-cm and 8-cm silicone catheter for peripheral vein insertion, which is a newer vascular access device than peripherally inserted central catheters (PICCs) and peripheral intravenous (PIV) catheter. Extended dwell peripheral intravenous catheters have been widely used in adults but evidence in neonates is lacking.

Purpose: To explore indwell time, success rate, catheter-associated complications, and cost among EPIV catheters, PICCs, and PIV catheters in neonates.

Methods: We retrospectively compare patient demographics, indwell time, success rate, and catheter-associated complications, and analyze the rate of hyaluronidase-treated intravenous (IV) fluid extravasation on neonates who had an EPIV catheter, a PICC, or a PIV catheter in a level III neonatal intensive care unit. We also estimate the insertion cost of these 3 vascular access devices on the basis of our hospital charges.

Results: Extended dwell peripheral intravenous catheters were inserted in 432 neonates with an indwell time of 4.0 ± 2.3 (mean \pm SD) days. Peripherally inserted central catheters were inserted in 202 neonates with an average indwell time of 7.3 ± 4.4 (mean \pm SD) days, which was longer than EPIV catheters ($P < .001$). Peripherally inserted central catheters had a higher success rate of 83.6% than 71.7% of EPIV catheters, meaning succeeded in lasting through the completion of therapy ($P = .001$). Peripherally inserted central catheters were associated with 4 cases of life-threatening complications; none was seen in the EPIV catheter group. The incidence of hyaluronidase-treated IV fluid extravasation was less in EPIV catheter recipients (1.2%) than in the PIV catheter recipients (3.9%) ($P = .004$); none was in the PICC group. Cost savings were noted with using an EPIV catheter.

Implications for Practice: Extended dwell peripheral intravenous catheter is a feasible option for neonatal vascular access.

What This Study Adds

- A retrospective analysis of the pros and cons of EPIV catheters, PIV catheters, and PICCs within the neonatal population, which is a step toward a larger, randomized control trial of neonatal vascular access.
- Information that allows the NICU clinician to make a more informed decision regarding the use of vascular access devices.

Implications for Research: These data provide a baseline for future studies to explore the efficacy and effectiveness of EPIV catheter in the neonates.

Keywords: catheter-associated complications, cost, extended dwell peripheral intravenous catheter, indwell time, midline intravenous catheter, neonates, peripheral venous catheter, peripherally inserted central catheter, placement success rate, vascular access

Background/Significance

Vascular access is often needed in neonatal intensive care unit (NICU) neonates. The majority of NICU neonates require vascular access during their stay for prolonged nutritional support and medications.

Establishing vascular access is challenging in NICU neonates due to their small and extremely fragile veins.¹ The 2 most commonly used neonatal vascular access devices are peripheral intravenous (PIV) catheter and peripherally inserted central catheter (PICC). However, both devices have well-known limitations and risks.² The neonatal extended dwell peripheral intravenous (EPIV) catheter is a new device that became available in recent years and seems to have advantages over the PIV catheter and PICC, but comparative effectiveness studies have not been reported from the NICU population.³

A PICC is an intravenous catheter that is inserted peripherally and threads into the central venous circulation and is made of silicone, polyurethane, or polyethylene.⁴ To be considered centrally placed, the tip of the PICC should be in the superior or inferior vena cava⁵ (Figure 1). It is intended for long-term nutrition and medication therapies as it can remain in place for months at a time. Peripherally inserted central catheter

Dr Chenoweth is with the Primary Children's Neonatal Nurse Practitioner Group, Intermountain Healthcare, Salt Lake City, Utah; Dr Guo is with the College of Nursing, University of Utah, Salt Lake City, Utah; Dr Chan is with the Division of Neonatology, Department of Pediatrics, University of Utah School of Medicine, Salt Lake City, Utah.

requires additionally trained nurses for insertion and radiographs to confirm correct placement.⁵ Peripherally inserted central catheter can be associated with complications including central line-associated bloodstream infection (CLABSI), phlebitis, infiltration, occlusion, catheter leakage leading to pleural effusion and peritonitis, cardiac arrhythmia, pericardial effusion, and cardiac tamponade.⁶ Peripherally inserted central catheter-related cases of CLABSI and pericardial effusion had been directly linked to neonatal death.⁶⁻⁸

The most widely used vascular access device in the NICU is a PIV catheter, which is commonly a 22- or 24-gauge Teflon radiopaque over the needle catheter.⁹ A PIV catheter is easier to place than a central catheter, but it does not last as long and can often take multiple attempts to be successfully placed.^{1,10-12} Most NICU nurses are competent at inserting a PIV catheter, which is usually placed in the extremities or the scalp.⁹ Despite the high rate of use and long history, PIV catheter still has a poor track record. One study (n = 72) among the neonatal population showed that the average length of time a PIV catheter was in place before complications required removal was 30 hours,¹³ while another larger study (n = 250) among the neonatal population showed 37 hours to be the average length of time.¹⁴ This is an extremely short period compared with the length of nutritional supplementation and medication needed in most NICU neonates. Approximately 95% of PIV catheters are removed before the completion of therapy generally due to complications such as infiltration, infection, clotting, or other problems.⁹ Infiltration rate among neonates is 57% to 70% and tissue damage from extravasation occurs in 11% to 25%.¹⁵ Extravasation can lead to tissue necrosis, infection, limb disfigurement, and functional loss.¹⁶ Treatments vary among each unit protocol including immediate line removal, limb elevation, saline washout, and thermal compress.¹⁶ Subcutaneous injection of hyaluronidase is one of the pharmaceutical treatments of IV extravasation. Hyaluronidase is an enzyme that helps absorb and disperse extravasated irritants, which has shown to reduce the severity of tissue damage.¹⁷

Extended dwell peripheral intravenous catheter, which is also known as a midline catheter, has been widely used in adults since the 1950s, but there is very limited information available regarding its use in the NICU population.³ In adults, EPIV catheter has been showed to reduce cannulation attempts and improve patient satisfaction and hospital efficiency; however, it is associated with complications such as phlebitis and thrombosis.^{18,19} Neonatal EPIV catheter was first introduced in 1992²⁰; its design has been evolving and improving since then. The latest generation of neonatal EPIV catheter is a short single lumen silicon catheter, manufactured as either a 6 cm or an 8 cm length for neonates (length used on the basis of neonate's size or unit preference), which is designed to remain intravenously for up to 29 days.²¹ Typically, the catheter is inserted into a peripheral vein on the forearm or leg, with the catheter tip located below the axilla of the arm (Figures 2A and B) or below the groin of the leg.⁶ Extended dwell peripheral intravenous catheter placement does not require X-ray film confirmation unless there is difficulty in insertion, advancement, or flushing.²² According to the Infusion Nurses Society's standards of practice, EPIV catheter is used as a peripheral vascular access which should not be used for "continuous vesicant therapy, parenteral nutrition, or infusates with an osmolality greater than 900 mOsm/L"²² including dextrose greater than 12.5% IV fluid, total parenteral nutrition greater than 900 mOsm/L, vasopressors,

chemotherapy, sodium chloride greater than 3%, and sodium bicarbonate.²³

Limited research points to the benefit of EPIV catheter over conventional PIV catheter for neonates because of the higher percentage of EPIV catheter staying in until the end of treatment and its comparative longer dwell time. Lesser et al¹² reported the use of EPIV catheters on 9 very low birth-weight (VLBW) infants, in which EPIV catheters had a longer indwell time than PIV catheters (9 vs 3 days).

Similarly, Wyckoff (n = 143 EPIV catheters)¹ and Dawson¹⁰ had separately suggested that EPIV catheter was associated with longer indwell time and fewer cannulation attempts than PIV catheter in neonates. Leick-Rude and Haney¹¹ conducted a non-randomized prospective study of 1130 EPIV catheters used in 858 neonates, who were ranging from 360 to 800 g in weights and 23 to 42 weeks of gestational age at birth. It has shown that the average indwell time for EPIV catheters was 8.7 days, with a success rate of 57% meaning the catheters staying in until the end of treatment.¹¹

In 2012, we devised and implemented the EPIV catheter protocol in our level III NICU. Along the process, we compiled detailed data regarding our EPIV catheter experience. As a step toward building an evidence-based EPIV catheter NICU practice, the purpose of this study was to explore indwell time, success rate, catheter-associated complications, and insertion cost among EPIV catheter, PICC, and PIV catheter in our NICU. This information may allow NICU clinicians to make a more informed decision regarding the choices of vascular access devices in neonates.

Methods

This retrospective study was conducted to compare patient demographics, indwell time, placement success rate, and catheter-associated complications among neonates who had an EPIV catheter, a PICC, or a PIV catheter in a level III NICU. Data

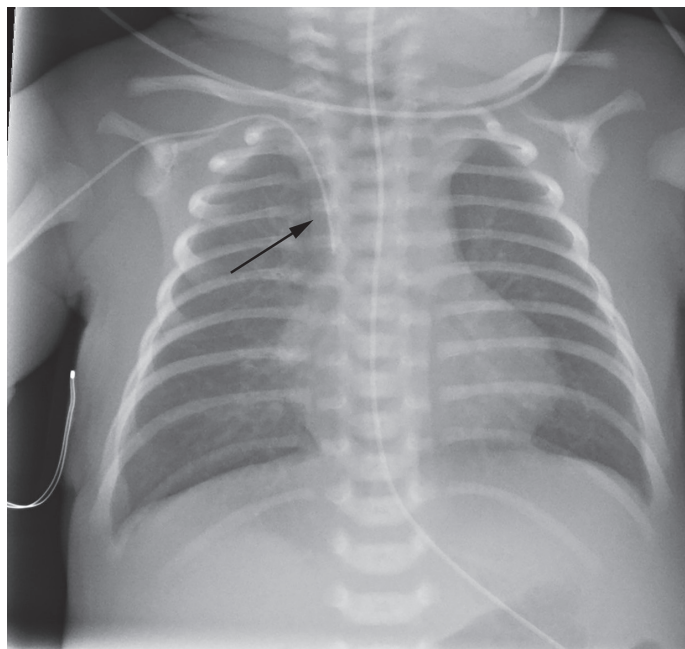


Figure 1. Chest radiograph of a neonate with a peripherally inserted central catheter (PICC) placed in the right arm. Arrow indicates the PICC is in the superior vena cava.

Table 1. Demographic Features of EPIV Catheter, PICC, and PIV Catheter Groups

	EPIV Catheter (n = 32)	PICC (n = 202)	PIV Catheter (n = 2828)	P
Gestational age at birth, mean (SD), wk	35.8 (2.6)	36.5 (2.7)002
Weight at birth, mean (SD), g	2687 (731.7)	2820 (756.7)200

Abbreviations: EPIV, extended dwell peripheral intravenous; PICC, peripherally inserted central catheter; PIV, peripheral intravenous.

*The statistical outcome of Mann-Whitney U test.

regarding IV fluid extravasation rate were collected on neonates with EPIV catheter, PICC, and PIV catheter. Insertion cost of these 3 vascular access options was estimated on the basis of our unit charges.

Settings

This study was conducted at a level III NICU in the Intermountain Medical Center at Salt Lake City, Utah, which is a 48-bed unit that provided care for more than 3000 admitted complex term and preterm neonates during the time frame of the study.

Sample

Between August 2012 and December 2016, 3526 neonates were admitted to the Intermountain Medical Center NICU. A retrospective review was performed on all neonates who were 32 weeks of gestation or older and weighed 1500 g or more at birth with EPIV catheter, PICC, and/or PIV catheter placements. In this study period, there were 2828 neonates who met the gestational age (GA) and birth weight (BW) inclusion criteria; all of them had PIV catheters inserted during their hospitalization. In addition to PIV catheters, 202 of these neonates required PICC placement and 432 of these neonates required EPIV catheter placement.

Measures

In our NICU, data sheets were created for all neonates, with each EPIV catheter and PICC insertion containing patient demographics and catheter-related data. The data collected for this study included GA at birth, BW, the reason for insertion, numbers of insertion attempts, indwell time, the reason for removal due to completion of treatment, and complications in neonates with EPIV catheter and PICC. Data on PIV catheter

insertion were not separately documented in the same extensive details as EPIV catheter or PICC insertion in our unit. With the retrospective nature of this study, we were unable to practically perform chart reviews on more than 2800 neonates who had PIV catheters during their hospitalization and to compare their demographics, indwell time, and success rate with EPIV catheter and PICC groups.

Hyaluronidase is the treatment of choice in our unit for neonates with significant IV fluid extravasation. Based on our pharmacy database, we studied the number of hyaluronidase doses used in neonates, which was used to compute the incidence of hyaluronidase-treated IV fluid extravasation associated with each type of catheter. Insertion cost of EPIV catheter, PICC, and PIV catheter was calculated on the basis of 3 categories: (1) direct supply costs, (2) labor costs, and (3) radiographic charges in Utah.

Statistics

Descriptive statistics was used to summarize and describe the numeric data such as GA and BW. The Mann-Whitney *U* test was used to assess differences in BW, GA, and indwell time between groups (eg, EPIV catheter, PICC); for easier understanding, we presented mean and standard deviation to describe the variables and the *P* values based on the Mann-Whitney *U* tests in Tables 1 and 2. The χ^2 test was used to assess differences in success rate and incidence of hyaluronidase-treated IV extravasation. All the descriptive and statistical analyses were made using the SPSS 24 for Windows and using a significance level of .050.

Procedure

Extended dwell peripheral intravenous catheter is a relatively new innovation having been available for neonates. With the

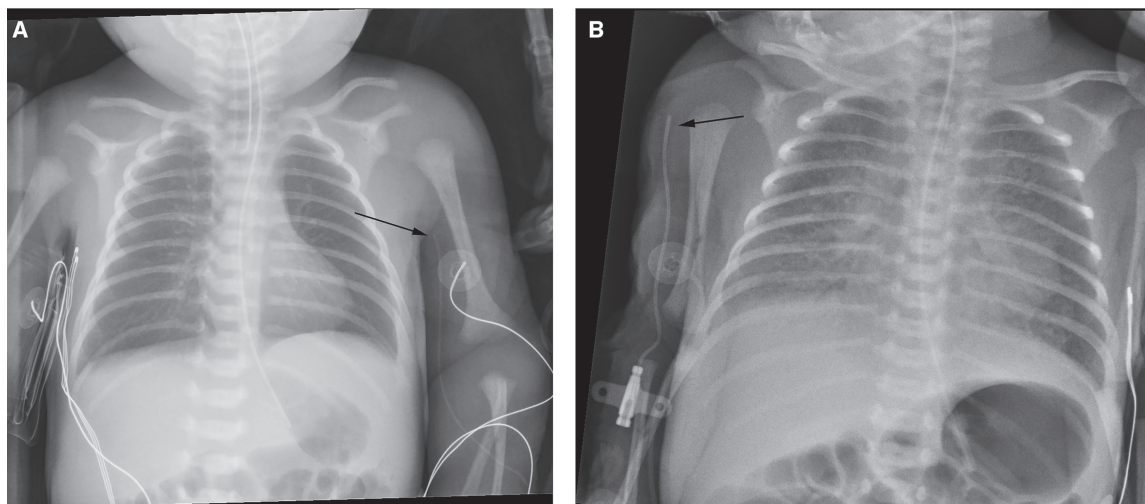


Figure 2. (A) Chest radiograph of a neonate with an extended dwell peripheral intravenous (EPIV) catheter placed in the left arm. Arrow indicates the tip of the EPIV catheter in the left brachial vein below the left shoulder. (B) Chest radiograph of a neonate with an EPIV catheter placed in the right arm. Arrow indicates the tip of the EPIV catheter in the right cephalic vein below the right shoulder.

Table 2. Placement Success, Complications, and Cost of EPIV Catheter, PICC, and PIV Catheter Groups

	EPIV Catheter (n = 432)	PICC (n = 202)	PIV Catheter (n = 2828)	P
Placement success				
Indwell time, mean (SD), d	4.0 (2.3)	7.31 (4.4)	...	<.001 ^a
Success rate, %	71.7	83.6001 ^b
Complications				
Life-threatening complication (cases per 1000 catheter days)	...	CLABSI (0.68/1000) Premature ventricular contraction (0.68/1000) Superior vena cava obstruction (0.68/1000) Peritonitis (0.68/1000)		
Incidence of hyaluronidase-treated IV fluid extravasation, %	1.2	...	3.9	.004 ^b
Insertion cost (for 1-wk use)^c				
Supplies	\$43.15	\$120.38	\$32.67	
Labor	\$30.00	\$60.00	\$67.50	
Radiography	\$0	\$410.00	\$0	
Total	\$73.15	\$590.38	\$100.17	

Abbreviations: CLABSI, central line-associated bloodstream infection; EPIV, extended dwell peripheral intravenous; IV, intravenous; PICC, peripherally inserted central catheter; PIV, peripheral intravenous; PVC, Premature ventricular contraction.

^aThe statistical outcome of Mann-Whitney U test.

^bThe statistical outcome of χ^2 test.

^cCost is based on Intermountain Medical Center charges in Utah.

knowledge gained through the literature review, our NICU RN vascular access team introduced the EPIV catheter product and developed the EPIV catheter protocol in 2012. The EPIV catheter used was a 1.9 Fr \times 6-cm and a 1.9 Fr \times 8-cm silicone-based catheter²¹ (Figure 3). Candidates for EPIV catheter insertion are selected by the healthcare team on the basis of the need for multiple days of IV antibiotics and/or IV nutrition. Inclusion criteria for EPIV catheter insertion include neonates who are 32 weeks of gestation or more and weighing 1500 or more at birth with difficult or limited venous access that is likely to be required up to 4 weeks. Neonates requiring fluid greater than dextrose 12.5% concentration, total parenteral nutrition osmolality greater than 900 mOsm/L, and/or medications that are administered via central catheters are excluded from receiving an EPIV catheter. Peripherally inserted central catheter or umbilical venous catheter is inserted in neonates who require central vascular access. Peripheral intravenous catheter is routinely the first vascular access placed on critically ill neonates admitted to NICU.

The data collection occurred after the privacy board of the Intermountain Healthcare Institutional Review Board and The University of Utah Institutional Review Board approved the study protocol. The privacy board granted a waiver from individual parental consent because this was a deidentified data-only retrospective study with appropriate privacy protection.

Results

Between August 2012 and December 2016, 3526 neonates were admitted to the Intermountain Medical Center NICU. During this time, EPIV catheters were inserted in 432 neonates who were born at 32 to 41 weeks of GA (35 ± 3 weeks, mean \pm SD), with BW 1500 to 4400 g (2700 ± 700 g, mean \pm SD) (Table 1). Total EPIV catheter days were 1735, with a mean indwell time of 4.0 ± 2.3 days (ranging 1-29 days). A portion of EPIV catheters (13.3%) was inserted less than 2 days prior to the completion of therapy. In neonates with an EPIV catheter, 71.7% of catheters

succeeded in lasting through the completion of therapy (Table 2). The others (28.3%) were removed before the completion of therapy because the catheters had failed. The reasons for failures were leaking (n = 37, 8.6%), infiltration (n = 29, 6.7%), palpable venous cord or hardening (n = 18, 4.2%), clotting (n = 15, 3.5%), accidental dislodgement (n = 14, 3.2%), or other reasons (n = 8, 1.8%) including sluggish when flushing, redness, swelling, phlebitis, broken catheter, or used more than 29 days as recommended by the manufacturer. We found no statistical significance in BW or GA ($P = .17$) comparing neonates with EPIV catheters that lasted with those that failed early.

During this time, PICCs were inserted in 202 neonates who were 32 weeks of GA or more (36 ± 3 weeks, mean \pm SD) at birth and weighing 1500 g BW or more (2800 ± 800 g, mean \pm SD) (Table 1).

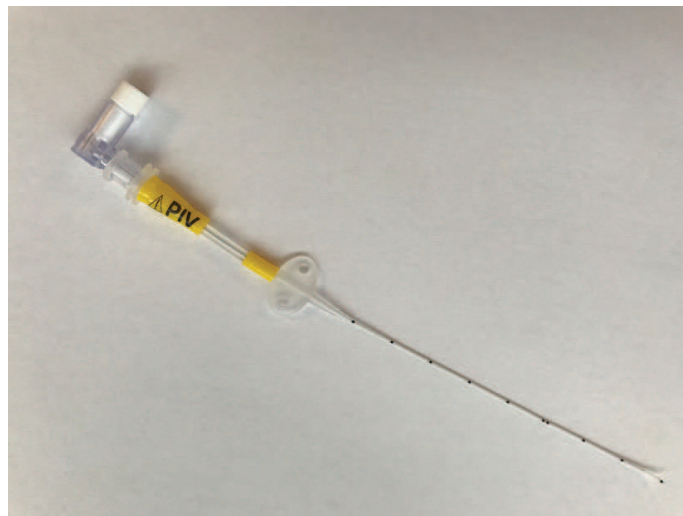


Figure 3. 1.9 Fr \times 8-cm extended dwell peripheral intravenous catheter with stylet from NeoMedical, Inc. (www.neomedicalinc.com).

Summary of Recommendations for Practice and Research

What we know	<ul style="list-style-type: none"> • Vascular access is a challenge in the NICU. • EPIV catheters are 6-cm and 8-cm silicone catheters inserted into neonatal peripheral veins. Similar devices have been safely used in adults but have not gained popularity in neonates due to a lack of evidence. • Overall, neonatal PIV catheters do not remain in place for long periods of time and multiple PIV catheters are replaced prior to the completion of therapy. • PICCs have longer indwell times than PIV catheters and EPIV catheters but are expensive and are associated with life-threatening complications.
What needs to be studied	<ul style="list-style-type: none"> • The efficacy of EPIV catheter within the neonatal population as compared with other more widely accepted forms of vascular access. • The safety of EPIV catheter compared with other vascular access devices used by neonates. • The cost-effectiveness of EPIV catheter as compared with other vascular access devices used in the same population.
What can we do today	<ul style="list-style-type: none"> • Provide a wide variety of vascular access devices for neonates including newer devices such as EPIV catheter. • Make informed decisions on which vascular access device to use with each neonate based on his or her individual needs. • Aim to increase available literature regarding vascular access within the neonatal population by gathering and publishing data.

Peripherally inserted central catheter group was 1 week older in GA at birth than the EPIV catheter group ($P = .002$). Total PICC catheter days were 1476, with a mean indwell time of 7.3 ± 4.4 days, which was longer than EPIV catheter indwell days ($P < .001$). The success rate of PICC was 83.6%, which was a higher success rate than EPIV catheter (71.7%) ($P = .001$) (Table 2).

Catheter-associated life-threatening complications are shown in Table 2. Peripherally inserted central catheters were associated with 1 case of each of the following: CLABSI (0.68/1000 catheter days), premature ventricular contractions (0.68/1000 catheter days), superior vena cava obstruction (0.68/1000 catheter days), and peritonitis (0.68/1000 catheter days). No life-threatening complications were seen in 1735 EPIV catheter days.

In the EPIV catheter group of 432 neonates, we identified 29 cases of IV infiltration and 5 of those significant cases were treated with hyaluronidase (5/432, 1.2%) (Table 2). During the same period, 2828 neonates who were born at 32 weeks of GA or more and weighing 1500 g or more BW were admitted to the NICU and had a PIV catheter inserted. Among those, 110 neonates were treated with hyaluronidase for PIV catheter-associated IV fluid extravasation injury. A higher rate of significant extravasation (110/2828, 3.9%) requiring treatment was observed in the PIV catheter group than in the EPIV catheter group ($P = .004$) (Table 2). No hyaluronidase was used in neonates with PICCs.

Insertion cost of 1-week use of EPIV catheter, PICC, and PIV catheter was estimated on the basis of the Intermountain Medical Center supply charge, hourly nursing wages, and X-ray film charges (Table 2). Peripheral intravenous catheter, EPIV catheter, and PICC supplies cost \$7.26, \$43.15, and \$120.38 each, respectively. As an average, PIV catheter is replaced every 1.5 days, or 4.5 PIV catheters in 7 days,¹⁹ 1-week PIV catheter supply costs a total of ($\$7.26 \times 4.5$) \$32.67. Inserting PICCs is more labor-intensive and time-consuming than inserting EPIV catheters, as they require precise catheter tip location with X-ray films confirmation. Labor cost is calculated on the basis of average nursing wages of \$30 per hour. Two nurses are typically needed to insert EPIV catheter and PICC, requiring 30 minutes and 60 minutes each, with an estimated labor cost of \$30 and \$60, respectively. Each PIV catheter placement with 2 nurses

assisting typically takes less than 15 minutes; however, labor cost accumulates up to \$67.5 for placing 4.5 PIV catheters over 1 week. An average of 2 radiographs (\$410 each) is needed to confirm appropriate placement of PICC; none is necessary for EPIV catheter and PIV catheter. As a result, 1-week costs of EPIV catheter were \$517 and \$27 less than PICC and PIV catheter.

Discussion

Extended dwell peripheral intravenous catheter has been available for more than a decade and has proven valuable for certain circumstances in adult patients.²⁴ However, a rigorous assessment of its indwell time, placement success rate, safety, and cost in a NICU setting has not previously been published. This study is an early step toward such an analysis.

We found that EPIV catheter indwell time averaged 4 days, with a 72% success rate. Previous reports of EPIV catheter use in neonates claimed an indwell time of 6 to 10 days, with less than 50% of the catheters remaining in place until they were no longer needed.^{1,10-12,25} Earlier data, as well as our own, support the conclusion that EPIV catheter use in neonates is more effective than a PIV catheter.

We reported a shorter average EPIV catheter indwell time than previous reports.^{1,10-12} Our experience suggests that we sometimes missed opportunities in maximizing EPIV catheter usage. Dawson¹⁰ suggested inserting EPIV catheter at the time of admission in all neonates who are expected to need at least 3 days of vascular access; our EPIV catheters were commonly inserted at the end of the treatment course after exhausting multiple PIV catheters, as 13% of our EPIV catheters were used for only 2 days or less. We speculated that, in some cases, EPIV catheter can be placed at the beginning of fluid or antibiotic treatment course, which maximizes EPIV catheter's indwell days to the entire time intravenous access is needed. In addition, prior studies included VLBW neonates (<1500 g), a group that typically requires more time to reach IV nutrition independence than do larger neonates, and thus need longer catheter indwell times.

We reported a much higher success rate than others. At the beginning of our EPIV catheter implementation, placement was not limited on the basis of BW or GA at birth. A high EPIV catheter failure rate (59%, $n = 22$) was found in VLBW neonates,

which is comparable with the previously published failure rate in similar population.¹¹ Thus, neonates with BW of less than 1500 g or GA of less than 32 weeks are excluded from our current EPIV catheter protocol. Also, some VLBW neonates require a parenteral nutrition composition and osmolality that is best provided using a PICC. Therefore, our unit considers using PICCs rather than EPIV catheters for VLBW neonates.

We observed a good safety profile of EPIV catheter. Neonates with EPIV catheter had a lower incidence of hyaluronidase-treated IV fluid extravasation than did those with PIV catheters. In addition, we detected no life-threatening complications or catheter infections associated with EPIV catheter. Four cases of PICC-associated life-threatening complications including CLABSI, arrhythmia, superior vena cava obstruction, and peritonitis were noted in this study group.

We recognize weaknesses in our study. First, our EPIV catheter experience involves a single center and is a retrospective analysis and thus lacks the rigor of a prospective randomized device trial. Since EPIV catheter tip is located in a peripheral vessel, its usage is not appropriate for neonates requiring high dextrose concentration, high total parenteral nutrition osmolality, or medications that should be given only through a central catheter. Neonates who have those needs would be considered for PICC placement instead. Therefore, our EPIV catheter recipients may have been, as a group, somewhat less ill than those in whom a PICC was used. We did not adjust the illness severity as a confounding factor. Also, we lack data on our PIV catheter indwell times and success rates and on the number of attempts per vascular access insertion. Finally, EPIV catheter seems to be less costly than PICC or PIV catheter for 1-week use; however, we recognize that our cost methods are imprecise and incomplete and that the value of any intravenous access varies substantially on a case-by-case basis. In fact, our determination of the cost advantages of EPIV catheter may be understated, because we did not attempt to include expenses of treating PICC-associated complications or lessening discomfort from repeated PIV catheter punctures.

We conclude that for selected NICU patients, EPIV catheter may have advantages over PIV catheter and PICC. A randomized prospective trial and additional studies are needed to validate the potential value of EPIV catheter usage for neonatal care.

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The Clinical Value of Infant Monitoring

Andre A Muelenaer, Jr, MD,MS, FAAP, FCCP

Infant Monitoring in the Hospital and Home provides clinical value to healthcare providers. This review is intended for clinicians who may encounter babies who are at risk for Apnea and Apparent Life Threatening Events (aka BRUEs) as well as those who routinely manage these babies through an Apnea Program or Durable Medical Equipment provider. This review focuses on the medical management of Apnea as a symptom of a broad range of possible conditions and the use of event-recording Cardiorespiratory Monitors for monitoring newborns in the hospital and home.

We will cover some background and definitions. We will focus on appropriate set up and use of a Cardiorespiratory Monitor, and how to gather and analyze the data from the monitor. Finally, we will touch on cost considerations of monitoring.

Formal definitions of Apnea, Bradycardia, and Tachycardia are shown in Figure 1:

Central Apnea: Pause in breathing > 20 seconds, or of shorter duration, associated with Bradycardia, Desaturation/Cyanosis/Pallor, Change in neurologic status

Obstructive Apnea: Respiratory effort with loss of air flow,

Mixed Apnea: Combination of Central and Obstructive Apnea

Neonatal bradycardia: Age related Norms

< 38 weeks: 100 bpm
39 - 44 weeks: 80 bpm
45-52 weeks: 70 bpm
53-66 weeks: 60 bpm

Tachycardia: Rhythm Disturbances such as SVT usually present with sustained heart rates much higher than the norms, ranging from 220-320 bpm.

Figure 1. Norms for Cardiorespiratory Events in Infants Apnea

All premature infants are at risk for apnea of prematurity. Apnea is rare among full-term healthy infants and, if present, usually indicates an underlying pathology. Closely associated with apnea of prematurity is periodic breathing. Periodic breathing (PB) is defined as a series of three or more respiratory pauses lasting 3

seconds or longer separated by 20 seconds or more of normal breathing. There are published norms for percentage of periodic breathing, but more importantly are the consequences, such as hypoxia.

Low O₂ saturations can be transient or chronic, each with associated risks such as pulmonary hypertension for chronic hypoxia, and developmental delays with frequent hypoxic arousals.

Additional terms that one should be aware of include SUID (Sudden Unexpected Infant Death), ALTE (Apparent Life Threatening Event), and BRUE (brief resolved unexplained event), as explained below.

SUID (Sudden Unexpected Infant Death): The death of an infant younger than 1 year of age that occurs suddenly and unexpectedly. After a full investigation, these deaths may be diagnosed as: Suffocation, Entrapment, Infection, Ingestion, Metabolic diseases, Cardiac arrhythmias, Trauma (accidental or non-accidental); or SIDS. SIDS (Sudden Infant Death Syndrome): One type of SUID, SIDS is the sudden death of an infant younger than 1 year of age that cannot be explained even after a full investigation that includes a complete autopsy, examination of the death scene, and review of the clinical history. Previously used terminology such as “near-miss sudden infant death syndrome” or “aborted crib death” should be abandoned because their use implies a possibly misleading close association between this type of spell and SIDS

ALTE (Apparent Life Threatening Event): An episode that is frightening to the observer and is characterized by some combination of: apnea (central or obstructive); color change (cyanotic, pallid, erythematous or plethoric); change in muscle tone (usually diminished); and choking or gagging.

BRUE: An event occurring in an infant <1 year of age when the observer reports a sudden, brief, and now resolved episode of ≥1 of the following: cyanosis or pallor; absent, decreased, or irregular breathing; marked change in tone (hyper- or hypotonia); altered level of responsiveness. Clinicians should diagnose a BRUE only when there is no explanation for a qualifying event after conducting an appropriate history and physical examination. The terms BRUE and ALTE mean the same type of event, but BRUE can be measured more objectively and should be used rather than ALTE.

Andre A Muelenaer, Jr is the Chief, Section of Pediatric Pulmonology/ Allergy, Carilion Children's Hospital, Professor of Pediatrics, Virginia Tech Carilion School of Medicine.

The ED physician may not experience many patients with pure apneic events but more likely will have an infant's caregiver come in and report that his or her child appeared to stop breathing, changed color, or became limp. This is a BRUE.

BRUEs are characterized as Higher-risk or Lower-risk. Lower risk BRUEs meet all of the following criteria:

- age >60 days
- gestational age ≥ 32 weeks and postconceptional age ≥ 45 weeks
- occurrence of only 1 BRUE (no prior BRUE ever and not occurring in clusters)
- duration of BRUE <1 minute
- no cardiopulmonary resuscitation by trained medical provider required
- no concerning historical features
- no concerning physical examination findings

Infants who have experienced a BRUE who do not qualify as Lower-risk patients are, by definition, at Higher-risk. Monitoring may be appropriate in Higher-risk infants who have experienced a BRUE. Infants who present in the ED with a Higher-risk BRUE may be discharged with Home Cardiorespiratory Monitoring. Clinicians should not initiate Home Cardiorespiratory Monitoring in infants presenting with a Lower-risk BRUE.

The consequences of Neonatal hypoxia

Apnea of prematurity can lead to death or permanent impairment of mental, psychomotor and functional development as well as cerebral palsy or blindness.

Infants in whom apnea exceeded 20 seconds have an increased incidence of, Intraventricular hemorrhage, Hydrocephalus, Prolonged mechanical ventilation, Abnormal neurologic development after their first year of life.

Infants with clinically significant apnea of prematurity do not perform as well as prematurely born infants without recurrent apneas during neurodevelopmental follow-up testing. The longer the occurrence of apnea of prematurity, the greater the neurodevelopmental impairment as measured by the Bayley scale for mental development and psychomotor development or by the occurrence of cerebral palsy or blindness. The longer the occurrence of apnea of prematurity, the greater the functional impairment as measured by the Vineland scale for Communication, Daily Living Skills, Socialization, and Motor Skills.

Conditions to Monitor

Apnea of prematurity is the most common problem in premature neonates. The earlier a baby is born before full term, the higher their likelihood of having apnea of prematurity.

Cardiorespiratory monitoring improves bedside detection of apnea of prematurity. Clinicians heavily rely on nursing documentation to make decisions. Yet published findings show that even highly trained observers miss more than 50% of apnea of prematurity episodes. At the same time, standard hospital monitors do not tell the whole story. They make continuous recordings, events are not easy to locate in the records and alarms are often ignored by hospital staff. Apnea, bradycardia, and desaturation events are subjective in nature unless the standard definition is strictly followed. Event recording Cardiorespiratory Monitors allow these standards to be strictly

followed and provide alarms when pre-set limits are exceeded. Precise diagnosis of apnea of prematurity requires multichannel recordings, which are most commonly measurements of thoracic impedance, heart rate, and O_2 saturation. Expanded testing may include air flow, electroencephalography and/or use of an esophageal pH probe. Accurate documentation of "spells" prior to discharge can aid in decision making.



Figure 2. Smart Monitor 2 from Circadian Event-recording Cardiorespiratory Monitor.

Babies are assessed prior to discharge in NICU or transitional space (step down nursery). Patients in step down units are commonly monitored with a Home Cardiorespiratory Monitor as central Cardiorespiratory Monitors found in the NICU may not be available.

Apnea of prematurity may not resolve at term and may persist for some time after hospital discharge. These babies should be considered for home monitoring if Apneas or Bradycardias persist as discharge date nears. Following recommendations by the American Academy of Pediatrics, these symptomatic preterm infants should be considered for monitoring in the home.

Home Monitoring allows management of infants discharged on caffeine citrate therapy. These infants are rarely sent home without a monitor as apnea may reoccur as the baby outgrows their therapeutic caffeine level. Without a monitor the caregiver may not recognize when apneas reappear. Cardiorespiratory monitoring after hospital discharge may be prescribed for some preterm infants with an unusually prolonged course of recurrent, extreme apnea.

Home Monitoring enables healthcare providers to manage outpatients with conditions that may affect breathing, Heart Rate or O_2 saturation. Figure 3 demonstrates the quality of the graphical data recorded when an event occurs.

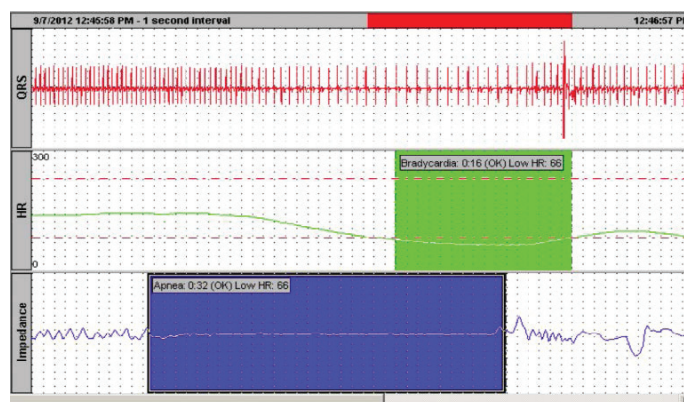


Figure 3. High quality waveforms enables diagnosis and management of conditions that may affect breathing, Heart Rate or O_2 saturation.

Event recording monitors enable healthcare providers to manage infants who may have subtle or intermittent problems such as cardiac conditions, seizures, parental neglect or abuse, or the onset of infections.

Infants who have experienced a Higher-risk BRUE may be appropriate candidates for home monitoring. Clinicians should not initiate Home Cardiorespiratory Monitoring in infants presenting with a Lower-risk BRUE.

Home Monitoring may be appropriate for discharged babies who have displayed cardiac abnormalities such as: Supraventricular Tachycardia, Ectopic atrial tachycardia, Atrial flutter, First - , second - , and third -degree heart block, Wolff - Parkinson - White Syndrome.

Home Monitoring may provide evidence to establish parental abuse or neglect, Munchausen Syndrome by Proxy or seizures. Many infants will present with a sudden increase in apnea alarms 12 to 24 hours before becoming clinically symptomatic with respiratory syncytial virus (RSV) or sepsis.

For caregivers of a subsequent child born after a sibling died from SIDS, monitoring may relieve anxiety related to fear of a second event, even when counseled about limitations of monitoring. This compassionate use of Home Cardiorespiratory Monitors may or may not be covered by the patient's insurance.

There are a variety of conditions to not use Cardiorespiratory Monitors. Cardiorespiratory Monitors are not recommended as a strategy to prevent SIDS. Commercial devices that are designed to monitor infant vital signs do not reduce the risk of SIDS. The American Academy of Pediatrics specifically recommends against using consumer oximeter devices that have not been cleared by the FDA.

Equally as important as criteria to initiate home monitoring are those to discontinue the monitor. Current evidence suggests that if such monitoring is elected, it can be discontinued in most infants:

- After 43 weeks' PMA unless indicated by other significant medical conditions
- Usually monitored for 4-6 weeks after cessation of events
- Off caffeine, oxygen, and occasionally, diuretics
- Caregiver comfortable with discontinuation



Figure 5. The Car Seat Challenge which is recommended by the American Academy of Pediatrics when discharging any newborn at less than 37 weeks gestational age or who was low birth weight even at full term.

Consideration for home monitoring is often a part of discharge planning. Usually, there are three conditions to be met for discharge of a preterm neonate:

- Oral feeding sufficient to support appropriate growth
- Ability to maintain normal body temperature in a home environment
- Sufficiently mature respiratory control

There is no consensus as to the apnea-free interval before discharge. In general:

- Babies should be apnea-free for 5-7 days before discharge. The interval is not clearly established, and some NICUs require longer intervals.
- Reducing this time facilitates earlier discharge, especially if monitors are available for home use.

Another consideration for discharge is the Car Seat Challenge. It is important because premature infants who are discharged from intensive care nurseries are known to be at increased risk for apnea, bradycardia, and oxygen desaturation while in the upright position. Car Seat Challenge is a period of monitoring in the infants own car seat to verify cardiac and respiratory stability while seated in the upright position. The test usually lasts for 90-120 minutes or the duration of the car ride home, whichever is longer. Data can be downloaded from the monitor for clinicians to evaluate when making discharge planning decisions. This

Recommended

- When Apnea of prematurity unresolved by discharge date
- As part of discharge planning
- Enables doctors to manage discharged infants with conditions that may affect breathing, Heart Rate or O2 saturation
- Enables doctors to manage discharged infants who may have subtle or intermittent problems like cardiac conditions, seizures, parental neglect or abuse, or the onset of infections.
- When babies present in the ED with Higher Risk BRUEs

Not recommended

- In full term healthy infants
- When Apnea of prematurity resolved by discharge date
- When babies present in the ED with Lower Risk BRUEs
- As a strategy to prevent SIDS.
- Commercial baby monitors, not cleared by the FDA, should not be used

Figure 4. Appropriate use of Cardiorespiratory Monitors. These recommendations are consistent with the guidelines provided by The American Academy of Pediatrics.

data can be included in patient medical record. The Car Seat Challenge which is recommended by the American Academy of Pediatrics when discharging any newborn at less than 37 weeks gestational age or who was low birth weight even at full term. The Car Seat Challenge is a billable procedure.

Earlier discharge from the ICU allows the pre-term baby to go home, which provides better quality of life for the baby and for the family, as well as lowers the cost of care and improves profitability for the hospital.

Home Monitoring

The home care provider should set up monitor in the NICU prior to discharge to enable the family to become familiar with the equipment and the alarms. Parents "room in" with their baby the last night in the hospital. Those caring for an infant with apnea of prematurity should be trained in CPR. This training in the NICU reduces caregiver anxiety and allows them to participate in the care of their infant. It reduces the number of calls to the home care provider office. Proper training reduces likelihood of broken equipment. And it helps achieve compliance.

One of the frequent complaints about home monitoring is the number of alarms. Alarms may be related to the condition of the baby, which are relevant to the babies care. They may also be related to the equipment which are considered clinically irrelevant alarms. Proper placement of leads will minimize alarms. Ensure electrodes are placed along the mid-line of the side; two finger widths below or lined up with the nipples.



Figure 6. Proper lead placement helps reduce clinically irrelevant alarms.

If a good signal is not achieved, observe the patient's breathing and reposition electrodes in the location of greatest chest excursion. Remind parent's to ensure that the baby's skin is dry and clean and free of lotions and oils. If using an electrode belt, remove it for an hour a day. Clean reusable electrodes daily. Add a drop of water on skin under carbon electrode to help improve conductivity.

Documentation

The event-recording Cardiorespiratory Monitor will provide important documentation including multi-parameter recording of ECG, heart rate, respiration, SpO₂ when an alarm or record setting is violated. An event-recording Cardiorespiratory Monitor provides near diagnostic quality ECG waveform to aid in the diagnosis and treatment of cardiac arrhythmias and respiratory anomalies, as was previously shown in figure 3. It also provides a complete record of events which helps document monitor usage and compliance, as clearly shown in the Figure 7.

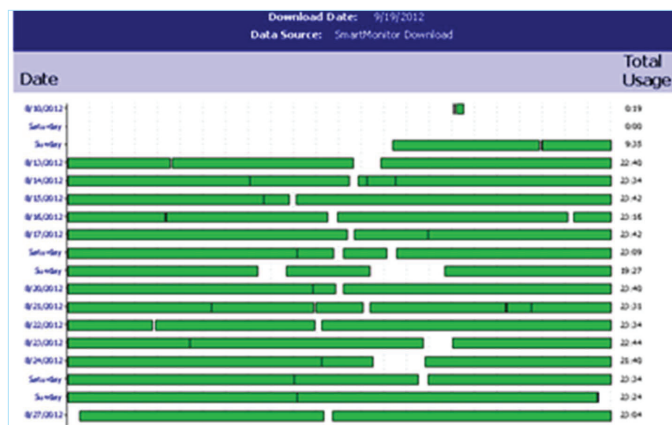


Figure 7. A compliance report provides a graphical record of when the infant was monitored.

Cost Considerations of Home Monitoring

If used correctly, Home Cardiorespiratory Monitors can save money. There is no standardization as to how long to keep premature infants in the NICU but many nurseries will put infants that are otherwise ready to be discharged (taking feedings well, able to maintain their temperature, and growing) on a 5-7 day "apnea/bradycardia" watch. That is, they keep the child in the NICU for 5-7 days after the last documented episode of apnea/bradycardia. However, earlier discharge from the NICU even within 3-4 days event-free and then sending home on a monitor for 1-2 months is much more cost effective.

One study resulted in out-patient management cost savings per eligible patient ranging from \$2,422 to \$62. Sensitivity analysis demonstrated few instances of decreased relative cost-effectiveness.

At my hospital, in the early 90s, we instituted a neonatal clinical pathway that promoted more rapid achievement of full feeds. When babies met this criteria, along with ability to maintain body temperature in an open crib, and not having significant cardiorespiratory events requiring aggressive intervention, they were discharged home on event-recording Cardiorespiratory Monitors. After 6 months of pathway introduction, we had reduced ALOS by 7.5 days, and average costs by \$19,400 per patient. This has become our standard of care and culture in the NICU.

Benefits of Cardiorespiratory Monitoring

Cardiorespiratory monitoring Improves bedside detection and assists in precise diagnosis of apnea of prematurity in the hospital. It enables the potential for earlier hospital discharge of premature infants. Earlier discharge provides better quality of life for the baby and for the family, as well as lowers cost of care and improves profitability for the hospital. Cardiorespiratory monitoring enables health care providers to manage discharged infants with conditions that may affect breathing, Heart Rate or O₂ saturation or who may have subtle or intermittent problems like cardiac conditions, seizures, parental neglect or abuse, or the onset of infections. Home Monitor alarms allow the parents to quickly respond in the event a pre-term baby stops breathing or has a bradycardia, and to have better peace of mind as the baby outgrows the need to be monitored. Cardiorespiratory monitoring provides documentation of the condition and management of at-risk infants throughout their hospital stay and subsequent treatment received in the home early in life.

Conclusion

Cardiorespiratory monitoring is clinically useful, technologically relevant, and economical. Monitoring enables the diagnosis and management of at-risk vulnerable infants to provide better outcomes. Monitoring improves the quality of life for a pre-term infant by enabling the baby to go home earlier, and peace of mind for their family, knowing that their baby will not suffer from undetected life threatening events. Monitoring lowers cost of care by providing a low cost alternative to hospital care, enabling earlier NICU discharge.

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Neonatal MARSI

Medical adhesives are a necessary part of modern medicine. Intravenous and intra-arterial lines, endotracheal tubes, and certain catheters must be tightly secured to prevent slippage, dislodgment, or even internal trauma to patients. On the other hand, medical adhesives are not without a certain amount of risk. Medical adhesives may cause mechanical problems, contact dermatitis, and other forms of local irritation and inflammation.

Premature and full-term neonates are at particular risk for problems with medical adhesives, yet securing medical devices in the neonatal intensive unit (NICU) is of the utmost importance. Thus, there is an inherent trade-off between keeping tubes and lines secure and preventing medical adhesive-related skin injury or MARSI. Fortunately, there are ways to avoid neonatal MARSI, including proper medical adhesive selection, placement, and monitoring.



What is MARSI?

MARSI is an acronym that stands for medical adhesive-related skin injury. MARSI is not a pressure injury; rather it results in trauma to the skin. Skin injuries caused by medical adhesives fall into three categories:¹

Mechanical trauma

- **Epidermal stripping** – One or more layers of the stratum corneum are forcibly torn off with the removal of adhesive tape
- **Tension injury/Blistering** – The epidermis separates from the dermis; may be caused by unyielding adhesive or improper tape application
- **Skin tearing** – Shear, friction, or blunt force trauma resulting in partial or full thickness skin damage

Dermatitis

- **Contact dermatitis** – Non-allergic reaction to chemicals within the adhesive or backing
- **Allergic dermatitis** – Cell-mediated allergic response to the adhesive or backing

Other

- **Skin maceration** – Wrinkled, light-colored skin that is susceptible to damage
- **Folliculitis** – Hair follicle inflammation that may or may not be suppurative (pus-filled)

Neonates are at risk for MARSI

The delicate tissues in the skin of premature neonates place them at increased risk of developing MARSI compared to older infants and children. At less than 30 weeks gestation, there may be as few as two or three layers of stratum corneum compared to 10 to 20 in the full term newborn or adult.² The dermis in even newborn infants is far thinner than it is in adult skin. Moreover, the junction between the dermis and epidermis is underdeveloped in preterm and young full-term infants, meaning there is less cohesion between the layers.²

The risk to immature skin is compounded by the use of medical adhesives, especially in the NICU. The more premature the infant, the longer the NICU stay generally is. Thus, the patient group with least-developed skin is exposed to the greatest amount of medical adhesives.

Epidermal stripping is the most common form of MARSI in neonates; the prevalence of skin stripping due to medical adhesives in infants is 17%.³ Tension injury and blistering may also occur.⁴ Infants in long-term intensive care may also develop skin maceration due to moisture trapped under medical tape. Contact and/or allergic dermatitis may occur; contact dermatitis resolves within 24-48 hours after the tapes is removed, while allergic dermatitis may last for up to a week.¹

Avoiding MARSI in the NICU

One way to reduce the occurrence of MARSI is to select the proper medical adhesive for the purpose. Critical devices such as chest tubes, endotracheal tubes, and vascular access devices require relatively aggressive medical adhesives for a secure hold. The term “relatively” is important because certain adhesives can be too aggressive for NICU patients. While a medical tape should hold strongly enough to serve its intended purpose, importantly, it should also be easy to remove and cause little to no damage to the skin.

It is also advisable to choose a latex-free product to reduce the chances of priming or exacerbating a latex allergy. The adhesive should also be waterproof in that it resists rolling and curling when subjected to fluids (e.g., perspiration, urine).

NICUs and nurseries often use Hy-Tape, which they commonly refer to simply as “pink tape.” Hy-Tape is an excellent all-purpose tape for use in the patient population. It provides relatively aggressive adherence and is suitable for use with critical devices.⁵ While it holds firm and conforms to body contours, “pink tape” can also be removed with ease. The adhesive in Hy-Tape leaves little or no residue when it is removed, and minimizes the risk of mechanical damage to the skin, specifically epidermal stripping, skin tearing, and tension injury or blistering. This is especially important for devices that need to be removed frequently and re-taped. “Pink tape” can reduce the risk of other forms of MARSI as well. Hy-Tape is latex-free and is not known to cause contact dermatitis or allergic dermatitis when used appropriately. Moreover, Hy-Tape contains a zinc oxide adhesive that is naturally soothing to even delicate, neonatal skin.



Lastly, devices can be made more secure by using particular application techniques. For example, the “chevron” technique, well known to nurses, helps provide maximal security with minimal adhesive contact with skin. The risk of MARSI can be reduced by avoiding tension on the skin at rest or leaving tape on too long. Always remember that any medical tape, including Hy-Tape, should be removed slowly, at a low angle, while supporting the skin. This is especially true in neonates and NICU patients.

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Fetal Cardiac Pacemaker: Connect the Dots

A Uryash, MD, BM Petrikovsky, MD, PhD, O Bockeria, MD, DSc

Fetal Cardiac pathophysiology

During cardiogenesis, the primitive heart tube produces peristaltic waves of contractions, due to stimulation provided by natural cardiac pacemaker activity produced by cells of the sinus node (SN) at approximately 5 weeks of gestation. The remainder of cardiac conduction system is fully developed at 16 weeks of gestation.¹

When the function of SN cells is compromised for, which may occur for various reasons, fetal arrhythmia develops. Transient fetal arrhythmias are more common than persistent fetal arrhythmias.² However, persistent severe bradycardia and sustained tachycardia cause an early grave prognosis and may cause congestive heart failure.⁴

The progression of congestive heart failure to a hydropic state is related to an elevation of venous pressure resulting in an increased capillary permeability and edema. Nevertheless, latest studies in fetal cardiology indicate that electrophysiological and functional changes appear mostly due to underlining defects in one or multiple molecular mechanisms of fetal cardiac contractility.⁵ The knowledge of these molecular pathways provides the clinician with a better understanding of abnormal development of the cardiac conduction system and aids in treatment choices.

Orderly propagation of cardiac electrophysiological excitation and recovery depends on a normal sequence of cardiac action potential (CAP) generated by myocytes.⁶ The depolarization and repolarization of CAP is mediated by multiple inward and outward currents.⁷ Recently, the cellular physiological role of cardiac calcium and potassium currents have been linked to fetal electrophysiological compromise.⁸⁻¹⁰ Normal cardiac function depends on the timing of excitation and contraction in the various regions of the heart.¹⁰ This complex task is implemented by the highly specialized electrical properties of the various elements of the cardiac system, including the sino-atrial node (SAN), atria, atrioventricular node (AVN), His-Purkinje conducting system, and finally the ventricles.¹¹ Additionally, different regions of the heart are endowed with various combinations of ion-channels, pumps and exchangers yielding distinct AP waveforms and durations.¹² Although all cardiomyocytes are initially endowed with pacemaker activity

in the early embryonic stages, most cardiac cells eventually differentiate into a working myocardium, which loses pacemaker properties.^{13,14}

The normal heart beat is generated by intrinsic pacemaker activity in the SAN.¹⁵ Shortening of the duration of action potential is often offset by increased calcium current. This results in SAN failure and ultimately bradycardia.¹⁶

Clinical implications of fetal cardiac arrhythmias were linked to sudden infant death syndrome (SIDS).⁹ Approximately 10% of SIDS may stem from so called cardiac channelopathies.¹⁷ Thus Kir6.1 (KATP) channel regulates vascular tone and cardiac responses to systematic stressors.¹⁸⁻¹⁹ KATP channelopathy-susceptibility genes may cause potentially lethal, ventricular fibrillation syndromes including but not limited to QT syndrome, catecholaminergic polymorphic ventricular tachycardia, and Brugada syndrome.²⁰⁻²²

Prevention of cardiac stressors by using an artificial fetal pacemaker during critical stages of heart development, can possibly bring electrophysiological and functional cardiac parameters to a norm.²³⁻²⁴

This approach is even more important in treating fetuses with additional pathological conditions, including hyperglycemia, hypoglycemia, ischemia, hypoxia, and inflammation, all of which have been implicated as possible contributors to SIDS.^{25,26}

Fetal Pacemaker

Perinatal mortality is almost 100% in fetuses with heart blockage and bradycardia at the stage of full-blown hydrops. Fetal cardiac pacing systems were developed to save these fetuses and consisted of pacing catheters and external pulse generators.²⁷ These generators are located outside the uterus and a pacing catheter passes through the abdominal wall, uterine musculature, across the amniotic fluid directly to the heart of the fetus. However, most efforts to save a fetus have so far met with failure due to, either dislodging of the catheter or umbilical cord complications. There were also attempts to perform an open hysterotomy to place epicardial fetal pacemakers via fetal thoracotomy.²⁷ Such approach cannot be applied to the sickest fetuses, since they could not survive outside the mother (due to immaturity and hydrops) in the event that fetal surgery leads to a pre-term delivery. Ovadia, et al.²⁷ proposed a permanent fetal pacemaker with the following features: a) to be implanted, the device does not use the umbilical vasculature and b) the

A Uryash is from Mount Sinai Medical Center, Miami, FL. BM Petrikovsky is from NY Institute of Technology. O Bockeria is from Bakulev Cardiovascular Institute.

cylindrical battery/pulse generator, was made short in length to avoid or decrease the chance of umbilical cord knotting or entanglement.

Recently, Stirnemann et al.²⁸ reported for the first time a successful fetal transesophageal pacing. Fetal echocardiography in this case was used to diagnose atrial flutter as the cause of fetal tachyarrhythmia. Medical treatment (digoxin, flecainide and finally amiodarone) failed to resolve fetal hydrops. Given the failure of medical treatment and progressive hydrops, in utero transesophageal pacing (IUTP) was considered the only lifesaving option. Fetal anesthesia was obtained by an injection of sufentanil in the umbilical vein under continuous ultrasound guidance. A 3-mm curved cannula with flexible fetoscope was then inserted in the fetal esophagus. The position of the distal tip of the cannula was placed right above the heart under ultrasound guidance. The fetoscope was then retrieved from the cannula and replaced by a bipolar pacing esophageal lead. The lead was then connected to an asynchronous esophageal pacemaker. The first two first 6-sec bursts with these settings were not effective. Pacing parameters were then set at 10 mA/5 msec. Two follow-up bursts of 6 sec each finally converted the abnormal rhythm to atrial fibrillation along with periods of a sinus rhythm. These authors concluded that IUTP is a potentially life-saving procedure that should be considered in the management of drug-resistant tachyarrhythmia, particularly atrial flutter, in combination with antiarrhythmic drugs.

New directions in fetal pacing-wireless pacemaker

Over the years development of cardiac pacing revealed the weakness of the wire component of the pacing system and led to the creation and manufacturing of the wireless or leadless pacemakers. However, despite the clear advantage of the leadless device, many technical problems still remain. A miniature pacemaker was proposed with a long electrode and a circuit board powered by a lithium battery. A charging system of this device works by using radio waves. The system is small and minimally interferes with fetal activity. This device is still under development and requires more work to achieve optimal performance.²⁹

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Newborn Infant Born with Digital and Nail Hypoplasia

Daniel A Nieto, Jaime J Baldeon, Zuleika E Parra and *Benamanahalli Rajegowda

Abstract

Term newborn infant, born with digital unnailed hypoplasia of distal finger and toes of both hands and feet, is a great concern for parents and must be differentiated from variety of causes including Genetic and non-Genetic syndromes.

Case Report

A full term adequate for gestational age female infant was born by normal spontaneous vaginal delivery at 39 weeks +2 days of gestation with birth weight 2750 grams (13%), head circumference 31.5 cm (8%), and length 48 cm (19%). The Mother was 28 years of age primigravida, who was followed as a high-risk pregnancy by maternal fetal medicine for maternal hypertension and seizure disorder. She was also seen by neurology for Dyke-Davidoff-Masson syndrome management. She was treated during pregnancy with 2 anti-seizure medications: Phenytoin 200mg BID and Levetiracetam 1500mg BID. She also received Folic acid 5mg, Ferrous Sulfate 325mg BID and daily Pre-natal vitamins throughout her pregnancy. The patient never experienced any seizures. Fetal ultrasound monitoring revealed normal fetal growth. Newborn examination at birth was noted only for hypoplasia of the distal digits as shown in figure 1 (A, B and C). The rest of the newborn physical examination was normal, and the rest of hospital course was uneventful. We did not take X-ray of the digits since it was not very useful, and it would unnecessarily irradiate the baby.

Discussion

The exact number of patients in the U.S. with a diagnosis of epilepsy is unknown. For 2015, CDC reported that 1.2% of the population had active or current epilepsy, which represents 3.4 million persons, represented in 3 million adults and 470,000 children living with this condition.¹ Most of these patients are currently managed with 1 or more antiepileptic drugs, increasing the likelihood of suffering adverse effects to medications. Women of reproductive age under treatment with anti-seizure medications are at increased risk of inducing teratogenic effects on fetuses. They represent about 2% of all pregnant women and 5-20% of them received treatment with phenytoin.²

The authors are with the Department of Pediatrics–Neonatology, Lincoln Medical Center in Affiliation with Weill Medical College/Cornell University;

*Corresponding Author, Department of Pediatrics and Neonatology, Lincoln Medical Center, 234 East 149 Street Bronx NY 10451; Professor Clinical Pediatrics, Weill Medical College/ Cornell University, Email: Benamanahalli.rajegowda@nychc.org, Tel #: 718-579-5360.



Figure 1. Image A (top), Image B (middle) and Image C (bottom, Bilateral feet). Digital and nail hypoplasia of all fingers and toes, with small distal phalanges bilaterally.

Approximately 33% of infants exposed to hydantoin in utero will express at least some features related to fetal hydantoin syndrome with only 5-10% will express the complete phenotype.² The typical dysmorphic features in a newborn will be microcephaly, short nose with broad nasal bridge, strabismus, malformed ears, cleft lip and cleft palate, hypertelorism, digital and nail hypoplasia, finger-like thumb and Simian crease.³ These patients may also suffer from developmental delay and growth retardation. Other defects that may be present are cardiac defects (ventricular septal defect, Tetralogy of Fallot, patent ductus arteriosus, valvular stenosis), hypospadias, inguinal and/or umbilical hernia, diaphragmatic hernia, and dislocation of the hip.³

In the case presented above the newborn physical examination was remarkable for small distal phalanges, and bilateral digital and nail hypoplasia, no facial dysmorphic features and other structural anomalies were present at birth. The exact mechanism of fetal and neonatal toxicity of varying degree is not known. However, several hypotheses are suggested by many authors namely type of drug used, mono or multiple drug therapy, their serum levels, folate deficiencies, vitamin K metabolites, ischemia and genetic predisposition. These findings were discussed with the mother in her preferred language of choice, as well as the possible long-term outcome and the importance of the compliance with every well child care visit. Taking into consideration the potential for developmental delay and growth retardation in these patients, it is important to perform adequate physical measurements and milestones evaluation in every visit, as well as an extensive physical examination with an emphasis on the cardiovascular setting. If abnormal findings are present during cardiac examination, echocardiography and cardiology evaluation may be required to rule out possible cardiac defects.

Summary

Pregnant women under treatment with phenytoin should be counseled about the potential effects of this therapy on the fetus. An adequate physical exam must be performed immediately after birth to identify any defects or complications related to this syndrome looking forward to preventing future complications and to give prompt treatment to improve long term outcome. Alternative therapies for women on reproductive age with diagnosis of epilepsy should be encouraged, as well as further research on anti-seizure treatment without teratogenic effects.

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Understanding Body Surface Area in Neonatal Phototherapy

Deepakshyam Krishnaraju, MSc, ME and Sivakumar Palaniswamy, MSc, BME

What is neonatal phototherapy?

Hyperbilirubinemia, a condition in which there is too much bilirubin in the blood, is the most common newborn condition requiring treatment. In the uterus, the fetus has extra red blood cells to carry oxygen and nutrients. After delivery, the red blood cells (RBC) no longer are needed. RBC break down, releasing bilirubin at a rate that may exceed the baby's ability to eliminate it. This excessive bilirubin can deposit in the skin, sclera, and mucous membranes causing them to appear yellow, or jaundiced. When the bilirubin level in the blood rises too high, the bilirubin can cross the blood-brain barrier and become neurotoxic, thus having the potential to cause lifelong neurological dysfunction or death. Newborn hyperbilirubinemia is treated with phototherapy, which converts bilirubin present in the superficial capillaries, interstitial spaces of the skin, and subcutaneous tissues into water-soluble isomers that are excretable without further metabolism by the liver.

The kinetics of phototherapy may be thought of in the same way as drug therapy, i.e., the dose response relationship of phototherapy is analogous to those of a medication administered to treat an illness. The dose delivered by a phototherapy device determines the efficacy of the treatment, and thus both dose and efficacy are determined by the amount of body surface area (BSA) treated and the spectral properties of the light used, such as peak wavelength, wavelength range, and irradiance delivered. Previous attempts to evaluate the efficacy of various phototherapy devices in the market with respect to BSA have fallen short due to inaccurate estimations of treated BSA. This paper proposes a new modality of calculating the treated BSA of a phototherapy device and offers a comprehensive comparison of leading phototherapy devices in the market.

What is treated BSA and why is it important for photo therapy?

Phototherapy is a multistep biomolecular process which involves the photoisomerization of bilirubin¹ found in the in the extravascular skin tissue and capillary flow. More skin exposure to the phototherapy light (treated BSA) results in faster photoisomerization of bilirubin and thus faster excretion.

Although prior research^{2,3} established a strong relationship between the irradiance of phototherapy lights and efficacy

of phototherapy, many investigators also highlighted the importance of treated body surface area as a key parameter in evaluating the efficacy of phototherapy devices.⁴⁻⁷ When fiber optic devices do not cover enough BSA, or when overhead devices are not able to cause a sufficient fall of bilirubin levels,² clinicians tend to use “double” and “triple” phototherapy in an attempt to improve the phototherapy dose by increasing the treated BSA.

How can the effectiveness of phototherapy be calculated?

The term “spectral power” (measured in W/nm) was coined to normalize parameters of phototherapy across treated body surface area.⁷ Spectral power is the product of phototherapy light irradiance in wavelength multiplied by the treated BSA:

When comparing the efficacy of various phototherapy devices, it is relatively simple to standardize the irradiance measurement by restricting the measurement window using the radiometer recommended by the phototherapy device's manufacturer. BSA is a 3-dimensional contour surface on a baby. Estimating BSA is a challenge requiring careful consideration to avoid the area of the skin receiving phototherapy receiving less irradiance than clinically needed.

Estimation of treated BSA of a baby, empirically, involves topographically mapping the 3-D surface of a baby onto a 2-D surface and then estimating the area of the resultant non-standard shape. Most studies comparing the efficacy of phototherapy devices have made a fair share of assumption(s): Maisels et al⁷ assumes that with fiber-optic phototherapy systems, the surface area of the infant exposed to phototherapy is equal to the illuminated area of the fiberoptic pad. In contrast, with overhead lights the whole surface of the infant facing the lights is assumed to be the surface area exposed. This may not be true, because light decay in overhead devices obeys the inverse square law. Thus, a patch may be illuminated but receive sub-par amounts of irradiance and therefore be non-conductive for treatment. In another example, Dicken et al⁸ assume that one-third of the area is estimated to be irradiated by the light source above the baby but does not offer a rationale. Finally, these studies, including the bench testing method proposed for evaluating the efficacy of phototherapy devices by Vreman et al,¹¹ do not account for the directionality of the light sources. The sides of the baby would receive less irradiance because they are not directly in-line with the light source. Such variance is difficult to capture numerically.

Deepak Shyam Krishnaraju is a Co-founder & Mechanical Engineer at NeoLight Medical. Sivakumar Palaniswamy is a Co-founder & CTO at NeoLight Medical.



Figure 1. 3D scanned model of term and pre-term baby



Figure 2. Depiction of phototherapy of a term baby

A new method for measuring treated BSA

The true treated BSA of a baby can be better estimated with the use of 3D-scanning technology. Here we propose a new method of measuring treated BSA and compare the treated BSA of the NeoLight Skylife™ phototherapy system with two competing devices. A 3D-scanned Computer Aided Design (CAD) model of term and preterm baby mannequins were used to map the true surface area of a baby. (Figure 1) The dimensions of Pampier diapers and Maxtec eye-masks were used to map the covered areas which would be untreated by phototherapy.

The phototherapy devices evaluated in this comparison included the NeoLight Skylife, the GE Giraffe Spot PT Lite, and the GE BiliBlanket. Spectral irradiance ($\mu\text{W}/\text{cm}^2/\text{nm}$) measurements were made using a calibrated GE BiliBlanket Meter II (GE Healthcare, Fairfield, CT). This meter was selected due to its wide sensitivity range (400–520 nm with peak sensitivity at 450 nm), which overlaps the bilirubin absorption spectrum and allows evaluation of both narrow and broad wavelength band light sources. The testing environment exhibited an ambient irradiance of $0.1 \mu\text{W}/\text{cm}^2/\text{nm}$ (in the radiometer sensitivity range). The baby mannequins were placed sequentially on the various phototherapy devices, and a side-view photograph was captured with an 8-megapixel camera. Automatic image they met this level of irradiance. The value $8.0 \mu\text{W}/\text{cm}^2/\text{nm}$ is considered the minimum acceptable intensity for conventional phototherapy.¹⁰ The points where intensity remained above $8.0 \mu\text{W}/\text{cm}^2/\text{nm}$ were identified in the captured images, and the Red-Green-Blue (RGB) code of the point was used to draw a demarcation line (using Matlab® image processing module) along the posterior surface of the CAD models. The demarcation

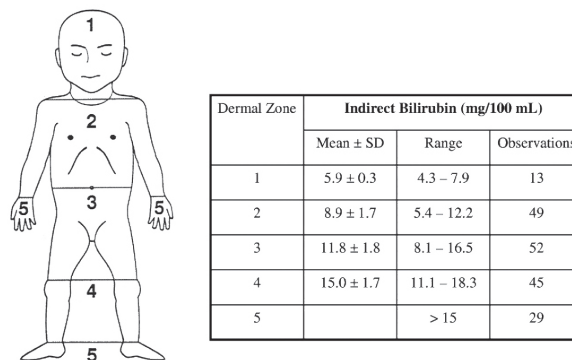


Figure 3. Cephalocaudal progression⁹



Figure 4. 3D light footprint of Skylife™

line was used to split the CAD model into two surface areas — treated and untreated. (Figure 2) To replicate a hospital setting, a diaper and eye mask were put on the mannequins but not shown in the figures. The blue area shown in Figure 2 represents the BSA covered by the respective phototherapy devices.

The BSA of various body parts was estimated, and the total treated BSA for term and preterm babies under various phototherapy devices was estimated by summing the treated BSA values for various body parts. The areas underneath the diaper and eye mask were subtracted from the treated BSA. The treated BSA was then represented as a percentage of the total BSA.

Comparison results and discussion

The treated BSA for term and preterm babies under NeoLight Skylife, GE Giraffe Spot PT Lite, and GE BiliBlanket are presented below in Table 1 and Table 2. Skylife has a significantly larger light source footprint (121.96 sq. in.) when compared to GE Giraffe Spot PT Lite (59.84 sq. in.) and BiliBlanket (20.76 sq. in.) and therefore offers superior light coverage to the legs, arms, and head. Furthermore, in addition to overall coverage, Skylife offers uniform head to toe irradiance. (Figure 5) Skylife delivers higher light coverage to the torso when compared to BiliBlanket, and higher coverage in the head compared to both Spot PT Lite and BiliBlanket. The slightly higher torso coverage shown by Spot PT Lite can be attributed to its irradiance of the anterior thoracic area, which is curved and represents a greater surface area compared to the back. The fiberoptic GE BiliBlanket has the smallest light source footprint and hence offers the least body surface coverage of the assessed devices. The BiliBlanket focuses its irradiance on the baby's back, leaving out a significant portion of the arms, legs, and head. Uniform irradiance of the various body parts is especially of interest because bilirubin deposition is not the same throughout the body, known to be higher at the head and decreasing directionally towards the toes (Figure 3).⁹

Table 1. Comparison of total BSA between devices across term and pre-term babies

Phototherapy device	Treated body surface area	
	Term baby	Preterm baby
Skylife™	40.26%	39.96%
GE Spot PT Lite	19.53%	22.95%
GE Bili Blanket	6.88%	12.13%

Table 2. Comparison of %BSA between devices for various body parts across term and pre-term babies

Phototherapy device	Term baby % BSA				
	Head	Torso	Arms	Legs	Overall
Skylife™	27.24%	48.09%	53.17%	66.42%	53.77%
GE Spot PT Lite	20.77%	54.92%	36.12%	7.65%	25.99%
GE Bili Blanket	6.47%	37.10%	2.38%	1.74%	9.20%

Phototherapy device	Pre-term baby % BSA				
	Head	Torso	Arms	Legs	Overall
Skylife™	41.65%	46.18%	56.03%	67.08%	56.06%
GE Spot PT Lite	30.67%	60.87%	45.59%	8.70%	32.13%
GE Bili Blanket	4.51%	38.80%	7.90%	21.64%	17.01%

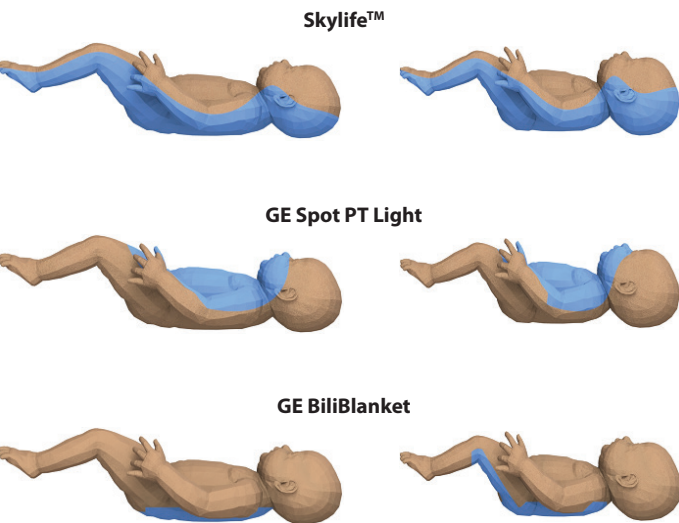


Figure 5. Visual comparison of treatment BSA coverage on term baby (left) and pre-term baby (right) between 3 marketed devices

The larger light foot print of SkyLife can be attributed to the 3D light profile generated by directing the light onto the sides of the patient. (Figure 4) Numerous optical simulations were used to determine the positioning and spacing of lights in order to achieve the highest light footprint with the fewest lights. Unlike the light profiles generated by competing devices, this unique 3D light footprint also illuminates the sides of the baby uniformly from head to toe.

There are limitations to this comparison. The baby dimensions used in this study only approximate the average sizes of term and pre-term babies. The actual treated BSA will vary from patient to patient. Further, results will vary based on the size and type of diaper and eye-mask chosen. Regardless, the values of BSA presented in this paper represent good approximations to help physicians, nurses, and researchers understand the efficacy of various phototherapy devices.

Conclusion

Treatment BSA is a key parameter of effective neonatal phototherapy. This paper proposed a new 3D method for measuring BSA covered by phototherapy lights and compared BSA coverage of three currently marketed phototherapy devices. SkyLife, through its unique 3D light profile, delivers the highest treatment BSA of the three devices compared. The additional BSA coverage may improve the efficacy of phototherapy by increasing the elimination rate of bilirubin, thus decreasing treatment time. These laboratory findings currently are being validated in clinical studies. Phototherapy with previously existing devices has an average treatment time of 48 hours.¹² A reduction in treatment time would reduce operational costs, allow a hospital to discharge babies earlier which could improve patient satisfaction, and free up beds allowing for additional admissions.

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Diagnostic Errors in the Neonatal Intensive Care Unit: A Case Series

Grant J Shafer, MD, and Gautham Suresh, MD

Abstract

Diagnostic errors remain understudied in neonatal intensive care units (NICUs). The few available studies are primarily autopsy-based, and do not evaluate diagnostic errors that did not result in the patient's death. This case series presents 10 examples of nonlethal diagnostic errors in the NICU—classified according to the component of the diagnostic process which led to the error. These cases demonstrate the presence of diagnostic error in the NICU and highlight the need for further research on this important topic.

A diagnostic error is defined as “a failure to establish an accurate and timely explanation for a patient's health problem.”¹ Such errors cause significant harm to patients, and were identified as a priority by the National Academy of Medicine in its 2015 report, *Improving Diagnosis in Health Care*. However, diagnostic errors remain largely unappreciated within the quality and patient safety movement in health care.^{2,3} In particular, diagnostic errors within a neonatal intensive care unit (NICU) are understudied.² NICU patients are fragile and often require multiple invasive interventions in a fast-paced, complex environment. As a result, they are at high risk of diagnostic errors that result in significant short-term and long-term health consequences.⁴

To date, however, the few studies on diagnostic errors in the NICU have been autopsy-based evaluations that did not assess nonlethal diagnostic errors.^{4,5}

In this case series, we present 10 examples of diagnostic errors which occurred in the NICU at this institution. These cases were identified by us during the course of our clinical work over a period of 9 months. We classify the errors by the component of the diagnostic process which led to the error in diagnosis: missed physical exam findings, misinterpreted vital signs, incorrectly interpreted radiographic imaging, delayed laboratory result interpretation, incorrectly interpreted echocardiographic imaging, inadequate team communication, and no fault. These cases serve as prototypical examples of diagnostic errors in the NICU, and highlight the need for further research in this field.

The authors are with the Division of Neonatal-Perinatal Medicine, Department of Pediatrics, Baylor College of Medicine, Houston, Texas and the Department of Neonatology, Texas Children's Hospital, Houston, Texas.

Cases

Missed Physical Examination Findings

Case 1

A 31-week gestation infant was born by spontaneous vaginal delivery (SVD) after preterm labor and prolonged (1 week) preterm premature rupture of membranes. The mother had received regular prenatal care, had negative results on prenatal tests for infections, and denied any history of herpes simplex virus (HSV) infection. On admission, the eyes were clear without discharge, with a bilateral red reflex. The patient had an uncomplicated NICU course until 5 weeks of age, when the infant developed eye redness and eyelid swelling of the right eye. Examination by an ophthalmologist revealed a geographic ulcer with central large epithelial defect that was suggestive of HSV keratitis. No eye exam had been documented in the daily progress notes in the week prior to the ophthalmology review. A viral culture of the eye discharge yielded HSV type 2. Blood and cerebral spinal fluid (CSF) cultures were negative for HSV and other infections. The patient received a 21-day treatment course of intravenous acyclovir as well as topical ganciclovir, then was switched to PO acyclovir only for suppressive therapy.

The patient has now been discharged from the NICU, and remains on PO acyclovir at home, which is being managed by the infectious disease outpatient team. The plan is for 12 months of suppressive therapy with PO acyclovir. The patient is also being followed in the ophthalmology clinic with slow improvement of the scarring from the infection noted in the most recent clinic notes. The patient's long-term vision prognosis remains unclear.

Case 2

A 40-week gestation infant was born by SVD after an uncomplicated pregnancy, then admitted to the well-baby nursery, where the admitting pediatrician documented a normal exam—including a patent and normally placed anal opening. Enteral feedings were then started. At 10 hours of life, the patient developed emesis and a distended abdomen. On reassessment, the infant was noted to have an imperforate anus. After transfer to the NICU a membrane covering a perineal fistula was excised by the pediatric surgery team at the bedside. Subsequently the patient fed well and passed stools normally.

Misinterpreted Vital Sign Findings

Case 3

A 37-week gestation infant was born by scheduled cesarean section (C-section) delivery. Prenatally multiple fetal congenital anomalies were identified, and fetal magnetic resonance imaging

Table 1 Initial presentation, missed diagnosis, main disease category, and etiology of the diagnostic error for the examples of diagnostic error presented in this case series

Case (n ¼ 10)	Initial presentation	Missed diagnosis	Main disease category	Etiology of the diagnostic error
1	Premature delivery at 31 wk	HSV keratitis	Infectious disease and ophthalmologic	Cognitive
2	Term delivery	Imperforate anus	Gastrointestinal	Cognitive
3	Multiple congenital anomalies	Coarctation of the aorta	Cardiovascular	Cognitive
4	Premature delivery at 34 wk after maternal PPROM	NEC and E. Coli bacteremia	Gastrointestinal and infectious disease	Cognitive and systems-based
5	Premature delivery at 24 wk with abdominal distension	Pleural effusion	Respiratory	Cognitive and systems-based
6	Term delivery with desaturations	13 ribs	Orthopedic	Cognitive
7	CDH with hematuria	Renal calculus	Renal	Cognitive
8	CDH with ventilator dependence	PAPVR	Cardiovascular	Cognitive
9	Premature delivery at 31 wk	TEF	Gastrointestinal	Systems-based
10	Persistent hyperglycemia in a critically-ill neonate with multiple congenital abnormalities	Neonatal diabetes related to chromosome 6 duplication	Endocrine	No fault

Abbreviations: CDH, congenital diaphragmatic hernia; E. coli, *Escherichia coli*; HSV, herpes simplex virus; NEC, necrotizing enterocolitis; PAPVR, partial anomalous pulmonary venous return; PPROM, preterm premature rupture of membranes; TEF, tracheoesophageal fistula.

(MRI) demonstrated bilateral cerebral ventriculomegaly with mass effect on the cerebellum, caudal regression spectrum, kyphosis, and scoliosis. A fetal echocardiogram (echo) revealed a ventricular septal defect (VSD) and biventricular hypertrophy. The cardiologist recommended an echo after delivery. On admission to the NICU, the systolic blood pressure in the upper limb was documented to be higher than that in the lower limb by 30 mm Hg. This result—a ‘red flag’ for aortic coarctation—was recorded in the electronic medical record, but was not flagged as abnormal or communicated by the bedside nurse to the neonatology clinician. Neither the neonatologist nor the cardiologist recognized this concerning vital sign during their initial review of the chart, and this abnormal result is not mentioned in any of the notes from the day of admission. As the patient was otherwise hemodynamically stable after being intubated, a postnatal echo was deferred until the following day, while imaging of the head and kidneys was performed that night. Aortic coarctation was suspected on an echo at 22 hours of life, and confirmed on computed tomography (CT) angiography scan. The patient received a prostaglandin E1 infusion to maintain systemic perfusion for several days, until the parents elected to redirect care due to the multiple other congenital anomalies not consistent with long-term survival.

Incorrectly Interpreted Radiographic Imaging and Delayed Laboratory Result Interpretation

Case 4

A 34-week gestation infant was born by C-section, then admitted to the NICU for prematurity and hypoglycemia. An umbilical venous catheter (UVC) could not be inserted, so a peripherally inserted central catheter (PICC) was inserted into the right femoral vein. Afterward, a radiograph of the chest and abdomen was obtained to confirm correct positioning of the PICC. The radiology report described “a bubbly pattern in the descending colon,” which was suggestive of pneumatosis. The pneumatosis was an incidental finding separate from the PICC insertion procedure, the placement of which did not have any influence on the development of the pneumatosis. There is a system in place at this institution by which a radiologist directly communicates

concerning findings on imaging to the bedside clinician, but in this case it was not utilized by the radiologist who read the radiograph, and the neonatologist remained unaware of pneumatosis or the comments on the radiology report. As the radiograph had been obtained for PICC placement, and the patient appeared clinically well, the neonatologist initiated enteral feeds. At 14 hours of life, a blood culture grew gram-negative rods (later identified as *Escherichia coli*). This was also not recognized by the on-call neonatologist for 6 hours. During this period, the enteral feeds were continued, and no repeat blood cultures were sent until 20 hours of life, when the patient developed bloody stools. A repeat radiograph at that time demonstrated diffuse pneumatosis consistent with necrotizing enterocolitis. Feeds were then discontinued, and a full sepsis evaluation including a lumbar puncture for CSF culture was performed. The infant was treated with antibiotics, required multiple surgical interventions for colonic stricture, and experienced long-term feeding difficulties.

Incorrectly Interpreted Radiographic Imaging

Case 5

A 24-week gestation infant was born by SVD after preterm labor. At 2 weeks of life, the patient developed abdominal distension. An abdominal radiograph was obtained to evaluate for an etiology of the abdominal distension such as pneumoperitoneum or pneumatosis. The radiograph demonstrated diffuse gaseous distension of the colon and small bowel, and also noted a right pleural effusion. However, as this was an abdominal radiograph, the lungs were not completely evaluated in this study. The radiology report indicates that the finding of the pleural effusion was communicated to “the physician taking care of the patient,” however, this was not noted in any of the documentation in the electronic medical record. Additionally, a dedicated follow-up chest radiograph was not obtained to fully evaluate the lungs. Instead the neonatology team focused on the abdominal distension, as the patient became critically ill with significant metabolic acidosis and decreased urine output concerning for an acutely evolving intraabdominal pathology. The following day, however, the patient had an acute respiratory decompensation

with prolonged desaturations not responsive to manual positive pressure breaths or increases in fraction of inspired oxygen (fiO₂) on the ventilator. A chest radiograph obtained at that time demonstrated a large pleural effusion with leftward mediastinal shift, which required an emergent needle thoracentesis and chest tube placement. The patient was found to have coagulase-negative *Staphylococcus* sepsis, which caused a septic ileus that led to the initial abdominal distension. The pleural effusion was a separate clinical event that temporally coincided with the abdominal distension, but was not recognized by the medical team as they prioritized evaluation for an intra-abdominal pathology, and initially ascribed the respiratory distress as secondary to a 'competitive abdomen' given the abdominal distension.

Case 6

A 40-week gestation infant was born by SVD. The mother had regular prenatal care with unremarkable prenatal imaging. After delivery, the patient was noted to have sustained desaturations, so the infant was transferred to NICU for further evaluation. A chest radiograph on admission demonstrated 13 ribs, which was not noted on the radiologist's report or recognized by the on-call neonatologist. The following day, the NICU team noted the presence of an additional rib on the radiograph as well as concern for cardiomegaly. At this time, the patient continued to have desaturations and developed clinical signs and symptoms of respiratory distress (retractions and tachypnea) including stridor. Further work-up was undertaken at that time of multiple organ systems. Follow-up chest radiographs confirmed the presence of 13 ribs. An echo demonstrated significant outflow tract dilation of both the aortic root and pulmonary artery in addition to large atrial septal defect and VSD. Bedside, flexible nasopharyngoscopy by a pediatric otolaryngologist demonstrated paralysis of the left vocal cord, which was the cause of the stridor. Renal and head ultrasounds (USs) were obtained and both were normal. This cardiac abnormality was concerning for an underlying genetic etiology, so a whole exome sequencing genetic test was performed at the request of the genetics team. The testing identified a single missense variant (c.829T > A; p.W277R) in the *TGFBR1* gene consistent with Loeys-Dietz type 1. The parents were counseled extensively on the diagnosis, then elected to proceed with cardiac repair. The patient has since been discharged from the NICU, and is being followed outpatient in the Cardiology, Genetics and Complex Care clinics. While the diagnostic error in this case did not markedly impact the patient's clinical status, we included it in this case series to highlight a diagnostic error which did not markedly impact the final outcome, but it demonstrates potential for improvement in the diagnostic process for the future.

Case 7

A 39-week gestation infant was born by scheduled C-section after a prenatal diagnosis of severe left-sided congenital diaphragmatic hernia (CDH). The patient was treated with extracorporeal membrane oxygenation (ECMO) for 16 days after delivery and underwent surgical repair of the CDH while on ECMO. After ECMO, the patient required long-term ventilator support in the NICU as well as tracheostomy and gastrostomy-tube (g-tube) placement. The patient was on prolonged diuretic therapy due to chronic lung disease. At 5 months of age, the patient had persistent feeding intolerance, so a CT abdomen was obtained to evaluate for reherniation of the CDH. Incidentally, the CT report noted a 5-mm nonobstructing calculus in the lower pole of the left kidney. This was not followed up on or noted

in the patient's chart by the neonatology team. At 7 months of age, the patient developed persistent hematuria. A renal US was obtained to evaluate for a cause of the hematuria and noted the calculus—which remained nonobstructive, but had grown in size. The neonatology team then became aware of the prior CT report of the calculus—the source of the persistent hematuria. The feeding difficulties slowly improved, and the patient was eventually able to tolerate full enteral feeds. As the renal calculus was not obstructive, the neonatology clinicians in consultation with the pediatric urology service elected to follow with serial imaging. The calculus has remained stable in size and no evidence of obstruction on follow-up USs. The hematuria has since resolved. If the calculus becomes obstructive or if the patient develops a urinary tract infection or urosepsis in the future, then the plan is for urologic intervention at that time.

Incorrectly Interpreted Echocardiographic Imaging

Case 8

A 34-week gestation infant was born by an ex utero intrapartum treatment (EXIT) procedure for severe left-sided CDH after in-utero placement of an airway balloon by a fetal surgeon to improve lung growth. Following a prenatal diagnosis of CDH and in-utero placement of an airway balloon by a fetal surgeon, the mother developed preterm labor, so the infant was delivered at 34 weeks of gestation by the EXIT procedure. A prenatal echo had demonstrated normal cardiac anatomy. A postnatal echo on the day of birth identified a pulmonary vein on the right side returning to the left atrium, but did not visualize a pulmonary vein on the left side. This was not followed up by the neonatologist or cardiologist. The patient was treated with ECMO and surgical repair of the CDH, followed by a prolonged NICU stay requiring long-term ventilator support. Over the course of 3 months, nine limited echos were performed to evaluate for pulmonary hypertension, but the full cardiac anatomy was not assessed on these studies. Several months later, a CT heart was obtained to evaluate for another medical issue, which incidentally noted partial anomalous pulmonary venous return (PAPVR) of the left lingular and lower pulmonary veins, which formed a confluent channel draining to the left innominate vein. This was confirmed by a repeat full anatomic echo. After further discussion with the cardiology and cardiothoracic surgery clinicians, it was determined that while this finding had been missed on previous studies, surgical intervention was not warranted at that time. The patient remained in the NICU for several months, and required tracheostomy placement due to inability to safely wean from the ventilator. There were no additional concerns from a cardiac standpoint during admission. The patient has now been discharged from the NICU, and is being followed in the cardiology clinic. The plan from a cardiac perspective is to allow the patient to continue to grow, then for surgical repair of the PAPVR at a yet to be determined date in the future.

Inadequate Team Communication

Case 9

A 31-week gestation infant was born by C-section due to poor fetal biophysical profile. A prenatal US had noted that the stomach was not visible. A subsequent US did not visualize the stomach or other portions of the gastrointestinal (GI) tract, a finding suggestive of tracheoesophageal fistula (TEF) or other GI tract abnormality. The obstetric team communicated the concern regarding the GI tract to the neonatologist attending the delivery, but these concerns were not relayed to the admitting neonatologist. No diagnostic testing was performed for GI

anomalies. An abdominal radiograph performed to evaluate placement of an UVC noted an incidental finding of a rounded air collection in the upper mediastinum. An orogastric tube (OGT) was placed, but could not be advanced, and a radiograph demonstrated the OGT in the upper mediastinum with air distally in the GI tract, a finding suggestive of esophageal atresia with a TEF. This was confirmed on subsequent radiograph, in which the OGT was curled in the upper esophagus, and could not be advanced distally due to esophageal atresia. The decision was made to proceed to the operating room for surgical repair, and upon thoracotomy by the pediatric surgery team, and a type-C TEF was found and subsequently repaired. The patient had an uneventful recovery postoperatively, however, did require g-tube placement for enteral feeds due to inadequate oral feeding skills. The patient was discharged after several months in the NICU breathing room air and on full enteral feeds via the g-tube. Since discharge, the patient has required esophageal dilation by pediatric surgery.

No Fault

Case 10

A 34-week gestation infant was born by stat C-section due loss of fetal heart tones during routine fetal monitoring while the mother was at a prenatal appointment. During the pregnancy, the patient was diagnosed with multiple congenital anomalies, and the mother had undergone a fetal MRI, which demonstrated atresia of the jejunum with perforation, formation of meconium pseudocyst, lower urinary tract obstruction, arthrogryposis, and bilateral clubfeet. Prenatal genetic testing showed a chromosome 6 triplication. The patient was treated with intubation for respiratory distress, mechanical ventilation, a laparotomy to excise the jejunal atresia and a meconium pseudocyst, and creation of a jejunostomy. Postoperatively, the patient required prolonged mechanical ventilation, vasoactive support, and high-dose steroid administration. Genetic testing confirmed a chromosome 6 triplication. The patient had persistent hyperglycemia, which was initially ascribed to high-dose steroid administration. An insulin drip was initiated, but the patient's blood glucoses remained persistently elevated. An endocrinology consult and a literature review yielded the information that neonatal diabetes can be associated with chromosome 6 triplication. The patient was ultimately diagnosed with neonatal diabetes secondary to the chromosomal abnormality, and not due to high-dose steroid requirement as initially thought. Due to the extremely rare nature of this chromosome 6 triplication, the association with neonatal diabetes would not generally be considered in the typical differential diagnosis for neonatal hyperglycemia.

Discussion

This case series, the first of its kind to describe nonlethal diagnostic errors in the NICU, includes 10 cases categorized as cognitive, systems-based, or no-fault diagnostic errors.⁶

The majority were cognitive in origin (see Table 1). We included an example of a no-fault diagnostic error—defined as a highly atypical presentation which is undetectable in spite of adequate diagnostic work-up⁶—to illustrate a diagnosis which would remain indiscernible despite a reasonable diagnostic evaluation, and thus would most likely not be amenable to interventions directed at improving diagnostic errors. Some of the cases had multiple diagnostic errors or involved multiple medical teams, which demonstrates the often multifactorial nature of diagnostic errors in a complicated environment such as

the NICU. The outcome of these diagnostic errors varied as well—from no obvious harm, as in the patient with the missed radiologic finding of 13 ribs, to life-threatening, as in the patient with the missed pleural effusion requiring emergent needle thoracentesis. Fortunately, no patient died from diagnostic errors in this case series. We identified these diagnostic errors during the course of our clinical work in our NICU without any attempt to systematically perform surveillance for such errors, and described these cases to raise awareness of this problem in neonatology, and to highlight the need to systematically study these errors, which have been thus far relatively neglected in the patient safety movement. The chief limitation of our study is our inability to perform an in-depth analysis of the causal and contributory factors (particularly the cognitive processes involved) to the diagnostic errors we described. Therefore the categorization of these errors is solely based on the information available to us on chart review. In conclusion, a wide range of diagnostic errors may occur in NICU patients, and further research should address methods to identify, measure, and classify these errors and their impact. We are currently conducting a formal study to determine the incidence, types, and impact of diagnostic errors in the NICU, and we are using the cases described in this manuscript as prototypical cases to develop and refine our detection instrument, a modification of the Safer Dx instrument.⁷

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Mothers' Depression, Anxiety, and Mental Representations After Preterm Birth: A Study During the Infant's Hospitalization in a Neonatal Intensive Care Unit

Carmen Trumello¹, Carla Candelori¹, Marika Cofini¹, Silvia Cimino², Luca Cerniglia³, Marinella Paciello³ and Alessandra Babore^{1*}

Aim: This paper aimed to explore psychological functioning and mental representations in mothers of preterm infants during the child's hospitalization in a Neonatal intensive care unit (NICU).

Methods: A sample including 62 mothers of premature infants (gestational age <37 weeks) was recruited in a NICU. According to the gestational age at the time of delivery, we considered two groups: Group A included mothers whose children were born before 32 weeks of pregnancy; Group B included mothers whose children were born at or after 32 weeks of pregnancy.

Within one week of childbirth, mothers were administered two self-report questionnaires: the Edinburgh Postnatal Depression Scale (EPDS) and the State-Trait Anxiety Inventory (STAI). When their infants' medical conditions became stable, the Clinical Interview for Parents of High-Risk Infants (CLIP) was administered to mothers.

Results: The results showed high levels of depression and anxiety in both groups of mothers, with higher state anxiety scores in Group A than Group B. Besides, a series of hierarchical regression analyses were conducted with STAI, EPDS, and gestational age as predictors on the CLIP scores. Results indicated that EPDS scores predicted CLIP scores on parental self-image, support system, and readiness for discharge ($p < 0.001$); moreover, the interaction among depression, anxiety, and gestational age predicted the CLIP dimension of feeling of mutual recognition ($p < 0.005$).

Conclusions: These findings suggested that a premature birth and the child's hospitalization might exert a negative effect on the mothers' emotional state, their perception of parental self-image and, consequently, the early bond with the child—independent from the infants' gestational age at the time of the preterm delivery.

The data underlined the importance of involving NICU nurses and clinicians in order to optimize the care for mothers immediately after the preterm birth and during the infant's hospitalization, taking into account psychological needs of mothers of both very preterm and moderately preterm infants.

Keywords: neonatal intensive care unit, mothers, prematurity, maternal representations, depression, anxiety

Introduction

Preterm birth is an important issue in public health and is a major part of worldwide neonatal mortality and morbidity (1). Research has shown that premature birth is a distressing event for parents that often report symptoms of post-traumatic stress for several years (2, 3). Latva et al. (4) have shown that even 5 or 6 years after the preterm birth, mothers might have negative views of their perinatal or postnatal period. Otherwise, it is reported that mothers with positive experiences after a preterm birth have a more effective mother-child communication than those mothers who have had negative experiences (5). Parents of preterm infants face various difficulties and sudden changes in the process of bonding with their baby. Bonding with infants begins before birth and develops after it, but if the birth occurs sooner than expected or even too early, the normal bonding process could be affected. Goldberg and Divitto (6) have demonstrated that a long stay in hospital might have a disturbing effect on the bonding process. Although in the last decade the Neonatal Intensive Care Units (NICU) have undergone some changes for facilitating the presence of parents during the hospitalization of their baby, NICU remains a stressful environment for parents, as demonstrated in many studies (7). The physical environment is characterized by monitoring equipment, tubes and wires connected to infant, noises, and chemical scents. However, the major stress experienced by parents is related to the separation from their baby and to the loss of their parental role as they had previously imagined it. As suggested by Flacking et al. (8), the feelings of separation and exclusion could be related to the lack of physical and emotional closeness which are important factors in the early relationship between parents and the newborn infant. In fact, as frequently reported in the literature, the first moments of postpartum period are fundamental for the construction of early parent-infant bonding (9, 10). During hospitalization of their baby, mothers may experience several and often contradictory emotional reactions, such as grief, sadness, guilt, fear, anger, loss of self-esteem, and sense of failure (11). In fact, this situation can be so overwhelming for mothers that they might react by emotionally distancing themselves from their children (12, 13). These emotional factors might negatively affect the mothers' ideas, thoughts, and representations about the child's appearance and behavior. In particular, mothers of preterm babies often have fewer positive ideas and expectations for their children than mothers of term babies (14,

¹Department of Psychological, Health and Territorial Sciences, Università degli studi G.D'Annunzio Chieti Pescara, Chieti, Italy, ²Department of Dynamic and Clinical Psychology, Faculty of Psychology, Sapienza University of Rome, Rome, Italy, ³Università Telematica Internazionale Uninettuno, Rome, Italy

15); these could be characterized by a communication about their child, generally positive, with specific and sensitive details about care (16). Crawford and Benoit's work (17) has shown that maternal representations could be influenced so much by traumatic events that the parent might become incapable of understanding their child's state of mind. So, when the child makes signals or expresses desires or needs, the parent might be unable to respond in a caring and appropriate way (18). As Deklyen and Greenberg's research (19) indicated, when this occurs, it constitutes a severe risk factor for mother-child relationship and for later psychopathology. Hall et al. (20) have shown that mothers, characterized by negative and unrealistic perceptions about their baby and the hospital environment, are often more intrusive, more withdrawn, and less sensitive toward the 6-month-old infants. In light of the aforementioned factors that might negatively affect the early postpartum period—considered the “sensitive time” (10) for mother-child bonding—it is very important to explore the mothers' emotional experience after a premature birth and during the hospitalization in the NICU. For this purpose, a useful tool that specifically explores parents' experience in NICU is the Clinical Interview for Parents of High-Risk Infants [CLIP; (21)]. The CLIP allows parents to reflect on and express their feelings and concerns; it could be useful to analyze the maternal representations after a preterm delivery and to detect early disruptions in the mother-infant relationship at the nursery (5, 22). Several studies have investigated the psychological symptoms in mothers of premature infants in terms of the symptoms of depression and anxiety. In fact, mothers of premature infants generally show higher rates of postpartum depression than mothers of full-term infants (23, 24). In literature, there is a broad consensus that early depressive symptoms of mothers have a negative effect on their relationship with the infant and on their parenting role, especially after a preterm birth (25). Mothers with depressive symptoms show negative perceptions of themselves, their baby, and their relationship (26, 27). Although most studies about the effects of mothers' postnatal mood on child development focus above all on postpartum depression, in the last decades, researchers have found that postpartum anxiety has independent effects, just as postpartum depression (28). In case of premature birth, mothers show high levels of anxiety symptoms (24, 29) that might compromise the maternal functions and the mother- infant interactions (30, 31). Besides, as Lotterman et al. (32) noticed in their recent study, a lot of research that explores psychological symptoms (including depression and anxiety) and the experience of mothers with premature infants in NICU, focuses mainly on very preterm gestational age range. Compared to this field of research, studies on moderate-to late preterm infants are less, although this gestational age range characterizes a high percentage of preterm births. Moreover, as far as we know, a few studies have compared maternal representations of moderately preterm and very preterm infants in the NICU during the first moments after birth. Despite the outcomes of very preterm birth are increasingly acknowledged, less attention is given to parents of moderately preterm infants. Furthermore, it remains unclear which specific factors could be most predictive of the quality of maternal representation in the NICU. Starting from the above considerations, our study aimed to more deeply explore the maternal and emotional experience in terms of mental representations, as reflected in the CLIP interview, considering depression, anxiety symptoms, and gestational age at the time of delivery.

Materials and Methods

Objectives

This paper overall aimed to explore differences in psychological functioning and mental representations of the infant and themselves as parents between mothers of moderately preterm infants and mothers of very preterm infants. In order to differentiate the two groups, we have referred to recent research that set the turning point at 32 weeks of gestational age (33, 34).

In particular, the current study considered two groups: Group A included mothers whose children were born before 32 weeks of pregnancy (very preterm); Group B included mothers whose children were born at or after 32 weeks of pregnancy (moderately preterm). The study had the following specific objectives:

- To verify whether Group A and Group B differ with regards to the possible presence of anxiety and depressive symptoms in mothers;
- To verify whether Group A and Group B differ with regards to the mothers' representations about the delivery and their relationship with the premature child;
- To verify whether the mothers' anxiety and depressive symptoms predict the quality of their representations of the child and of themselves as parents, considering gestational age.

Participants

Our study is part of a longitudinal project in which mothers and fathers of preterm infants were followed since the hospitalization in NICU till up to 2 years post-partum.

The participants were 62 mothers of preterm babies born before 37 weeks of gestation recruited in NICU of the Chieti University Hospital with the Director's, pediatricians', and nurses' collaboration. Inclusion criteria were: absence of child's genetic illnesses, neonatal deformities, and neurological damages clinically identifiable at birth, mother's age at least 18-year-old, mother's good knowledge of the Italian language, and absence of mother's drug or alcohol addiction.

Maternal and infants' basic characteristics are shown in Table 1. All parents were Caucasian and most (79%) were of middle socio-economic status [SES; (35)]. A majority (95%, $N = 59$) of the parents lived together, 80.6% ($N = 50$) of the mothers were employed, and 69.4% ($N = 43$) of the children were firstborn. The mean age of the mothers was 33.98 years (standard deviation [sd] = 4.76). The children were 45% ($N = 28$) males and 55% ($N = 34$) females.

Procedures and Measures

Within one week after the childbirth, a group of trained psychologists administered the mothers a demographical and anamnestic form and two self-report questionnaires: Edinburgh Postnatal Depression Scale [EPDS, (36)], State-Trait Anxiety Inventory [STAI, (37)].

The EPDS is a uni-dimensional self-reported checklist, designed as a screening tool for identifying mothers at risk for post-partum depression in community settings. Subjects were asked to rate their symptoms in the past seven days on one of four response categories ranging from “0” = “not at all” to “3” = “most of the time/quite often.” The possible scores, after reversing all positive-worded items, ranged from 0 to 30 with a higher score reflecting a higher risk for post-partum depression (PPD). In

TABLE 1 | Maternal and infant characteristics at NICU (*N* = 62).

Characteristics	Frequency (%)	<i>M</i>	<i>SD</i>
MOTHERS			
Age		33.98	4.76
Education (Years)		14.62	3.30
Middle school	8 (13.6%)		
High school	34 (54.6%)		
University	20 (31.8%)		
Maternity			
Primipara	43 (69.4%)		
Multipara	19 (30.6%)		
Currently Employed			
Yes	50 (80.6%)		
No	12 (19.4%)		
Marital Status			
Married or cohabitating	59 (95%)		
Not married or cohabitating	3 (5%)		
INFANTS			
Gender			
Male	28 (45%)		
Female	34 (55%)		
Gestational Age (In Weeks)		32.28	2.352
< 32 weeks	40 (35.5%)		
≥ 32 weeks	22 (64.5%)		
Birth weight (gr)		1685.42	525.394

the present paper, we used the Italian validated version and its related cut-off, ie, 8/9 (38).

The STAI is a self-report anxiety behavioral instrument consisting of two separate 20-item subscales that measure trait (baseline) and state (situational) anxiety in adults. The STAI trait subscale measures relatively stable individual differences in their proneness to anxiety (ie, differences in the tendency to experience anxiety), and the STAI state subscale measures transitory anxiety state (ie, subjective feelings of apprehension, tension, and worry that vary in intensity and fluctuate based on the situation). In this paper, we used the Italian validated version and its related cut-off, ie, 39/40 (39).

For the second step, when the infants' medical conditions were stable, a clinical interview [CLIP, (21)] was administered to the mothers by a second group of psychologists who were blind to its administration and the results of self-report questionnaires.

The CLIP was originally developed by the authors to assess the feelings and perceptions of preterm children's parents. It consists of a semi-structured interview allowing the clinician to extensively explore the parental experience. Further, its flexibility allows the clinician to adapt the questions according to the conversational flow, to better explore the parent's emotional experience. This interview requires about 1 h to be completed and addresses eight main areas: infant's current condition, pregnancy course, labor and delivery, relationship with the baby and feelings as a parent, reactions to NICU environment and staff, relationship with the family and social support, discharge and beyond, and a final wrapping up.

The CLIP is audio-recorded and transcribed verbatim; the authors recommended coding the interview through a content

analysis; afterwards, Keren et al. (5) developed a coding system to analyze two areas: "readiness for parenthood" and "parental rejection."

Clinical interviews were administered in an empathetic and understanding environment. The interviews lasted an average of 1 h and were audio-recorded with the mothers' permission and subsequently transcribed verbatim, as previously indicated by the authors.

After administering all the measures, two sub-groups were created on the basis of gestational age (33, 34, 40, 41): Group A (very preterm) included mothers whose children were born between 28 and 31 weeks; Group B (moderately preterm) included mothers whose children were born between 32 and 36 weeks of pregnancy.

Participation in the study was voluntary. All the participants received a letter containing detailed information on the main aims of the study and signed a written informed consent. The questionnaires were alphanumerically coded in order to guarantee anonymity. In the current observational study any diagnostic process was performed; in addition, it involved women who had no history or ongoing evidence of any psychiatric illness; hence, we believe that the approval of the study by the Ethics Committee was not appropriate. Nevertheless, an additional opinion was asked to the Psychological Review Board of our Department. The Board found that all the employed procedures and measures were fully compliant with the Ethics Code of the Italian Board of Psychology—the national authority that provides ethical guidelines for research and clinical practice.

Data Analysis

Descriptive analyses attested that all variables were normally distributed. The analyses of variance (ANOVAs) were used to test significant differences between Group A and Group B scores on STAI, EPDS, and CLIP, and Bonferroni's post hoc tests were applied. The calculated p-values are reported with their respective F statistics and degrees of freedom (*df*), with values < 0.05 being considered significant. Mean values are reported with standard deviations (*sds*). Finally, a series of hierarchical regression analyses were conducted to investigate the influence of specific anxious and depressive symptoms (STAI and EPDS) on the mothers' representations about the delivery and their relationship with the premature child (CLIP). In all the analyses we conducted, the child's gender and mothers' age showed no significant effect on the variables. All analyses were performed on the SPSS software (Version 18.0).

Results

Differences in Group A and Group B Scores on the Symptoms of Anxiety and Depression

An ANOVA conducted on Group A and Group B scores on STAI-Y1 showed a group effect [$F_{(1,60)} = 7.418$; $p < 0.01$]. Post-hoc analysis showed that Group A has significantly higher scores than Group B on STAI-Y1 (State Anxiety) ($p < 0.01$); 72% of the subjects in Group A and 45% in Group B exceeded the clinical cut-off for STAI-Y1 for the Italian population (39).

An ANOVA conducted on Group A and Group B scores on STAI-Y2 showed no group effect [$F_{(1,60)} = 0.647$; $p > 0.5$]. Although no statistically significant differences were found between the two groups on STAI-Y2 (Trait Anxiety), 36% of subjects in Group

TABLE 2 | Mean scores and standard deviations [M(sd)] values of STAI-Y1, STAI-Y2 and EPDS in Group A and Group B.

	STAI-Y1	STAI-Y2	EPDS
Group A	48.55 (13.68)	38.27 (8.64)	13.05 (5.25)
Group B	42.85 (12.69)	37.21 (10.36)	11.33 (5.78)
<i>p</i>	<0.01	n.s	n.s

A, and 37.5% in Group B exceeded the clinical cut-off for STAI-Y2 for the Italian population (39).

An ANOVA conducted on Group A and Group B scores on EPDS showed no group effect [$F_{(1,60)} = 0.66$; $p > 0.5$]. Although no statistically significant differences were found between the two groups on EPDS, 68% of subjects in Group A and 60% in Group B exceeded the clinical cut-off for EPDS for Italian population (38). Table 2 shows mean scores and standard deviations values.

Differences in Group A and Group B Scores on the Mothers' Representations About the Delivery and Their Relationship With the Premature Child

An ANOVA conducted on Group A and Group B scores on CLIP showed a group effect on several dimensions ($p < 0.05$). Post-hoc analysis showed that Group A had significantly higher scores than Group B on CLIP dimension of: perceived infant's current condition ($F_{(1,60)} = 0.016$; $p < 0.05$), first feelings toward baby ($F_{(1,60)} = 0.035$; $p < 0.05$), readiness for discharge ($F_{(1,60)} = 0.003$; $p < 0.05$), and organization of content ($F_{(1,60)} = 0.016$; $p < 0.05$). No other statistically significant difference was found on the other CLIP subscales ($p > 0.5$). Table 3 shows mean scores and standard deviations values.

Impact of Mothers' Anxiety and Depressive Symptoms on the Quality of Their Representations of the Child and of Themselves as Parents, With Respect to the Gestational Age

A series of hierarchical regressions have been conducted with STAI, EPDS, and gestational age as predictors on the CLIP scores. The results showed that EPDS scores predicted CLIP scores on parental self-image, support system, and readiness for discharge ($p < 0.01$); gestational age predicts scores on the CLIP main area of course of pregnancy ($p < 0.05$); STAI-Y1 scores, interacting with gestational age, predict the CLIP main area of affect ($p < 0.01$). EPDS, interacting with STAI-Y1, STAI-Y2 scores, and gestational age, predict the CLIP subscale scores of feeling of mutual recognition ($p < 0.05$). Table 4 shows results and values of the regression analyses (significant results only).

Discussion

Premature delivery and the subsequent hospitalization in NICU are considered early adverse experiences, which could affect the emotive states of mothers, their mental representations, their perceptions of infants, and their relationship in the early postpartum moments, that are assumed to be significant for maternal bonding to the infant.

Our study aimed to explore the maternal emotional states in NICU, with reference to anxiety and depressive symptoms, mental representations, and gestational age at the time of delivery.

With regard to the first aim, results showed that mothers of premature babies experience high levels of psychological

TABLE 3 | Mean scores, standard deviations and *p*-values on CLIP main areas and subscales in Group A and Group B.

CLIP main area	CLIP subscale	Group A	Group B	<i>p</i>
Infant's current condition		0.68 (1.68)	0.35 (0.70)	<0.05
Pregnancy	First reaction to pregnancy	1.32 (0.65)	1.18 (0.45)	n.s
	Planned pregnancy	1.45 (0.51)	1.38 (0.49)	n.s
Course of pregnancy	Physical and/or emotional complications	2.05 (1.13)	2.48 (1.24)	n.s
	Timing of "pregnancy feeling real"	2.14 (1.11)	1.97 (1.12)	n.s
Labor and delivery	Readiness for delivery	2.45 (0.60)	2.41 (0.64)	n.s
	Fear of loss during delivery	2.32 (0.65)	2.05 (0.57)	n.s
Relationship with baby and feelings as a parent	First feelings toward baby	1.55 (0.60)	1.20 (0.41)	<0.05
	Present feelings toward baby	1.33 (0.48)	1.15 (0.36)	n.s
	Feeling of mutual recognition	1.52 (0.68)	1.46 (0.55)	n.s
	Parental self-image	1.33 (0.58)	1.33 (0.53)	n.s
Reaction to NICU	Reaction to staff	1.43 (0.51)	1.32 (0.53)	n.s
	Reaction to NICU setting	1.67 (0.62)	1.93 (0.92)	n.s
Support system		1.32(0.48)	1.30 (0.46)	n.s
Discharge and beyond	Foreseen future for baby	1.50 (0.67)	1.23 (0.43)	n.s
	Readiness for discharge	1.70 (0.70)	1.24 (0.43)	<0.05
Affect		1.68(0.65)	1.53 (0.56)	n.s
Organization of content		1.36(0.58)	1.26 (0.44)	<0.05
Richness of content		1.62(0.59)	1.46 (0.60)	n.s

distress in both the investigated groups, namely very preterm (Group A) and moderately preterm (Group B) children.

In reference to symptoms of anxiety, the mothers' scores significantly differed between the two groups. More specifically, the State Anxiety seemed to be the only one influenced by the baby's gestational age, in fact mothers in Group A showed higher anxiety levels than those in Group B.

These findings are consistent with the previous studies reporting that mothers of very preterm infants may be more concerned and worried about their babies' survival as compared to those of moderately preterm infants (42, 43).

On the contrary, there are no differences in Trait Anxiety levels when the two groups were compared, despite a large number of mothers of the whole sample exceeding the clinical cut-off for the Italian population (39). This result is in line with other ones that highlight elevated anxiety symptoms following a premature delivery (44, 45). An alternative explanation of the high levels of state anxiety in our sample may not exclude a post-traumatic state of the mothers, following the very preterm delivery. In fact, several recent studies found that posttraumatic stress represented the most common reactions after a premature childbirth (46, 47). However, this hypothesis could be more suitably explored in future research using the STAI alongside with other more specific tools for post-traumatic stress disorder.

If we move to consider depressive symptoms, contrary to general expectations, we do not find significant differences between the two groups, despite a high percentage of mothers exceeding the clinical cut-off for EPDS for the Italian population (38), regardless of the gestational age at the time of delivery. In

TABLE 4 | Results and values of the regression analyses (significant results).

STAI/EPDS/gestational age	CLIP main areas and subscales			
	R ²	β	t	p
EPDS			Parental self-image	
	0.061	0.671	29.431	<0.001
			Support system	
	0.031	0.767	32.123	<0.001
			Readiness for discharge	
	0.045	0.369	3.475	<0.001
Gestational age			Course of pregnancy	
	0.069	0.537	2.465	<0.05
STAI-Y1 • gestational age			Affect	
	0.052	0.613	2.324	<0.001
EPDS • STAI-Y1 • STAI-Y2 • gestational age			Feeling of mutual recognition	
	0.089	0.413	2.328	<0.005

• Scores in association with.

our sample, during the infant's NICU hospitalization, maternal depressive symptoms in both the groups were equally elevated which was in line with other studies (48–51).

We may hypothesize that, in case of preterm birth, the precarious conditions of the child, the cold and sterile environment of the NICU, and the ambiguity of maternal role in the hospital setting make the mothers more vulnerable to depressive symptoms, even in the case of moderately preterm infants.

The mothers' feelings of helplessness, exclusion, and alienation could further increase the level of distress and might thus impact their transition to motherhood (52, 53). In fact, previous studies showed that the prevalence of postpartum depression after premature delivery can be estimated up to 70% (54–56).

Our finding of higher levels of anxiety and depressive symptoms in mothers of preterm infants is consistent with other research that explored the distress in mothers of premature infants as compared to mothers of full-term infants (31, 57, 58).

In the literature, few studies have examined the level of symptoms immediately after birth or during NICU hospitalization. The current study has estimated maternal symptomatology during the infant's hospitalization, 1 week after delivery. Our results showed that beyond the infant's gestational age, mothers present a high risk of anxious and depressive symptomatology. Therefore, it could be important to pay close attention to mothers' emotional experiences related to premature birth since the first moments after delivery.

Since the first contact between a mother and her child takes place inside the NICU, it is very important to provide the mothers with psychological support or assistance right from birth in order to ensure their well-being and prevent future problems.

Another purpose of this research was to deeply explore the maternal representations during the NICU stay. More specifically, with regard to the second aim, mothers of very preterm infants differ from mothers of moderately preterm infants only in four areas of maternal representations, as reflected in the CLIP. Specifically, as compared to the mothers

of moderately preterm infants, mothers of very preterm babies showed more negative experiences and perceptions relating to their infants and their relationship with them. In fact, these mothers were characterized by a greater "fear of loss of the baby" (a dimension related to the area of maternal perception of the child's current condition) and more negative "first feelings toward the baby." Additionally, they did not feel ready for discharge and the narratives of their representations were disorganized.

These major difficulties of mothers of very preterm children in the narrative organization of representations, their negative feelings toward the infant, and the low confidence in their role could be related to the perception of greater vulnerability of their baby, that increases their fear of loss (59). Seeing their infants as fragile and in danger in the NICU is very stressful for mothers, and it may generate an "emotive crisis" (7, 60).

The mothers of preterm infants often show feelings of ambivalence about their relationship with their child and feelings of unreality of "being mothers" during the NICU stay (61). In fact, in the case of very preterm infants, mothers spend more time in the NICU, where they are continuously in touch with the experience of the infants' fragility and risk of mortality (62). Living in a state of psychological and physical separation from their babies is intensified by the artificial environment of the NICU. All these early and difficult experiences could affect the development of maternal mental representations.

Finally, in reference to the third objective of the study, according to our results, depressive symptoms were the strongest predictors of the quality of maternal representations of the child and of themselves as mothers and of the child. In particular, depression seemed to predict more areas of representations with respect to the other variables we had considered. It predicted an insecure parental self-image, negative perception of support system, and lower readiness for discharge (this last area investigated the mothers' impression and expectations about homecoming and the baby's future development).

Generally, premature birth is considered a stressful and potentially traumatizing event (63) followed by the hospitalization in the NICU, where there is a prolonged separation between the mother and the infant. This situation might generate feelings of depression and the mothers' poorer psychological well-being which may lead to lesser psychological investment in relationship with the infant (15) and altered perception of both the mothers' parental role and the support system.

In addition, our findings showed that depressive symptoms, in interaction with anxiety (Trait and State) and gestational age, predict the CLIP area "feeling of mutual recognition," regarding the mothers' perception of being recognized by their children in their parental role. It could be concluded that in presence of the comorbidity of anxiety and depression, the lower the gestational age at the birth, the less the mothers feel to be recognized by their infants.

As suggested by Feldman (64), close proximity, nurturing, and interaction with the baby play an important role for the early mother-child interaction, consolidating mothers' confidence in her parenting role. In the NICU, these conditions are absent: the early separation between the mothers and their infants,

the loss of maternal role (60), the feeling of responsibility for the unhealthy state of the infants (65), and negotiation of the infant's care with nurses and medical staff within the unit (66) are associated with a higher risk of long-term psychological problems, such as depression, anxiety, feelings of isolation, and fear for the child's well-being (67). These emotive and psychological states, with a lower gestational age, that usually requires prolonged hospitalization, seem to influence above all the aspect concerning "recognition" and "reciprocity." In fact, physical closeness represents the prerequisite for early parent-to-infant bonding for maternal behaviors and for reciprocity between the mother and her child (64, 68). These data are in line with other research that underlined that the NICU stay could hinder the development of the intuitive parental capacities in the mothers of very preterm infants (69, 70).

Further research is needed to explore the mechanism behind the development of maternal representations in the particular situation of premature birth. Indeed, several studies have demonstrated that maternal representations influence the way in which a mother interacts with her baby (71).

Overall, our research highlights some important aspects of mothers' experience and their emotional state in the early moments of the child's life during the hospitalization in NICU in a situation of high risk for the infant.

Nevertheless, our study has some limitations, such as the small sample size and its recruitment in only one NICU; this may limit the generalizability of the results. In addition, we did not consider a comparison group of mothers with full-term children to test depressive and anxiety levels. Hence, future research could try to replicate these findings using larger and more diversified samples, also referring to non-Italian mothers, given the wide cross-cultural variations in maternal reactions to preterm delivery.

However, the present study makes a relevant contribution to knowledge regarding the emotional state of the mothers of premature babies, highlighting a difficult emotional situation not only for the mothers of very preterm babies but also for those of moderately preterm babies. Often, it happens that high-risk mother-infant dyads receive more psychological attention than low-risk ones (5). To improve care, it is very important to also understand the experiences of these mothers who are at the risk of being neglected. In addition, our study integrated different tools (questionnaires and interviews) and the use of a clinical interview tool—the CLIP—built specifically for parents of premature babies, that allowed us to extensively analyze maternal representations, retracing the path from pregnancy to experience in NICU with the mothers. Undeniably, not prematurity in itself but the presence of certain emotive states, negative thoughts, and perceptions in parents might be indicative of the difficulties in parent-infant relationship (72).

Parenting interventions in the NICUs play an important role in facilitating the bonding between the mother and the infant, providing support for these vulnerable families. Benzies et al. (73), in their meta-analysis, showed that early interventions in NICU decreased maternal anxiety and depressive symptoms and increased the mothers' sense of self-efficacy.

In fact, although NICU's primary function is medical assistance for infants, it is also the place where there is the first mother-

child encounter and where all the early dynamics of their relationship begin. For this reason, it is crucial to conduct further research in this area.

Author Contributions

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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* Outcome measures were statistically based on mean weight data.

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