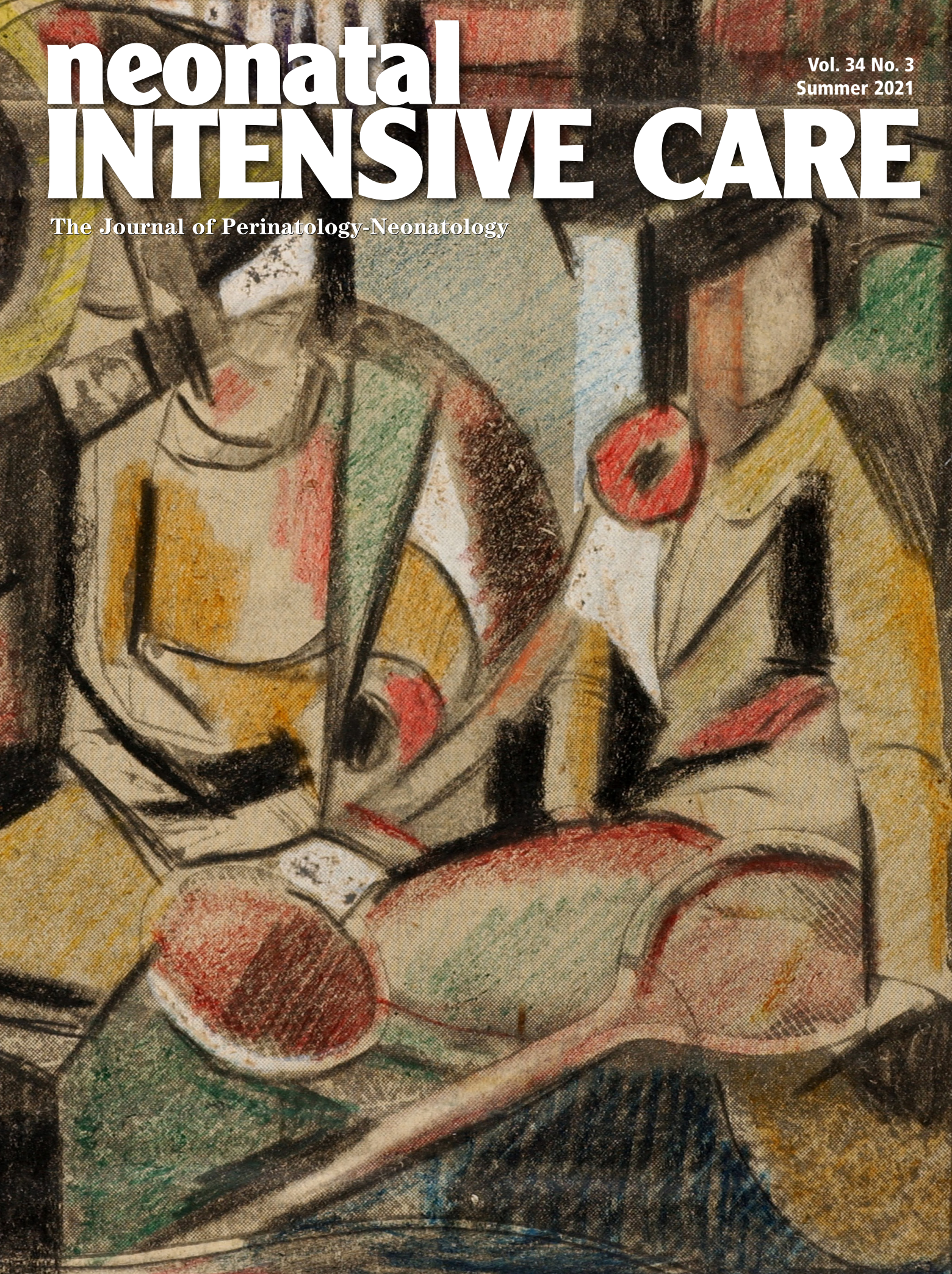


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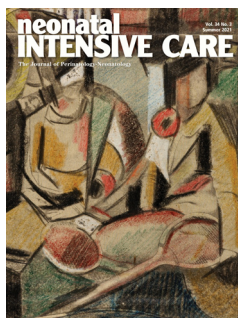
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## Company Introduces Neonatal Transilluminator for Single Patient Use

Neotech is proud to introduce a neonatal transilluminator developed specifically for single patient use: NeoGlo Disposable. NeoGlo Disposable is available with red or white LED lights. It is lightweight, compact, and features a USB power connector. No batteries required. "Infection in general, and especially cross contamination, is a great concern in the NICU. I approached Neotech to develop a small, inexpensive neonatal transilluminator that could be used for one patient and then discarded when the patient is sent home," Professor Ruben Bromiker, Neonatologist said. "I'm thrilled to see this product come to fruition. Having one transilluminator per patient will also make it more available, thus encouraging the staff to use it. And studies show that the use of transillumination improves the chances of success; reducing the number of pricks we give a patient." After the successful launch of the original NeoGlo, Neotech set out to deliver Dr Bromiker's original, hospital-driven concept. "Dr Bromiker came to us with a fairly simple idea: an affordably-priced device that could be plugged into a USB power source," Sara Dimmitt, Manager of New Product Development said. "It was focused on the needs of the international market. After some market research in the US, his idea evolved into a reusable neonatal transilluminator with multiple light settings.

But we always intended on revisiting a disposable option. And with Philips discontinuing their Wee-Sight, it's perfect time to introduce NeoGlo Disposable to the market." Now, Neotech offers two great transillumination options. The original reusable and the new NeoGlo Disposable.

## 55 New Chemicals Found in Pregnant Women, Their Newborns

Fifty-five chemicals never before reported in humans were found in pregnant women, according to a study from the University of California San Francisco. The chemicals likely come from consumer products or industrial sources, researchers say. Findings were published online in *Environmental Science and Technology*. Co-first authors Aolin Wang, PhD, and Dimitri Panagopoulos Abrahamsson, PhD, postdoctoral fellows in UCSF's obstetrics and gynecology department, and colleagues found 109 chemicals in the blood of pregnant women, including 42 "mystery chemicals" whose sources and uses are not known. The chemicals were also found in their newborns, tests from umbilical cord blood show, suggesting the chemicals cross through the placenta. Among the chemicals, 40 are used as plasticizers, 28 are used in cosmetics, another 25 are used in consumer products, 29 as pharmaceuticals, 23 as pesticides, three as flame retardants, and seven are PFAS [per- and polyfluoroalkyl substances] compounds used in multiple applications including carpeting and upholstery, the authors report. Senior author Tracey Woodruff, PhD, MPH, characterized their discoveries as "disturbing." "We know it's a chemical registered to be manufactured and it's used in commerce, but we don't know where," she explained. "That's very disturbing that we can't trace them and that shows a failure in public policy and government." "Exposures are occurring without our consent," said Woodruff, a former US Environmental Protection Agency scientist, who directs the Program on Reproductive Health and the Environment (PRHE) and the Environmental Research and Translation for Health (EaRTH) Center, both at UCSF.

## Blood Markers May Help Predict Delivery Time

Scientists have identified markers in blood that may indicate labor is approaching, according to a new study. Through an analysis of blood samples gathered during the second and third

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Cover: Two Women with Tennis Racquets.  
Artist: Carl Newman. Source: Smithsonian American Art Museum

trimesters of 53 women, researchers identified a combination of factors that predicted the approach of labor to within a two week window, according to the report published in Science Translational Medicine. “Currently it is hard for an obstetrician to give an accurate time when a woman is going to go into labor,” said coauthor Dr Brice Gaudilliere of Stanford University. “This can be an issue both for pregnancies that turn out to be preterm and those complicated by being post term.” “By measuring various factors that represent many physiological systems that are important in the maintenance of pregnancy—in particular the immune system—we are able to predict when labor will occur without relying on an estimate of the gestational age,” Gaudilliere said. Gaudilliere and his colleagues analyzed blood samples from 53 women who went into labor spontaneously, including five who delivered preterm. Blood was collected two or three times from the women during the last 100 days of their pregnancies, with each sample analyzed for 7,142 metabolic, protein and single-cell immune features. The data was plotted against the number of days before labor that each sample was collected, and via mathematical modeling, the researchers identified which features in the blood best predicted the onset of labor. Once they had isolated the factors that appeared to presage the onset of labor within a window of two weeks, Gaudilliere and his team tested their results on the pregnancies of 10 more women, which confirmed the researchers were on the right track. Overall, the researchers found that a surge in steroid hormone metabolites and interleukin-1 receptor type 4 preceded labor, coinciding with a switch from immune activation to regulation of inflammatory responses. Gaudilliere and his team hope that the study’s findings will yield a test that obstetricians can use to predict labor within the next two to three years.

#### Latest Data Added to Poster

Mallinckrodt plc, a global biopharmaceutical company, announced that data from its Phase 4 observational registry comparing the safety and effectiveness of INOmax (nitric oxide) gas, for inhalation, in term and near-term (TNT) neonates to that in preterm (PT) neonates with pulmonary hypertension (PH) will be presented in a poster at The Pediatric Academic Societies (PAS) 2021 Virtual Meeting. The safety and efficacy of INOmax in premature neonates has not been evaluated by the US Food and Drug Administration. INOmax has been on the market in the US since 2000 and 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. The primary outcome measure of the registry was the number of PT neonates and TNT neonates with a significant response to INOmax, which was defined as at least a 25 percent improvement (decrease) from baseline in oxygenation index or surrogate oxygenation index (OI/SOI) during INOmax treatment. A total of 50 (90.9 percent) PT and 75 (88.2 percent) TNT neonates achieved a  $\geq 25$  percent decrease in OI/SOI during treatment with INOmax. Efficacy in the PT group demonstrated non-inferiority (95 percent confidence interval: 0.0267 [-0.0333, 0.0868], with a pre-defined margin of -0.1452). In addition, the proportion of neonates with  $\geq 25$  percent decrease in OI/SOI was similar across severity groups with no significant difference in time to improvement between groups. “These registry findings help expand our understanding of a potential role of inhaled nitric oxide therapy in preterm infants with hypoxic respiratory failure with pulmonary hypertension,” said study author Leif D. Nelin,

MD, Division Chief of Neonatology at Nationwide Children’s Hospital. Persistent pulmonary hypertension of the newborn (PPHN) is a serious and sometimes fatal cardiorespiratory complication of the transition to extra-uterine life. The registry trial was conducted to examine the utility of INOmax in pre-term neonates. Due to the seriousness of the condition, a randomized controlled trial cannot be conducted in the pre-term neonate population. Overall, 21 adverse events of special interest were reported in 17 patients, all of which were classified as serious events, and no serious adverse events were attributed to the study drug. “After ending this registry much earlier than anticipated last year based on positive findings, Mallinckrodt is extremely pleased to be able to share these important data with the healthcare community and add to the body of research and real-world data for this vulnerable patient population,” said Steven Romano, MD, Executive Vice President and Chief Scientific Officer at Mallinckrodt.

#### Parents Battle Hospitals Over Rights

Ashley Lamendola was still a teen when medical staff at St Petersburg General Hospital delivered the awful news that would change her life forever: Her newborn son, Hunter, had suffered profound brain damage and would do little more than breathe without help. “It was like an atomic bomb went off in my life,” she said. Lamendola believed the hospital was partly responsible for Hunter’s birth injuries. But Florida is one of two states that shield doctors and hospitals from most legal actions arising from births that go catastrophically wrong. Lamendola filed a lawsuit against St Petersburg General anyway, and when it appeared she was gaining traction, the hospital advanced an extraordinary argument. It suggested that Hunter’s mother was not acting in her son’s best interest and that a critical decision about his future care should be put in the hands of an independent guardian and a judge. Lamendola, attorneys said, was pursuing her own self-interest by refusing to participate in the quasi-government program that compensates the families of children injured at birth. Under the program, known as the Birth-Related Neurological Injury Compensation Association, or NICA, the state provides \$100,000 upfront and pays for “medically necessary” care for the child’s lifetime. In exchange, parents give up their right to sue hospitals and doctors, lawsuits that can result in judgments or settlements in the tens of millions of dollars. By choosing to “pursue her own speculative, complicated civil lawsuit” rather than permitting her son to accept his “vested” NICA benefits, Lamendola was trying to profit from Hunter’s injuries, St Petersburg General attorneys argued in a court filing. They underscored the words “her own.” Had she accepted Hunter’s inclusion in NICA, “the Mother would be unable to pursue her own civil lawsuit, seeking her own separate monetary damages for the Child’s injuries,” the lawyers added. “You carry a child for nine months, and then you finally get to hold them—eventually in my case,” said Lamendola, who was employed as a customer service rep at an AutoZone when she gave birth. “And you take care of their every want and need, and you put a child before you. I mean, once you have a child, there is no more *you*. It’s them. It’s us. It’s that baby that needs you and needs everything from you. I didn’t understand how somebody who wasn’t me could know what he wants and needs. I knew every sound, every movement, every seizure that he had,” Lamendola said. “And to think that somebody thought they knew better than me. It was wild to me.” The battle between parents like Lamendola and hospitals like St Petersburg General can seem like a gross mismatch: Lamendola was a single mom who made \$10.50 an hour and lived with her mother. HCA Healthcare,

which owns St Petersburg General, is one of the nation's largest for-profit hospital chains, with 180 hospitals, 280,000 employees and revenues of \$51.5 billion in 2020. For hospitals facing stunningly high settlements or verdicts, NICA, the state's no-fault program, is a valuable legal tool—a club to bat away expensive lawsuits. At the cost of \$50 per live birth, hospitals can protect themselves from multimillion-dollar judgments. Paolo Annino, who heads the Children's Advocacy Clinic at the Florida State University College of Law, said attempts to restrict a parent's authority through the appointment of a guardian are unusual: In child welfare disputes, for example, parents must be found unfit by a judge before being stripped of their right to decide what's best for their children. "What we have here is a scenario where there's no allegation of offending parents at all," he said. "The parent is, with very few exemptions, the one who makes the child's health care decisions." NICA came under fire this month after a series of reports by the Miami Herald and the investigative reporting newsroom ProPublica. Families complained that the \$100,000 grant—unchanged since 1988—is inadequate, and that payments for medical procedures or equipment are routinely slow walked or denied entirely. After the articles were published, state leaders professed outrage and promised a comprehensive fix to the program. Here is how NICA works:

After a baby is born brain damaged, parents can file a lawsuit against the hospital and doctor. The defendants then can ask the judge to pause the suit and order the parent to file a NICA claim. That petition is heard in a separate venue by an administrative judge, who then decides if the case is "compensable." Ultimately the administrative judge determines whether NICA applies or if the parents can resume their lawsuit. To qualify for NICA, in addition to having physical and cognitive impairments, a

child must weigh at least 2,500 grams (5.5 pounds) at birth and be delivered in a hospital. When children don't fit those criteria, parents retain the ability to sue. For the roughly 440 Florida children covered by NICA over the past 33 years, some of them now deceased, the program wasn't really a choice. It was a mandate, with a few exceptions. One exception is when OB-GYNs fail to pay a \$5,000 annual assessment. Nearly 1 in 4 licensed obstetricians statewide does not pay. Another is when a hospital doesn't pay its \$50-per-birth fee. Parents can also argue that they weren't properly notified by their hospital or doctor of their participation in NICA with enough lead time to choose

another provider. When parents like Lamendola attempt to invoke these exceptions, the fight can become fierce—and expensive.

### Stethoscope and Doppler May Outperform Newer Fetal Monitoring Tools

For intrapartum fetal surveillance, the old way may be the best way, according to a meta-analysis involving more than 118,000 patients. Intermittent auscultation with a Pinard stethoscope and handheld Doppler was associated with a significantly lower risk of emergency cesarean deliveries than newer monitoring techniques without jeopardizing maternal or neonatal outcomes, reported lead author Bassel

H. Al Wattar, MD, PhD, of University of Warwick, Coventry, England, and University College London Hospitals, and colleagues. "Over the last 50 years, several newer surveillance methods have been evaluated, with varied uptake in practice," the investigators wrote in the Canadian Medical Association Journal, noting that cardiotocography (CTG) is the most common method for high-risk pregnancies, typically coupled with at least one other modality, such as fetal scalp pH analysis (FBS), fetal pulse oximetry (FPO), or fetal heart

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electrocardiogram (STAN). “Despite extensive investment in clinical research, the overall effectiveness of such methods in improving maternal and neonatal outcomes remains debatable as stillbirth rates have plateaued worldwide, while cesarean delivery rates continue to rise,” the investigators wrote. Previous meta-analyses have relied upon head-to-head comparisons of monitoring techniques and did not take into account effects on maternal and neonatal outcomes. To address this knowledge gap, Dr Al Wattar and colleagues conducted the present systematic review and meta-analysis, ultimately including 33 trials with 118,863 women who underwent intrapartum fetal surveillance, dating back to 1976. Ten surveillance types were evaluated, including intermittent auscultation with Pinard stethoscope and handheld Doppler, CTG with or without computer-aided decision models (cCTG), and CTG or cCTG combined with one or two other techniques, such as FBS, FPO, and STAN. This revealed that intermittent auscultation outperformed all other techniques in terms of emergency cesarean deliveries and emergency cesarean deliveries because of fetal distress. Specifically, intermittent auscultation significantly reduced risk of emergency cesarean deliveries, compared with CTG (relative risk, 0.83; 95% confidence interval, 0.72-0.97), CTG-FBS (RR, 0.71; 95% CI, 0.63-0.80), CTG-lactate (RR, 0.77; 95% CI, 0.64-0.92), and FPO-CTG-FBS (RR, 0.81; 95% CI, 0.67-0.99). Conversely, compared with IA, STAN-CTG-FBS and cCTG-FBS raised risk of emergency cesarean deliveries by 17% and 21%, respectively. Compared with other modalities, the superiority of intermittent auscultation was even more pronounced in terms of emergency cesarean deliveries because of fetal distress. Intermittent auscultation reduced risk by 43%, compared with CTG, 66% compared with CTG-FBS, 58%, compared with FPO-CTG, and 17%, compared

with FPO-CTG-FBS. Conversely, compared with intermittent auscultation, STAN-CTG and cCTG-FBS increased risk of emergency cesarean deliveries because of fetal distress by 39% and 80%, respectively. Further analysis showed that all types of surveillance had similar effects on neonatal outcomes, such as admission to neonatal unit and neonatal acidemia. Although a combination of STAN or FPO with CTG-FBS “seemed to improve the likelihood of reducing adverse neonatal outcomes,” the investigators noted that these differences were not significant in network meta-analysis. “New fetal surveillance methods did not improve neonatal outcomes or reduce unnecessary maternal interventions,” Dr Al Wattar and colleagues concluded. “Further evidence is needed to evaluate the effects of fetal pulse oximetry and fetal heart electrocardiography in labor.”

### Latest Emollient Data Discouraging for Atopic Dermatitis Prevention

Emollients don't prevent atopic dermatitis (AD), but they might have untapped potential as treatment, two new studies suggest. The results of a prevention study, in which parents slathered their babies with petrolatum, are particularly discouraging. Earlier studies had led researchers to hope this approach could stop not only AD but perhaps other related allergic conditions. Instead, the babies who were in the petrolatum group in the Barrier Enhancement for Eczema Prevention Study (BEEP) were more likely to develop food allergies as well as skin infections than babies who received standard skin care. “So, the parents of newborn babies should not be advised to use emollients to prevent eczema developing,” said Joanne Chalmers, PhD, a senior research fellow at the Center of Evidence Based Dermatology, University of Nottingham, Nottingham, United



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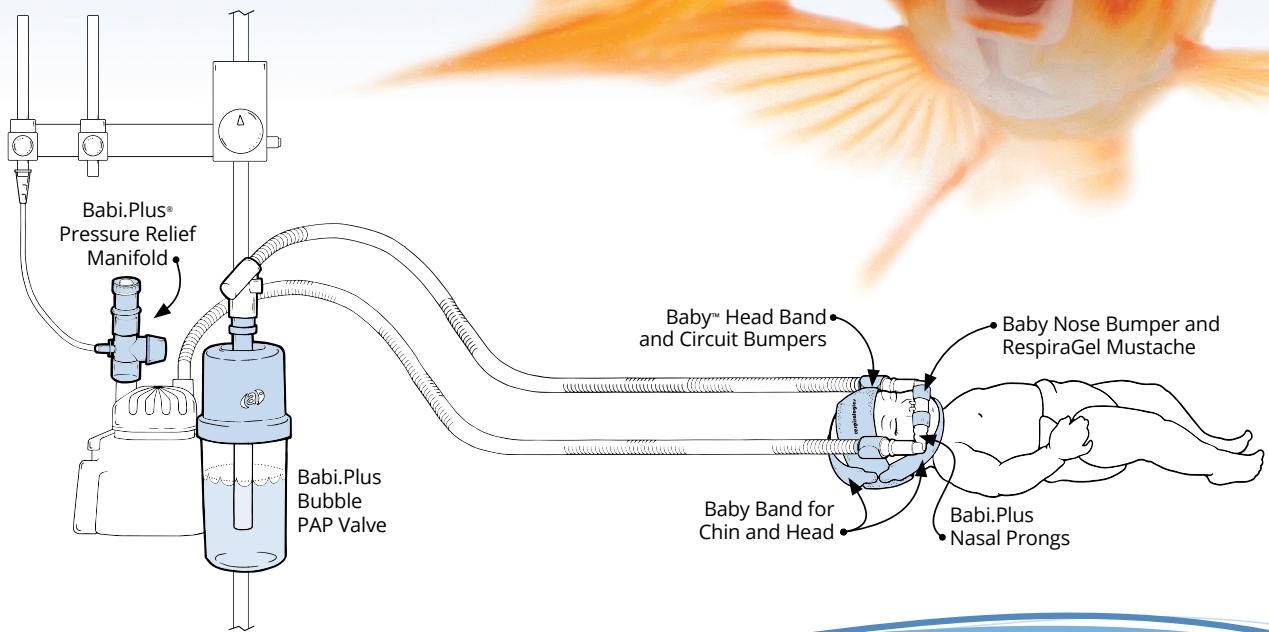




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Kingdom. In another study, an experimental nanofiber dressing impregnated with palmarosa oil significantly improved symptoms of the condition. Both studies were presented at the International Society of Atopic Dermatitis (ISAD) 2021 Annual Meeting. The BEEP results were also published in *The Lancet*. A “sizeable body of evidence” supports the use of emollients for the treatment of mild AD and flares, Chalmers said. Skin barrier dysfunction precedes the development of AD. Mutations in the filaggrin gene are associated with skin barrier dysfunction and the development of AD. There is no cure, and treatments are burdensome. On the basis of these data, Chalmers and her colleagues thought applying emollients to babies was worth a try. They approached families with newborn babies who were at high risk of developing AD because they had at least one first-degree relative with AD, allergic rhinitis, or asthma.

### **Neonatal Nurses, Doctor Help Woman Who Gave Birth to Baby on Plane**

Three neonatal intensive care nurses and a family physician were in the right place—on an airliner traveling to Hawaii—at the right time—when a woman unexpectedly delivered a baby prematurely on the flight. The medical professionals sprang into action to keep baby Raymond, who came into the world at 29 weeks, healthy until the flight got to Honolulu, according to a news release from Hawaii Pacific Health. Dale Glenn, MD, a family physician with Hawaii Pacific Health, said there was an emergency call for a doctor halfway through the Delta flight that left Salt Lake City for Honolulu on April 28. “I let the flight attendant know that I’m a physician and she said we have a woman having a baby, so I hurried over to see what I could do,” he said, according to the release. Three NICU nurses from North Kansas City Hospital—Lani Bamfield, Amanda Beeding, and Mimi Ho—answered the call. “I went to see what was going on and see her there holding a baby in her hands, and it’s little,” Bamfield said, according to the news release. The mom, Lavinia “Lavi” Mounga of Orem, Utah, said she was more than a little surprised. “I just didn’t know I was pregnant,” Mounga said in a video interview released from Hawaii Pacific Health, according to Q13 Fox of Seattle. “And this guy just came out of nowhere.” The nurses and the doctor improvised to keep Raymond safe for the rest of the flight. Glenn said they used shoelaces to cut and tie the umbilical cord, made baby warmers out of bottles that were microwavable, and measured the baby’s heart rate with an Apple Watch. “We didn’t have the usual tools found in a neonatal intensive care unit, so there were a lot of vital signs we couldn’t track,” Glenn said.

### **Breastfeeding Safe for Mothers With COVID-19 Infection**

Nursing mothers who receive a COVID-19 vaccine may pass protective antibodies to their babies through breast milk for at least 80 days following vaccination, suggests new research from Washington University School of Medicine in St Louis. “Our study showed a huge boost in antibodies against the COVID-19 virus in breast milk starting two weeks after the first shot, and this response was sustained for the course of our study, which was almost three months long,” said first author Jeannie Kelly, MD, assistant professor of obstetrics and gynecology. “The antibodies levels were still high at the end of our study, so the protection likely extends even longer.” Based on the small study, involving five mothers who provided frozen breast milk samples after receiving the two-dose Pfizer-BioNTech coronavirus vaccine, the research provides some of the first peer-reviewed evidence that breastfeeding confers a long-lasting immune response in the nursing infants and

toddlers of vaccinated mothers. “There is so much vaccine misinformation out there right now—really scary, misleading posts on social media that are designed to scare moms—so we felt like we needed to look at the science,” Kelly said. “We know that these types of antibodies coat babies mouths and throats and protect against disease when a baby is drinking breast milk. So, getting vaccinated while breastfeeding not only protects mom, but also could protect the baby, too, and for months.” Published March 30 in the *American Journal of Obstetrics and Gynecology*, the study tracked levels of COVID-19 antibodies in breast milk from a baseline before the mothers’ first vaccinations and on a weekly basis for 80 days after those initial vaccinations. While other recent research has shown that COVID-19 vaccines generate antibodies that are passed to nursing infants through breast milk, this is thought to be the first study to track specific levels of these antibodies in breast milk over an extended time period. The babies of women included in the study ranged in age from one month to 24 months old. To gauge immune response in the breast milk, researchers monitored levels of the immunoglobulins IgA and IgG, which are antibodies deployed by the immune system to fight infections in babies. Findings confirm that breast milk contains elevated levels of the IgA and IgG antibodies immediately following the first dose of vaccination, with both antibodies reaching immune-significant levels within 14 to 20 days of first vaccination in all participants. “Our study is limited by a small number of participants, but the findings provide encouraging news about the potential immune benefit to breast-feeding infants after vaccination,” said study senior author Misty Good, MD, an assistant professor of pediatrics, also at Washington University. “Our paper is the first that has shown COVID-19 antibodies persist in breast milk for months following the mother’s vaccination.” The Washington University findings are similar to prior studies on maternal vaccination, which have shown high levels of antibodies in breast milk for up to six months following vaccination for influenza and whooping cough. While further studies of maternal COVID-19 vaccination are needed to characterize the length of antibody production in breast milk and the effect on infant infection rates, recent research continues to confirm that the COVID-19 vaccine offers real benefits for protecting both mother and child. “We do know that COVID-19 infection is more severe during pregnancy and the main benefit of vaccination is to provide protection for moms before they become really sick, which can also be dangerous to their fetus,” Kelly said. “There have now been almost 70,000 pregnant people vaccinated against COVID 19 with no evidence of harm.” “We’re now seeing a cascade of new data that indicate maternal vaccines are also going to help protect babies—both through transfer of antibodies through the placenta during pregnancy and through the breast milk during lactation,” Kelly said. “This is information we didn’t have a few months ago and it’s really helping us better counsel our patients who are considering getting the vaccine. I’m telling my pregnant and breastfeeding moms that I strongly recommend that they get vaccinated as soon as possible.”

### **Ocular Abnormalities Not Likely in Newborns of SARS-CoV-2-infected Mothers**

Unlike pathogens such as Cytomegalovirus and Zika, SARS-CoV-2 is not likely to cause ocular problems in newborns whose mothers were infected with the virus during pregnancy, a new case series suggests. In an analysis of data from 165 infants born in Sao Paulo, Brazil, researchers found that just six newborns had positive PCR findings for SARS-CoV-2, and none of the six displayed ocular abnormalities, according to the report

published in JAMA Ophthalmology. “Vertical transmission is a serious complication of viral diseases occurring during pregnancy and often may lead to ocular manifestations,” said the study’s lead author, Dr Olivia Kiappe, a retina and vitreous fellow and researcher at the Federal University of Sao Paulo. “Cytomegalovirus and Zika virus are examples of viral infections that can have devastating consequences to the eye of the newborn,” she said in an email. “This study suggests that there is not a moderate or high increased risk of ocular abnormalities

in newborns of mothers with COVID-19,”

Dr Kiappe said. “Although more data are needed, vertical transmission of SARS-CoV-2 seems possible and should be a concern. Considering the noninvasive nature of the ophthalmological examination, ocular manifestations should be further investigated.”

To investigate the possibility that SARS-CoV-2 transmitted in utero by pregnant women could cause eye problems, Dr Kiappe and her colleagues enrolled 165 newborns whose mothers had been diagnosed with SARS-CoV-2 infections. The babies were born at three maternity hospitals in Sao Paulo between April and November of 2020. Of the 165 infants, 123 (74.5%) were

born full-term, while 42 (25.4%) were born preterm. Six of the newborns had positive PCR tests of oronasopharyngeal swab samples for SARS-CoV-2. One infant tested positive within 18 days, suggesting possible horizontal transmission, the authors note, while the other five tested positive on the first day of life, suggesting vertical transmission. None of these newborns had ocular abnormalities. Among the newborns who tested negative, one presented with venous engorgement and vascular tortuosity, while seven had intraretinal hemorrhages and two

were diagnosed as having retinopathy of prematurity. It will be important to do long-term follow-up on these babies because they were examined so early in life, said Dr Christopher Golden an associate professor of pediatrics at the Johns Hopkins University School of Medicine, in Baltimore. “The developing eye is at risk any time there is an infection involved, especially when the infection occurs when the mom is still pregnant,” Dr Golden said. “Infections can alter the way the nervous tissue in the eye develops.” As for the findings in children who tested

negative for the virus, “they could be the result of C-section delivery or just premature delivery,”

Dr Golden said. The new report is looking at “something that is really worth studying being that some of the systemic findings in COVID-19 are heavily involving vasculature and clotting and since the eye is one of the most heavily vascularized organs,” said Dr Erin Walsh, the co-director of pediatric ophthalmology and strabismus services at Mount Sinai in New York City. “There has been a study showing some issues in the retinas of adults with COVID-19. So, I definitely think it’s worth looking for.” One issue of with the current study is “a lack of any sort of real discussion on what normal birth patterns of the retina are,” Dr Walsh said.

Moreover, “there was no comment on other systemic issues such as cardiovascular health (that might have explained the findings in the infants who did not test positive for COVID-19).” After the experience with Zika, it makes sense to look for possible eye issues relating to COVID-19, Dr Walsh said. “With all the multisystemic inflammation that’s been occurring in kids, I would bet, down the road, when rigorous studies are done, researchers might actually find some subtle or not so subtle vascular findings in the retina.”



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## Extreme Premies With Neurodevelopmental Impairment at Age 2 May Improve by Age 10

More than one quarter of babies who were born extremely premature and display neurodevelopmental impairments at age 2 may improve significantly by age 10, according to a new study. An analysis of data from 802 children who were born extremely premature, revealed that 63% of 227 classified as having moderate to severe neurodevelopmental impairment (NDI) at age 2, had none to mild NDI at age 10. Among 108 children classified as having profound NDI at 2 years, 36% had none to mild NDI at 10 years, researchers report in *Pediatrics*. Overall, 67% of the children had no change in NDI classification between 2 and 10 years of age, 27% improved and 5% worsened, the authors note. “I hope these findings will allow parents and medical professionals to leave room for optimism when they hear a baby has been born extremely premature with profound neurodevelopmental impairments,” said Dr Genevieve Taylor, an assistant professor in the division of neonatal and perinatal medicine at the University of North Carolina, Chapel Hill. “It’s definitely a complex issue and there are limitations to our study, but it’s exciting that in this cohort we found even in those kids classified as having severe neurodevelopmental impairment at age 2, many went on to have improved classifications at 10.” The study underscores how plastic kids’ brains are at age 2, Dr Taylor said. “It demonstrates that kids at age 2 are still developing and that kids are resilient,” she added. “It also shows that there are some limitations of assessing neurodevelopmental impairment at age 2.” To take a closer look at how very premature children who start out with severe NDI develop over time, Dr Taylor and her colleagues turned to data from the Extremely Low Gestational Age Newborn (ELGAN) Study, a cohort of children born extremely premature at multiple sites in the US who had neurodevelopmental assessments at 2 and 10 years of age. The researchers hypothesized that NDI at age 2 would have limited predictive accuracy for NDI at age 10. Out of 1,506 infants, 80% survived. Data were sufficient for analysis in 67% of those children (802), of whom 5% were born at 23 weeks’ gestation, 15% at 24 weeks, 20% at 25 weeks, 25% at 26 weeks, and 35% at 27 weeks. When the children were 2, trained examiners administered the Bayley Scales of Infant Development Second Edition (BSID-II), performed a standardized neurologic examination, and assigned Gross Motor Function Classification System (GMFCS) scores. For children with an impairment that precluded BSID-II testing as well as those for whom more than two test items were omitted, the Vineland Adaptive Behavior Scales Motor Skills Domain was used instead of the BSID-II. At age 10, IQ was assessed with the Differential Ability Scales, Second Edition (DAS-II). The proportion of children classified as having profound NDI decreased from 13% at age 2 to 6% at age 10. The proportion classified as having moderate to severe NDI decreased from 28% to 17%. The proportion classified as having none to mild NDI increased from 58% to 77%. “Having a premie is very scary,” said Kimberly Blair, an associate professor of psychiatry at the University of Pittsburgh and senior academic director of the UPMC Matilda Theiss Early Childhood Behavioral Health Program.

## Pediatricians Call on Biden to Overturn Trump Neonatal Care Order

Pediatric bioethicists are calling for President Joe Biden to revoke a Trump Administration executive order that restricts physicians’ ability to withhold therapies from extremely premature newborns. The 2020 Executive Order on Protecting Vulnerable Newborn and Infant Children “reduces the complex

and nuanced discussion of the outcomes of prematurity to a single sentence and single outcome: mortality,” Dr Jennifer Kett writes in a new *Pediatrics* perspective. Even when physicians have no medical treatment to offer babies born before 24 weeks, the order could compel them to intervene in an effort to keep their hearts beating, said Kett, associate medical director for pediatric palliative care at Seattle Children’s Research Institute. “These are very difficult, nuanced decisions we make in consultation with families,” Kett told Reuters Health in a phone interview. “The worry is that physicians and medical teams may be less willing to consider or counsel families about other challenges of extremely pre-term birth besides survival.” Measures the order would require could extend a newborn’s painful life with no long-term hope, she said. “The order’s really focused on survival. There are other factors besides the risk of dying,” she said. The 2020 order is the most recent in a line of legislative actions dating back to the Baby Doe regulations, inspired by the prolife movement, of the 1980s, the perspective says. The Baby Doe regulations restricted the ability of families and physicians to consider quality of life in decision-making about infant care. In the decades since Baby Doe, improvements in neonatal treatments have led hospitals to offer interventions to younger and younger newborns. At the same time, clinical practice has increasingly incorporated parents into decisions about the best interests of their premature newborns, and hospital ethics committees have formed to respond to conflicts when they arise. The Trump Administration order risks undermining the progress, and it portrays the relationship between families and doctors as adversarial, the perspective says.

## Enrollment Completed in Clinical Trial Evaluating Effect of Exclusive Human Milk Diet

Prolacta Bioscience, the world’s leading hospital provider of 100% human milk-based nutritional products, announced today that enrollment is now complete in a clinical trial evaluating the effect of an exclusive human milk diet (EHMD), including a specialty fortifier, for term infants who have undergone a corrective procedure for single ventricle physiology (SVP), a life-threatening congenital heart defect (CHD). SVP refers to many types of CHDs that include specific anatomical conditions that result in the body having only one functioning heart ventricle. Because the body needs two healthy heart ventricles to pump blood around the body successfully, infants with SVP may have severe complications unless treated through a series of surgeries shortly after birth. “We’re hopeful that an EHMD, including a specialty fortifier, will demonstrate improved short- and long-term health outcomes for this population of fragile term infants,” said principal investigator Dr Cynthia Blanco, MD, of the University of Texas Health Science Center in San Antonio. “This study allows us to examine the role of human milk nutrition for this specific infant population who require a great deal of nutrients to catch up on growth, heal from multiple surgeries, and avoid further health complications.” Blanco approached Prolacta about developing a fortifier for infants requiring cardiac surgery. SVP is rare, with only approximately 1,500 infants a year born in the US with this condition. These infants face growth and feeding intolerance issues, which are further complicated by the infants being severely fluid restricted. To meet the specific nutritional needs of these fragile infants requiring surgery, a specialty fortifier was developed and evaluated for potential use in this specific patient population. “We were moved by Dr Blanco’s commitment to her patients and wanted to help her feed these fragile single ventricle physiology infants undergoing

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# NOXIVENT<sup>®</sup> Indication and Important Safety Information

## Indication

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## Important Safety Information

### Contraindications

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

### Warnings and Precautions

**Rebound:** Abrupt discontinuation of Noxivent may lead to worsening oxygenation and increasing pulmonary artery pressure.

**Methemoglobinemia:** Methemoglobin levels increase with the dose of Noxivent; it can take 8 hours or more before steady-state methemoglobin levels are attained. If methemoglobin levels do not resolve with decrease in dose or discontinuation of Noxivent, additional therapy may be warranted to treat methemoglobinemia.

**Airway Injury from Nitrogen Dioxide:** Monitor nitrogen dioxide (NO<sub>2</sub>) levels. Nitrogen dioxide may cause airway inflammation and damage to lung tissue.

**Heart Failure:** In patients with pre-existing left ventricular dysfunction, Noxivent may increase pulmonary capillary wedge pressure leading to pulmonary edema.

## Adverse Reactions

The most common adverse reaction of Noxivent is hypotension.

## Drug Interactions

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a corrective procedure,” said Scott Elster, CEO of Prolacta. “It is gratifying to have the opportunity to provide human milk nutrition to other infant populations in need—regardless of the relative size of that patient population.” The study, “A Randomized Controlled Trial to Evaluate Growth Velocity and Clinical Outcomes of Infants With Single Ventricle Physiology Fed an Exclusive Human Milk Diet With Early Nutritional Fortification Following Surgical Repair,” successfully enrolled 107 infants undergoing a corrective procedure for SVP. These infants were randomly assigned to receive either Prolacta’s human milk-based fortifier as part of an EHMD, or a cow milk-based fortifier as part of a human/cow milk diet (depending on hospital protocol). The trial was conducted at major medical centers in Texas, Ohio, Oklahoma, California, Illinois, New York, and Florida.

### **Evolve BioSystems, Inc. Announces the Use of Activated *B. infantis* EVC001 to Study the Prevention of Type 1 Diabetes in Children**

Evolve BioSystems, Inc. announced that its product, activated *B. infantis* EVC001, will be used in one of the largest international clinical studies on preventing type 1 diabetes (T1D) in genetically predisposed children. The randomized, controlled, double-blind, multicenter trial will be conducted across eight major research centers in five European countries. The Leona M. and Harry B. Helmsley Charitable Trust is funding the study and the continuation of the established newborn screening with more than \$30 million. The SINT1A study (*Supplementation with B. infantis for Mitigation of Type 1 Diabetes Autoimmunity*) aims to show that the daily administration of activated *B. infantis* EVC001 through the first year of life to children genetically predisposed to T1D will significantly reduce the development of beta-cell autoantibodies in the blood. Beta-cell autoantibodies are produced by the immune system as part of the process that destroys insulin-producing cells in the pancreas, thus leading to T1D onset early in life. “The prevalence of T1D has grown dramatically over the past 60 years, so the results of this study could have an enormous impact on public health if the increasing incidence of T1D, and its physical, emotional and financial consequences, could be turned back,” said Dr. David Kyle, Chief Scientific Officer, Evolve BioSystems, Inc. “We hope to show that a simple intervention of activated *B. infantis* EVC001 starting in infancy could be life-altering in reducing the prevalence of this autoimmune condition, which would have far-reaching economic and societal benefits.” T1D, also known as juvenile diabetes or autoimmune diabetes, can develop in the first years of life, and affects 1.6 million Americans today. It is a lifelong disease for which there is no cure, no means of prevention, and that requires multiple daily insulin injections to manage. Gut inflammation is often caused by an imbalance in the infant gut microbiota in the first few months of life as the result of a deficiency of the key gut bacteria, *Bifidobacterium infantis* (*B. infantis*). A substantial body of evidence has connected gut inflammation with improper immune programming and the subsequent development of autoimmune conditions including T1D, atopic dermatitis, food allergies and asthma. A randomized controlled trial in Finland, previously announced in March 2020 by Evolve and in collaboration with Janssen Research & Development, LLC, one of the Janssen Pharmaceutical Companies of Johnson & Johnson, is underway to assess the impact of activated *B. infantis* EVC001 on inhibiting the onset of atopic dermatitis in the first year of life. SINT1A is an investigator-initiated, randomized, placebo-controlled, double-

blind multi-center intervention study across eight trial sites. Research teams will operate under the direction of renowned T1D researcher Anette-G. Ziegler, Director of the Institute for Diabetes Research at Helmholtz Zentrum München and founding member of GPPAD. “There is a great deal of evidence pointing to the importance of having a healthy gut microbiome in early childhood for preventing immune-mediated diseases like type 1 diabetes,” said Dr Ziegler. “By identifying children genetically predisposed to type 1 diabetes early in life and treating their gut imbalances, we could potentially protect them from developing this dangerous and costly disease.” The study, among the largest T1D studies to date, will screen approximately 300,000 newborn babies for high genetic predisposition for T1D. Researchers will enroll 1,144 participants. Within the first six weeks of life through to age 12 months, half of the study participants will receive the dietary intervention of *activated B. infantis* EVC001 and the other half will receive a placebo. The intervention phase will be followed by observational follow-up every six months up to a maximum age of 6.5 years to assess the presence in the blood of autoantibodies associated with T1D. The study plans to enroll its first patients in April 2021.

### **Maternal Caffeine Consumption May Reduce Neonatal Size**

For pregnant women, just half a cup of coffee a day may reduce neonatal birth size and body weight, according to a prospective study involving more than 2,500 women. That’s only 50 mg of a caffeine day, which falls below the upper threshold of 200 mg set by the American College of Obstetricians and Gynecologists, lead author Jessica Gleason, PhD, MPH, of the Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, Md, and colleagues reported. “Systematic reviews and meta-analyses have reported that maternal caffeine consumption, even in doses lower than 200 mg, is associated with a higher risk for low birth weight, small for gestational age (SGA), and fetal growth restriction, suggesting there may be no safe amount of caffeine during pregnancy,” the investigators wrote in JAMA Network Open. Findings to date have been inconsistent, with a 2014 meta-analysis reporting contrary or null results in four out of nine studies. Dr Gleason and colleagues suggested that such discrepancies may be caused by uncontrolled confounding factors in some of the studies, such as smoking, as well as the inadequacy of self-reporting, which fails to incorporate variations in caffeine content between beverages, or differences in rates of metabolism between individuals. “To our knowledge, no studies have examined the association between caffeine intake and neonatal anthropometric measures beyond weight, length, and head circumference, and few have analyzed plasma concentrations of caffeine and its metabolites or genetic variations in the rate of metabolism associated with neonatal size,” the investigators wrote. Dr Gleason and colleagues set out to address this knowledge gap with a prospective cohort study, including 2,055 non-smoking women with low risk of birth defects who presented at 12 centers between 2009 and 2013. Mean participant age was 28.3 years and mean body mass index was 23.6. Races and ethnicities were represented almost evenly even across four groups: Hispanic (28.2%), White (27.4%), Black (25.2%), and Asian/Pacific Islander (19.2%). Rate of caffeine metabolism was defined by the single-nucleotide variant rs762551 (CYP1A2\*1F), according to which, slightly more women had slow metabolism (52.7%) than fast metabolism (47.3%). Women were enrolled at 8-13 weeks’ gestational age, at which

*Continued on page 18...*



# Benefits of Using 100% Human Milk-based Fortifiers in the NICU

In this feature, Neonatal Intensive Care interviews clinicians and healthcare providers about the actual application of specific products and therapies. This interview is with Brandee Grenda, Clinical Nutrition Manager at Sinai Chicago, and Katrina Conine, System Vice President of Women and Children, Surgical and Ancillary Services for Sinai Chicago

## Neonatal Intensive Care: How is Sinai Chicago working to close the health and inequity gap for premature infants?

Sinai Chicago's neonatal intensive care unit (NICU) is working to close the health and inequity gap for premature infants by adopting Donors Breast Milk and Prolacta Bioscience's 100% human milk-based fortifiers as part of an Exclusive Human Milk Diet (EHMD) to deliver the high-quality neonatal nutrition to the communities it serves.

As Chicago's largest private safety net health system, we serve a high percentage of low-income, minority patients, many of whom may not otherwise have access to this standard of neonatal nutrition that their premature infants need to survive and develop. At Sinai, we're addressing this problem head-on by making an EHMD accessible to underserved families.

## Why has Sinai Chicago chosen to use Prolacta Bioscience's nutritional products in their neonatal intensive care unit (NICU)?

Sinai Chicago chose to use Prolacta Bioscience's 100% human milk-based fortifiers in our NICU because they are the only human milk fortifier. This product has clinically proven to reduce mortality, improve health and growth, and reduce complications such as NEC, BPD, ROP, sepsis in premature infants. Premature infants do not have a mature gastrointestinal track which can create obstacles if a formula is introduced too early. Although not always, some studies have shown cow milk-based fortifiers can trigger feeding intolerance and increase mortality in premature infants due to the risk of severe complications.

Offering Prolacta's fortifiers as part of an EHMD in our NICU is a monumental step forward for the premature babies born at Sinai each year. For these vulnerable babies, access to an EHMD may be the difference between life and death. Not only will this give them the best chance to survive prematurity, but also to go on to thrive as healthy infants, children, and adults.

## What are the benefits of EHMD with Prolacta's fortifiers? Why is this diet an improvement from cowmilk for these infants?

Premature infants require 20% to 40% more calories and protein than a full-term baby to make up for the growth they missed in

the third trimester. To provide this extra nutrition, NICUs add a fortifier to mother's own milk or donor breastmilk. Prolacta's fortifiers are made of 100% donor breast milk, which replace cow-milk fortifiers.

Studies have shown cow milk-based fortifiers can lead to the development of devastating, and potentially terminal complications in premature infants, including necrotizing enterocolitis (NEC), a disease of the intestines.

Prolacta's products are 100% breast milk. The fortifiers are concentrated to include all protein or all fat which are vital components to the growth of a premature infant. Most importantly, adding Prolacta to a mother's or donor's breast milk ensures an EHMD. Breast milk is the gold standard for feeding infants and strongly recommended by the Academy of Pediatrics for the first six months of life, with continued breastfeeding with complementary foods for one year or longer. Breast milk provides fewer complications and improved health outcomes, giving babies the best possible chance in life.

## Can you please explain the significance of Illinois House Bill 3509 to Sinai Chicago and why this is a big development in terms of access to donor breast milk and donor breastmilk-based products?

Sinai Chicago's implementation of an EHMD is a result of Illinois House Bill 3509, which was passed and signed into law in 2020, which provides that pasteurized donated human breastmilk and breastmilk-based fortifiers shall be covered under health insurance and the medical assistance program under the Illinois Public Aid Code for premature and at-risk infants.

Sinai Chicago is the first system in Illinois to implement both an EHMD and these nutritional products since the legislation went into effect.

## What does it mean to you to be the first safety net hospital in Illinois to implement both an EHMD and Prolacta's products since the new legislation went into effect? Has this been a long time coming? How did the decision to change the standard of care come about?

As Chicago's largest private safety net health system, Sinai Chicago serves a high percentage of low-income, minority patients, many of whom are Black women who would not otherwise have access to this standard of neonatal nutrition that their premature infants need to survive and develop. We are dedicated to serving our community and providing for high

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Brandee Grenda, Clinical Nutrition Manager at Sinai Chicago. Katrina Conine, System Vice President of Women and Children, Surgical and Ancillary Services for Sinai Chicago.

quality care for our patients. This means we have to look at all aspects of health and nutrition from prematurity to geriatrics. We're addressing one potential issue of health and nutrition in prematurity head-on by making an EHMD accessible to underserved families.

### **Are there any outcomes/anecdotal evidence you can share about patients benefiting from EHMD?**

It is still too soon to report and evaluate this data. Our sample size is not yet large enough to provide a statistical analysis. Donor's breast milk with Prolacta products first came available to our unit November of 2020 as a result of several implementation needs ranging from coding to education to logistics. As we are moving forward with the program, we are collecting information as the products are offered.

### **Why are there so many racial and socioeconomic disparities and inequities when it comes to preterm birth? Aside from increasing access to an EHMD, what must be done to combat these disparities & inequalities?**

When it comes to preterm birth, there are several racial and socioeconomic disparities that need to be addressed. While 1 in 10 babies are born prematurely each year, the preterm birth rate for Black women is 50% higher than for all other women in the U.S., and prematurity is the leading cause of death among Black infants. Premature infants are at an increased risk for problems with the lungs, brain, eyes, and other organs, as well as long-term intellectual and developmental disabilities.

Offering Prolacta's products as part of an EHMD in our NICU is a monumental step forward for the premature babies born at Sinai Chicago each year. For these vulnerable babies, access to an EHMD may be the difference between life and death. Not only will this give them the best chance to survive prematurity, but also to go on to thrive as healthy infants, children, and adults.

### **Can you elaborate on Sinai Chicago's NICU services and how they are providing the highest level of care available to premature infants?**

The health disparities in the NICU are based on a variety of factors, including race, ethnicity, and income level, among others, and we are committed to ensuring that all premature infants have access to the high-quality care.

Sinai Chicago offers high-quality OB/GYN services—including Level III neonatal intensive care and maternity care recognized by the Illinois Perinatal Collaborative for Excellence as well as Blue Cross Blue Shield's "Blue Distinction" awards—at its north campus located at Mount Sinai Hospital. Its Level III NICU provides the comprehensive care for newborns just steps from the delivery room.

### **Is there anything else you would like to add or comment on?**

The communities we serve at Sinai Chicago face some of the country's most severe systemic barriers and suffer the greatest health disparities. By adopting Prolacta Bioscience's nutritional products as part of an EHMD, we're providing access to a standard of neonatal nutrition that premature infants in this community would not otherwise have. I'm so proud to be part of this momentous time at Sinai Chicago as we address this problem head-on by making an EHMD accessible to underserved families.

*News...continued from page 16*

time they underwent interviews and blood draws, allowing for measurement of caffeine and paraxanthine plasma levels, as well as self-reported caffeine consumption during the preceding week. Over the course of six visits, fetal growth was observed via ultrasound. Medical records were used to determine birth weights and neonatal anthropometric measures, including fat and skin fold mass, body length, and circumferences of the thigh, arm, abdomen, and head. Neonatal measurements were compared with plasma levels of caffeine and paraxanthine, both continuously and as quartiles (Q1,  $\leq 28.3$  ng/mL; Q2, 28.4-157.1 ng/mL; Q3, 157.2-658.8 ng/mL; Q4,  $> 658.8$  ng/mL). Comparisons were also made with self-reported caffeine intake. Women who reported drinking 1-50 mg of caffeine per day had neonates with smaller subscapular skin folds (beta =  $-0.14$  mm; 95% confidence interval,  $-0.27$  to  $-0.01$  mm), while those who reported more than 50 mg per day had newborns with lower birth weight (beta =  $-66$  g; 95% CI,  $-121$  to  $-10$  g), and smaller circumferences of mid-upper thigh (beta =  $-0.32$  cm; 95% CI,  $-0.55$  to  $-0.09$  cm), anterior thigh skin fold (beta =  $-0.24$  mm; 95% CI,  $-0.47$  to  $-0.01$  mm), and mid-upper arm (beta =  $-0.17$  cm; 95% CI,  $-0.31$  to  $-0.02$  cm). Caffeine plasma concentrations supported these findings. Compared with women who had caffeine plasma concentrations in the lowest quartile, those in the highest quartile gave birth to neonates with shorter length (beta =  $-0.44$  cm;  $P = .04$  for trend) and lower body weight (beta =  $-84.3$  g;  $P = .04$  for trend), as well as smaller mid-upper arm circumference (beta =  $-0.25$  cm;  $P = .02$  for trend), mid-upper thigh circumference (beta =  $-0.29$  cm;  $P = .07$  for trend), and head circumference (beta =  $-0.28$  cm;  $P < .001$  for trend). A comparison of lower and upper paraxanthine quartiles revealed the similar trends, as did analyses of continuous measures. "Our results suggest that caffeine consumption during pregnancy, even at levels much lower than the recommended 200 mg per day of caffeine may be associated with decreased fetal growth," the investigators concluded.

### **Maternal COVID-19 Vaccination Protects Fetus, Infants, Study Shows**

Researchers at Massachusetts General Hospital (MGH), Brigham and Women's Hospital and the Ragon Institute of MGH, MIT and Harvard have found the new mRNA COVID-19 vaccines to be highly effective in producing antibodies against the SARS-CoV-2 virus in pregnant and lactating women. The study also demonstrated the vaccines confer protective immunity to newborns through breast milk and the placenta. The study, published in the American Journal of Obstetrics and Gynecology (AJOG), looked at 131 women of reproductive age (84 pregnant, 31 lactating and 16 non-pregnant), all of whom received one of the two new mRNA vaccines: Pfizer/BioNTech or Moderna. The vaccine-induced titers—or antibody levels—were equivalent in all three groups. Reassuringly, side effects after vaccination were rare and comparable across the study participants. "This news of excellent vaccine efficacy is very encouraging for pregnant and breastfeeding women, who were left out of the initial COVID-19 vaccine trials," said Andrea Edlow, a maternal-fetal medicine specialist at MGH, director of the Edlow Lab in the Vincent Center for Reproductive Biology and co-senior author of the new study. "Filling in the information gaps with real data is key—especially for our pregnant patients who are at greater risk for complications from COVID-19. This study also highlights how eager pregnant and lactating individuals are to participate in research." According to the Centers for Disease Control and Prevention, individuals who are pregnant are more likely

*Continued on page 30...*

# Surprising Case of a Rare Congenital Diaphragmatic Hernia with Successful Outcome

Syeda Zabreen Afzal, MD, Shabih Manzar, MD, Nitin Walyat, MD, and Emily Adams, MD

## Summary

We describe a case of congenital diaphragmatic hernia (CDH) that was incidentally discovered in a newborn who presented with signs of respiratory distress. During surgery, the defect was identified and hernia was reduced. The interesting observation was the presence of a sac containing the hernial content. The pathology of the sac revealed fibrofatty connective tissue with mesothelial epithelium. There is limited extensive medical literature on the association between CDH and the presence of a sac.

## Introduction

The clinical presentation of congenital diaphragmatic hernia (CDH) is described as varying degree of respiratory distress after delivery of a term neonate. The difference in severity of the symptoms depends on different factors including the severity of the defect, the location of the defect and the degree of pulmonary hypoplasia. Often, this anomaly is diagnosed in utero via fetal anatomic ultrasound but can be missed. We present a successful case of a CDH in a term infant who had normal fetal ultrasound and was diagnosed via physical exam and chest x-ray.

## Case Report

The patient is a female neonate born at 39 weeks via spontaneous vaginal delivery to a 27 year old G5P4014 mother with a past medical history of preeclampsia without severe features and serofast RPR. All other prenatal labs were unremarkable. The delivery was uneventful and Apgar scores were 8 & 9 at 1 and 5 minutes, respectively. The infant was taken to the newborn nursery for transitioning where she developed increased respiratory effort after her bath. Her physical exam demonstrated mild subcostal retractions with a respiratory rate of 65-70. The oxygen saturation ranged between 88-90%. Bowel sounds were present in the left lung field. Heart rate and rhythm were regular with grade 1/6 systolic murmur at the right > left upper sternal border with point of maximal intense displaced to the right. The patient was transferred to the neonatal intensive care unit (NICU).

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In the NICU, she was placed on high flow nasal cannula 2LPM which improved her oxygen saturation to 95%. A CXR was obtained which demonstrated a left diaphragmatic hernia and enlarged cardiac silhouette (Figure 1). Patient was immediately made NPO, placed on intermittent wall suction, intubated and placed on a ventilator. A umbilical vein and artery catheter was placed. The patient's respiratory status started to decline requiring high flow oscillation ventilation and nitric oxide. (Table 1) An echocardiogram demonstrated a tiny muscular VSD, bidirectional flow through the PDA and a PFO vs ASD, compatible with persistent pulmonary hypertension. Her blood pressure also declined and she required inotropes for blood pressure stabilization (dopamine, hydrocortisone and milrinone) to maintain a normal BP. Pediatric surgery was consulted.

The patient underwent bedside surgery and upon entry into the abdominal cavity a large defect was appreciated in the left diaphragm. This was found to be a large diaphragmatic hernia sac containing abdominal contents which were reduced back into the abdominal cavity. The sac was excised using electrocautery and sent to pathology for evaluation which revealed fibrofatty connective tissue with mesothelial epithelium (Figure 2 & 3). Using the remaining diaphragm tissue along with portions of the hernia sac, the defect was closed primarily with several 3-0 prolene sutures and pledgets. The surgery was successful and over the next week the patient was weaned off inotropes and eventually respiratory support. Recovery complications include withdrawal symptoms from prolonged fentanyl use and the patient was treated with morphine. A chromosomal microarray was performed which was normal. No clinically relevant copy number changes or regions with absence of heterozygosity were observed.

## Discussion

In neonates, the clinical presentation of congenital diaphragmatic hernia (CDH) varies in the degree of respiratory distress. The difference in severity of the symptoms depends on different factors including the severity of the defect, the location of the defect and the degree of pulmonary hypoplasia. Often, this anomaly is diagnosed in utero via fetal anatomic ultrasound but can be missed. A study done in European countries demonstrated a sensitivity of 59% for prenatal ultrasounds in regards to diagnosing CDH. This leaves a large percentage of CDH undiagnosed. Additionally, the mean gestational age of diagnosis was 24 weeks and the likelihood of diagnosis is increased with an associated malformation.<sup>1</sup>

	1	2	3	4	5	6	7*	8	9
Time and date	2/4/20 1333	2/5/20 0432	2/5/20 1034	2/5/20 1347	2/6/20 1212	2/6/20 1311	2/6/20 <b>1442</b>	2/6/20 2105	2/7/20 0954
Hg		16.1	15.9	16.4	15.1	15.1	<b>15.1</b>	15.9	15.1
PH	7.274	7.273	7.252	6.952	7.167	7.131	<b>7.329</b>	7.37	7.427
CO2	52.8	44.2	57.2	122	66.3	78.0	<b>44.6</b>	45.7	45.2
O2	36.6	387	353	77.7	288	158	<b>345</b>	353	374
MethHb				2.0	3.5	3.5	<b>3.3</b>		
Lactate			1.4	0.8	1.0				1.6

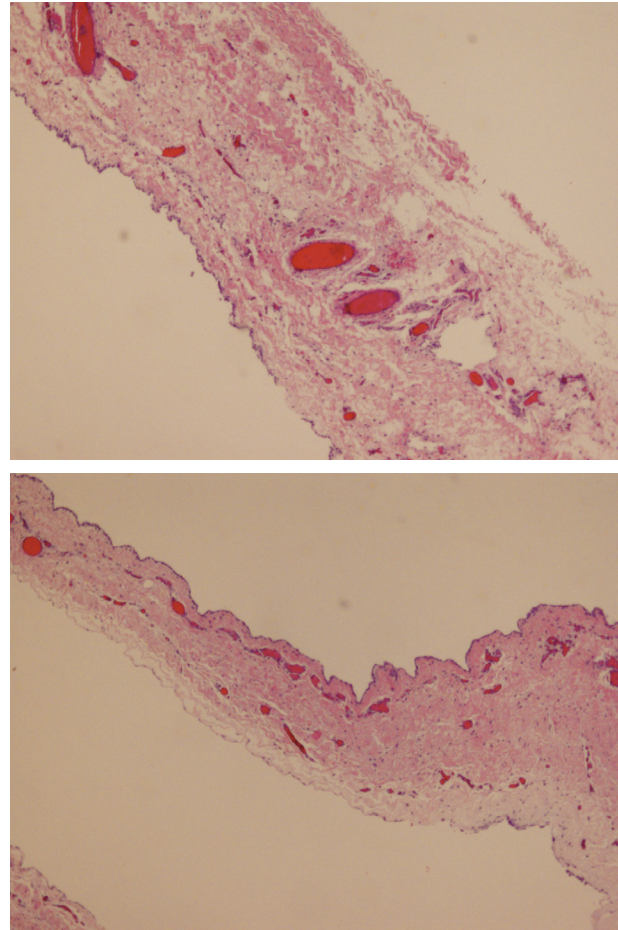
**Table 1.** Initial arterial blood gas values pre and post-surgery.

\*= values after surgical intervention

Approximately 10-30% of CDH cases are associated with chromosomal defects such as trisomy 18, tetrasomy 12p or Fryns syndrome.<sup>2,3</sup> Other times, the defect is an isolated finding with or without other structural abnormalities. Most commonly, these include congenital heart defects, renal, brain and gastrointestinal abnormalities. An extensive literature review demonstrated that 11-15% of CDH without other recognizable genetic syndromes also had cardiovascular malformations.<sup>4</sup>

The prognosis of CDH depends on multiple factors (ex. Type of defect, location of defect, associated genetic abnormalities) with the survival rates approximating around 70%.<sup>5</sup> The diaphragm develops around the 4-8th week of gestation and this defect is thought to be due to failure of the pleuroperitoneal folds and septum transversum to fuse and close.<sup>6</sup> The two types of defects are Bochdalek and Morgani, which are classified by their location. A Bochdalek hernia is a defect of the posterior and lateral musculature with 85% occurring on the left side. As opposed to the second most common hernia, Morgnani, which is an anterior retrosternal or parasternal hernia.<sup>7</sup> Bochdalek hernias account for approximately 85% of cases and are due to an abnormal pleural-peritoneal fold development with 85% of these occur on the left side and 10% on the right.<sup>3</sup>

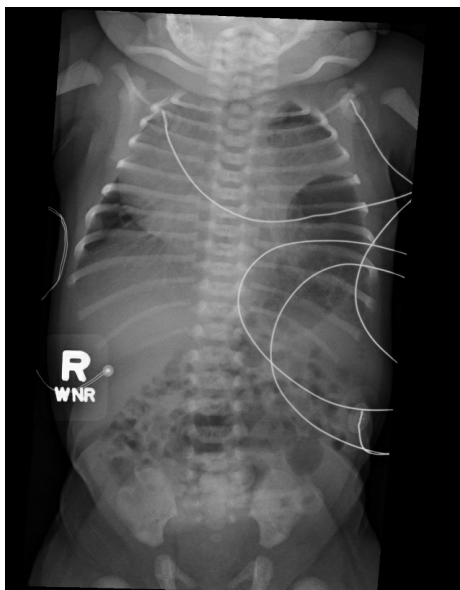
Interestingly, unilateral postero-lateral defects were associated with late presenting CDH cases.<sup>8</sup> These cases present with acute symptoms and do not have associated anomalies. Some cases



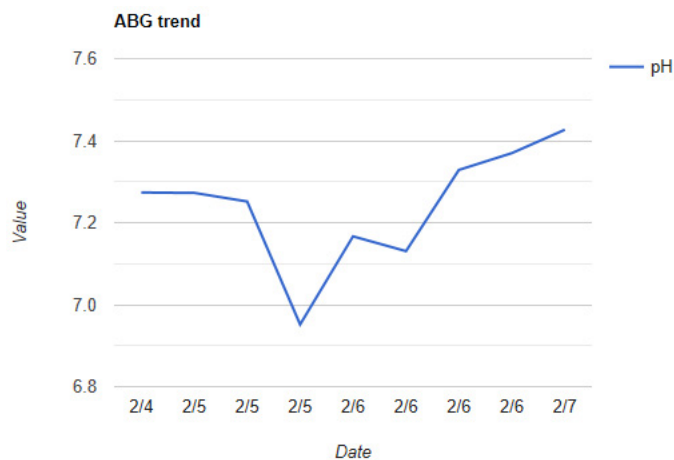
**Images 2 & 3.** Fibrofatty connective tissue with mesothelial epithelium, consistent with a hernia sac

may even have acquired the defect secondary to GBS pneumonia causes diaphragmatic necrosis.<sup>9</sup>

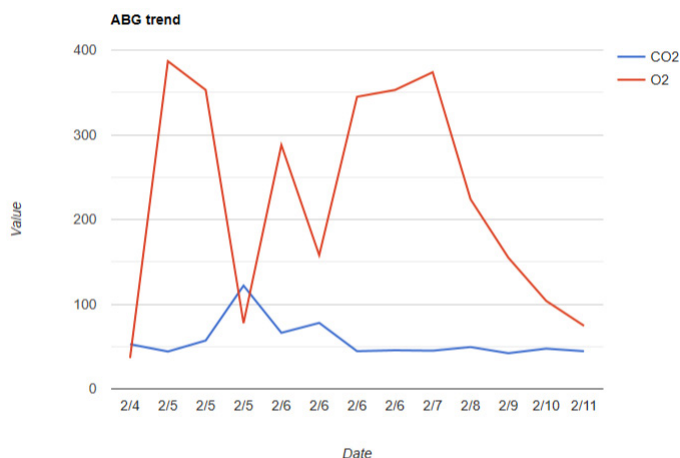
Like other hernias, these defects can be associated with a hernia sac. The embryo-genetic basis of the hernia is presumed to be abnormal connective tissue. In the patient discussed, pathological examination revealed fibro fatty connective tissue, similar to what is normally seen in hernia sacs. The presence of a sac ultimately yields a better prognostic outcome. The survival of infants at 6 months was greater for isolated CDH with a hernia sac was studied to be 100% versus 60%.<sup>10</sup> A study between 2004 and 2011, of 148 neonates treated for CDH only 20% had a hernia sac. These neonates had significantly lower requirements for ECMO, shorter duration of mechanical ventilation and hospital stay.<sup>11</sup>



**Image 1.** CXR- Congenital left-sided diaphragmatic hernia containing the stomach



Graph 1. pH trend



Graph 2. PO2 and PCO2 trends

The exact development of the hernia sac is relatively unknown and there is limited studies to determine the embryological cause. Given the improved prognosis with a hernia sac it is vital to understand the development of the hernia sac with CDH to help improve outcomes.

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# Rest and Readiness in Unit-based Specialty Care Perinatal Transport Team Clinicians: A Pilot Study

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## Abstract

**Background:** Unit-based specialty care perinatal transport team clinicians commonly perform bedside patient care in addition to out-of-hospital medical transport missions. No study has explicitly focused on how this amalgamation of responsibilities impacts rest and readiness. The purpose of this pilot study was to begin to explore how providing bedside patient care between out-of-hospital medical transport missions impacts sleepiness and fatigue in a group of unit-based specialty care perinatal transport team clinicians and compare these findings with a group of non-hospital-based medical transport team clinicians who do not provide bedside patient care.

**Methods:** A quasi-experimental pre-test and post-test design method and survey were employed for longitudinal data collection over a thirty consecutive day period. Sleepiness and fatigue data collected pre-and-post-shift from unit-based specialty care perinatal transport team clinicians who performed bedside patient care between out-of-hospital medical transport missions, and non-hospital-based medical transport team clinicians who did not provide bedside patient care between medical transport missions were summed per group, and statistical analyses were used to explore differences.

**Results:** Statistically significant increases in sleepiness and fatigue in unit-based specialty care perinatal transport team clinicians were found to be predominantly due to the provision of bedside patient care between out-of-hospital medical transport missions.

**Conclusions:** This exploratory pilot study suggests initial evidence that the provision of bedside patient care between out-of-hospital medical transport missions may negatively impact the rest and readiness of unit-based specialty care perinatal transport team clinicians. Further research is warranted.

**Keywords:** Neonatal Intensive Care, Perinatal, Medical Transport, Neonatal Transport, Maternal Transport, Rest And Readiness, Sleep, Fatigue, Patient Safety, Shiftwork.

**Acknowledgement:** We would like to formally acknowledge Travis County STAR Flight for their invaluable support of this research effort.

## Background

The term “rest and readiness” is a collective nomenclature pertaining to clinician mission preparedness that is commonly used in the medical transport profession. For the purposes of this study, the term “mission” was delineated as the departure from a principal workplace location (i.e., hospital, base, or station) to participate in job duties or tasks directly related to the role of a medical transport team clinician.

Rest and readiness is a notable concern among specialty care perinatal transport team (SCPT) clinicians and administrators. Sleep and fatigue are influential and relevant to mission preparedness, and the improvement of rest and readiness policies, procedures, and tools for this unique population of healthcare providers has merit.<sup>1</sup> Unit-based SCPTs are typically composed of various small cohorts of specialized clinicians, including a registered nurse (RN), registered respiratory therapist (RRT), paramedic (EMT-P), and occasionally a neonatal nurse practitioner (NNP) or physician (MD) under requisite context.<sup>2</sup> The primary responsibilities of unit-based SCPT clinicians includes providing bedside patient care and performing advanced clinical procedures to vulnerable patient populations, including critically ill premature infants and high-risk obstetrical patients in the neonatal intensive care unit (NICU) and associated maternal units. However, unit-based SCPT clinicians perform secondary, combined responsibilities regularly participating in interfacility and high-risk out-of-hospital (OOH) medical transport missions via rotary-wing (helicopter), fixed-wing (plane), and ground (ambulance) modes.

The combination of aforementioned job duties should generate legitimate concern regarding the rest and readiness of unit-based SCPT clinicians. Their primary responsibilities alone likely carry the propensity to provide deleterious impacts upon their rest and readiness. Unit-based SCPT clinicians frequently work consecutive, lengthy 12-hour shifts requiring highly detailed task performance and prolonged attention to detail while receiving very little recovery time, which is associated with sleep deprivation, an increase in fatigue, decreased performance,

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medical errors, reduced patient safety<sup>3-9</sup> and may subsequently lead to lower quality patient care.<sup>10,11</sup> Concern should escalate when considering that unit-based SCPT clinicians are regularly required to leave their primary responsibilities with little to no notice and participate in OOH medical transport missions. These missions often include the provision of direct patient care to high-risk critically ill patients under stressful conditions using specialized equipment in confined spaces, high altitudes, loud noises, vibrations, and unknown external weather conditions<sup>3,12</sup> which may increase the intensity and stress of the mission.

Despite this, to our knowledge no study has explicitly focused on understanding the impact that the combined responsibilities of unit-based bedside patient care and OOH medical transport has upon rest and readiness in SCPT clinicians. The purpose of this pilot study was to provide an initial exploration of how this relationship of providing bedside patient care and OOH medical transport missions impacts sleepiness and fatigue in a group of unit-based SCPT clinicians, and compare findings with a group of non-hospital-based air medical transport team (AMT) clinicians who do not provide combined responsibilities.

## Methods

This study was approved by all participating institutional review boards. All collected data remained anonymous.

Nonprobabilistic purposive sampling and a quasi-experimental pre-test and post-test design method were utilized to collect and compare data vis-à-vis clinicians from two groups of medical transport teams. Both medical transport teams operated utilizing comparable rest and readiness policies, procedures, and education and were selected for analogous purpose (medical transport), proximal geographic location, and shift length (12-hour). A unit-based SCPT and a non-hospital-based AMT served as the experimental and control groups, respectively. The unit-based SCPT primarily comprised of intensive care clinicians from a level four (IV) neonatal intensive care unit (NICU) and its accompanying maternal unit. Included were one certified neonatal intensive care registered nurse (RNC-NIC), one registered respiratory therapist credentialed as a neonatal and pediatric specialist (RRT-NPS), and one labor and delivery certified obstetric registered nurse (RNC-OB) when requisite. At no point during this study was a clinician from the unit-based SCPT consciously assigned a full patient workload assignment in their respective unit. Instead, they were designated for performing advanced bedside clinical procedures, attending high-risk deliveries, and were responsible for providing other direct patient care or unit needs when deemed necessary, which may have comprised contributions toward a portion of unit workload assignments. The non-hospital-based AMT comprised of one critical care flight paramedic (FP-C) and one critical care flight registered nurse (CFRN) who did not provide bedside patient care between medical transport missions. Aviation pilots and ground ambulance operators were excluded from participation in this study.

Two surveys (instruments) were compiled and employed for data collection with an emphasis on soundness, present time state, and rapid administration. One instrument was administered immediately pre-shift, and the other administered immediately post-shift to each clinician from each respective transport team for a total longitudinal data collection period of thirty (30) consecutive days. The two primary components of each instrument included the modified Karolinska Sleepiness Scale

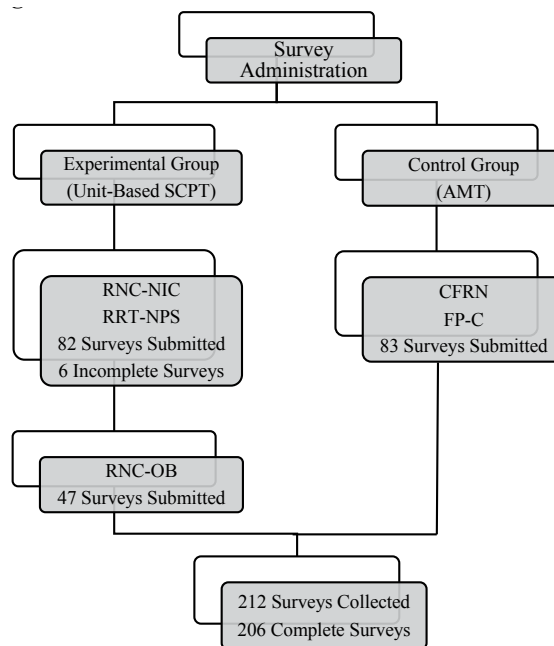


Figure 1. Overview of Data Collection Process

(KSS) and the Fatigue State Questionnaire (FSQ). The KSS is a succinct self-report questionnaire that measures sleepiness at any given time point and is scored using a 10-point scale in which a higher score is indicative of a greater level of sleepiness.<sup>13,14</sup> The FSQ is a brief self-report questionnaire that measures moment-to-moment changes in state-level fatigue, with possible scores ranging from 0 to 16 with a higher score indicative of a greater level of fatigue.<sup>15</sup>

The pre-shift instrument also collected general information regarding shift (day, night, swing), shift scheduling (scheduled, unscheduled, called-in/extra/overtime), hours of sleep obtained prior to current shift, number of consecutive shifts prior to the current shift, and if caffeine was consumed prior to the current shift. In addition to asking whether direct bedside patient care was performed between missions, the post-shift instrument included number of missions participated in, the average overall intensity of those missions (1 = low, 9 = high), whether rest or sleep was obtained between missions, whether the shift was held over (involuntarily extended due to a mission or job task), the average overall intensity of the shift (1 = low, 9 = high), as well as number of rotary-wing, fixed-wing, and ground missions participated in during the shift. The instruments remained identical for both medical transport teams at all times.

## Statistical Analysis

Collected data was categorized into respective experimental (SCPT) and control (AMT) groups, summed and conveyed to IBM SPSS Version 25<sup>16</sup> for statistical analyses. More specifically, descriptive and correlational statistics were used to explore group differences. The provision of bedside patient care between missions served as the independent variable. Sleepiness and fatigue served as the dependent variables. The initial multivariate analysis was a repeated-measures MANOVA used to measure the impact of providing bedside patient care between OOH medical transport missions on sleepiness and fatigue. Conditional on a significant finding, a series of repeated measure follow-up MANCOVA/ATIs that included potential intervening variables as covariates; more specifically the provision of bedside patient

care, shift, shift scheduling, hours of sleep prior to current shift, number of consecutive shifts, if caffeine was consumed prior to current shift, number of missions during shift, mission intensity, rest or sleep between missions, if shift was involuntarily held over, shift intensity, and the number of rotary-wing, fixed-wing, and ground missions during shift.

## Results

The instrument was administered to 212 collective participants. There was an exceptional response rate of 97%. Only six of the collected instruments were dismissed secondary to incompleteness, thus yielding data from 206 (n=206) complete pre-and-post shift instruments for inclusion in statistical analysis (see Figure 1).

Table 1 presents descriptive shift statistics pertaining to the experimental and control groups.

Correlational analysis, presented in Table 2, revealed that inclusion in the experimental group was positively associated with the provision of bedside patient care  $r=.932 p>.001$ , rest or sleep obtained between missions  $r=-.837 p>.001$ , shift intensity  $r=-.394 p<.001$ , number of ground missions  $r=-.376 p>.001$ , change in fatigue  $r=-.14 p=.044$ , post-shift fatigue  $r=-.177 p=.01$ , and post-shift sleepiness  $r=-.239 p=.001$ . Membership in the experimental group was negatively associated with the number of consecutive shifts  $r=-.327 p>.001$  and the number of rotary-wing missions  $r=-.381 p>.001$ . The provision of bedside patient care between transport missions had a positive correlation with obtaining rest or sleep between missions  $r=.796 p>.001$ , shift intensity  $r=.392 p>.001$ , the number of ground missions  $r=.376 p>.001$ , change in fatigue  $r=.164 p=.018$ , changes in sleepiness  $r=.137 p=.05$ , post-shift fatigue  $r=.177 p=.01$ , and post-shift sleepiness  $r=.239 p=.001$ . The provision of bedside patient care between missions displayed a negative relationship with the number of consecutive shifts worked  $r=-.327 p>.001$  and the number of rotary-wing missions  $r=-.36 p>.001$ . Other variables are listed in Table 2.

**Table 1.** Mean and Standard Deviations Regarding Shift Information.

Variables	Experimental Group		Control Group	
	Mean	SD	Mean	SD
Beside patient care	.94	.02	.00	0
Hours slept before shift	5.63	1.72	5.74	2.41
Number of consecutive shifts	.67	.93	1.46	.14
Fatigue pre-shift	4.38	.22	4.23	.36
Sleepiness pre-shift	4.11	1.85	3.68	1.97
Fatigue post-shift	6.47	2.86	5.29	3.71
Sleepiness post-shift	4.2	2.25	5.17	1.73
Fatigue change post-shift	2.09	3.53	1.06	3.94
Sleepiness change post-shift	1.07	2.29	.52	.29
Number of missions during shift	.52	.68	.72	.11
Mission intensity	1.72	.2	1.99	2.7
Rest/sleep obtained between missions	1.96	.02	1.13	.04
Held over (involuntarily extended)	1.85	.35	1.88	.04
Shift intensity	4.32	2.19	2.44	.21
Number of rotary-wing missions	.15	.03	.72	.98
Number of fixed-wing missions	.01	.09	0	0
Number of ground missions	.39	.6	0	0

Note: Values reflect summation per group over data collection period.

The multivariate repeated-measures MANOVA revealed a significant between-group difference across time, Wilks' Lambda  $F(2, 205)=6.08 p=.003$  with a small effect size  $\eta^2=.056$  and within-group change across time Wilks' Lambda  $F(2, 205)=18.41 p<.001$  with a medium effect size  $\eta^2=.15$ . The Univariate analysis suggest that both groups displayed a significant change in fatigue  $f(1,206)=36.98 p<.001 \eta^2=.15$  (medium) and sleepiness  $f(1,206)=21.1 p<.001 \eta^2=.9$ (medium). The Univariate Analysis also revealed a significant interaction between location and fatigue  $(1,206)=4.09 p=.04 \eta^2=.02$  (small). The experimental group was significantly more fatigued  $F(1,206)=3.75 p=.05 \eta^2=.02$  (Small) and sleepy  $F(1,206)=11.06 p=.001 \eta^2=.05$  (Small).

The multivariate analysis was replicated with the inclusion of providing bedside patient care between missions as a covariate. When the provision of bedside patient care was added as a covariate, the analysis did not reveal a significant between-groups difference  $F(2,201)=2.25 p=.108$  or within-group differences across time  $F(2,201)=2.38 p=.095$ . Univariate analysis suggests that while participants tended to show more fatigue  $F(1, 202)=4.58 p=.033 \eta^2=.02$  (Small), the impact of time on sleep was just short of significant  $F(1, 202)=3.56 p=.06$ . Moreover, there was no significant interaction for time and group on fatigue  $F(1, 202)=4 p=.528$  or sleepiness  $F(1, 202)=.485, p=.487$ . The statistical significance changes suggest that the changes in fatigue and sleepiness found in the initial study were mostly due to differences in the provision of bedside patient care between medical transport missions.

When rest or sleep between medical transport missions was included as a covariate, the multivariate analysis yielded results similar to the provision of bedside patient care between missions. Specifically, there was not a significant between-group difference  $F(1,201)=2.586 p=.078$ , within-group differences  $F(1,201)=.139 p=.87$ , or interaction between the provision of bedside patient care between missions and time  $F(1,201)=.322 p=.011$ . Univariate analysis did not show any significant changes over time in sleepiness  $F(1,201)=.016 p=.898$ , fatigue  $F(1,201)=.191 p=.662$ , or interactions between obtaining rest or sleep between missions, time, and sleepiness  $F(1,201)=.86 p=.355$  or fatigue  $F(1,201)=2.218 p=.011$ . These results suggest that sleep between missions is an intervening variable.

Several follow-up repeated measures MANCOVA analyses were conducted to explore the link between other variables on between-group differences. These variables included hours of sleep before the shift, working consecutive shifts, use of caffeine prior to shift, number of missions during shift, mission intensity, held over shift, shift intensity, number of rotary-wing missions, number of fixed-wing missions, and number of ground missions. While many of them were associated with group differences, changes in sleep and fatigue (see table 2), none of these follow up analyses were associated with a loss of statistical significance between (F scores range from 5.831  $p=.003$  to 7.48  $p=.002$ ) and within-group differences (F scores range from 4.388  $p=.014$  to 18.483  $p=.003$ ).

## Discussion

Results from this exploratory pilot study generate several interesting points of discussion in an effort to better understand the role of rest and readiness as it pertains not only to transport medicine in general, but also to the unique responsibilities and demands placed on unit-based SCPT clinicians. Initial evidence suggests providing bedside patient care between OOH medical



**Table 2.** Correlation Table for Factors Associated with Experimental and Control Groups.

	G	BC	HS	#S	Cf	#M	MI	SB	HO	SI	#R	#F	#G	FC	SC	PF	PS
G	1																
BC	.93**	1															
HS	.04	.01	1														
#S	.32**	.33**	-.01	1													
Cf	-.01	.03	.05	-.17	1												
#M	.11	.11	-.07	.01	.01	1											
MI	.06	.06	-.06	.01	-.01	.8**	1										
SB	.84**	.77**	.06	.26**	-.01	-.01	.03	1									
HO	-.03	.02	.12	-.06	.17**	.28**	.25**	.04	1								
SI	-.39**	.39**	-.02	-.09	-.05	.36**	.49**	.4**	-.31**	1							
#R	.38**	-.36**	-.08	.08	.02	.8**	.62**	.22**	.22**	.21**	1						
#F	-.06	-.08	.01	.00	.09	.03	-.02	.05	.18**	-.05	-.04	1					
#G	-.38**	.35**	-.09	-.02	.46**	.41**	.32**	.32**	-.1	.28**	-.16*	-.03	1				
FC	-.15**	.16*	-.16*	.04	.21**	.20	.19**	.17*	.06	.27**	.19**	-.03	.07	1			
SC	-.11	.14*	-.17*	.1	-.13	.16*	.08	.13*	.07	.06	.17*	-.02	.02	.75**	1		
PF	.18**	.21*	-.29**	.03	-.16*	.15*	.19*	.2**	-.04	.36**	.14	-.04	.04	.7**	.47**	1	
PS	-.24**	-.24**	-.32**	.08	.1	.08	.09	.22**	.14*	.18**	.08	-.03	.01	.53**	.65**	.77**	1

Note: \*p < .05. \*\*p < =.01.

Abbreviations: G = Group, BC = Bedside Care, HS = Hours slept pre-shift, #S = Number of consecutive shifts worked, Cf = Caffeine pre-shift, #M = Number of missions during shift, MI = Mission intensity, SB = Sleep/rest between missions, HO = Held over shift, SI = Shift intensity, #R = Number of rotary-wing missions, #F = Number of fixed-wing missions, #G = Number of ground missions, FC = Fatigue change, SC = Sleepiness change, PF = Post-shift fatigue, PS = Post-shift sleepiness.

transport missions may negatively impact the rest and readiness of unit-based SCPT clinicians regarding sleepiness and fatigue measures. This does not necessarily provide implication that unit-based SCPT clinicians are less capable of performing their associated job responsibilities than other medical transport team clinicians. Moreover, it is arguable that unit-based SCPT clinicians may be more clinically adept due to their combined job responsibilities, regularly providing highly detailed specialized skills and performing advanced bedside clinical procedures and interventions requiring prolonged attention to detail to critically ill patients in their respective units between OOH medical transport missions.

Medical transport teams vary tremendously in terms of personnel structure, location, site, specialty, patient population, number of missions, and non-transport clinical responsibilities. It may be plausible that non-hospital-based or even stand-alone medical transport team clinicians who do not provide bedside patient care between transport missions have a greater amount of time allocated for recuperation between missions. In contrast, unit-based SCPT clinicians' specialized clinical skills and scope of practice where the team member performs advanced bedside clinical procedures and assessment of critically ill patients between OOH medical transport missions are often critically important to the function of their respective units, as well as to the maintenance of clinical competency. As the field of transport medicine works towards developing best practices, understanding the differences and identifying the unique demands placed on the various team structures will be important. Unit-based SCPTs specialized clinical skills and scope of practice are innate to their respective units, and this growing branch of perinatal medical transport team remains deficient in thorough investigation toward best practices.

It is reasonable that unit-based SCPT clinicians are at a constant high level of alertness for the vast majority of their shifts, which may interfere with a large-scale brain network known as the default mode network (DMN). The DMN activates in response to

the brain at rest and is associated with cognition.<sup>17-20</sup> Changes in DMN functional connectivity and activity have been associated with fatigue and sleep deprivation and their impact on attention and task performance.<sup>17,21</sup> Previous research findings suggest that DMN activity changes predict task performance decline after prolonged attention.<sup>22</sup> Given the overlap between rest, social processing, fatigue, sleep, and workplace performance, one possible reason for clinician fatigue in either group could be compassion fatigue resulting from acute-on-chronic over-activation of the DMN during shiftwork. This connection could explain why both sleep or rest between OOH medical transport missions and the provision of bedside patient care predicted group differences during the post-test. Indeed, previous researchers have suggested that interventions targeting the DMN may be beneficial in this occurrence.<sup>23</sup>

It is plausible that there is a lack of specific tools available to address the phenomena at hand within such a unique population of unit-based SCPT clinicians who perform combined job responsibilities. Despite operating under similar policies, procedures, and education, the unit-based SCPT clinicians presented as sleepier and more fatigued than the control group. Unit-based SCPT administrators may consider investigation toward the amendment and improvement of rest and readiness education included in their policies and procedures. The provision of on-shift recuperation time may also be a consideration moving forward. However, this may prove difficult to preserve such clinical adeptness while maintaining unit-based SCPT clinicians' specialized skill sets, unit productivity, and highly reliable safe patient care. There may be a future determination point regarding the equilibrium of the amount and type of bedside patient care and OOH medical transport missions, and administrators will likely need to consider this notion moving forward. Future studies may consider the inclusion of exploring the link between compassion fatigue and the DMN and as well as interventions associated with rest, improved DMN function, and mindfulness. At the very least, unit-based SCPT administrators should question acceptable

levels of sleepiness, fatigue, mission preparedness, clinician effectiveness, and whether or not the inclusion or construction of associated tools, policies, and procedures should be implemented as best practices in their respective medical transport teams.

An important limitation to note is that the data collection instrument used in this study was based upon self-report measures. Thus, it may carry an inherent possibility of comprising subjectivity among study participants. We also cannot rule out the possibility of a slower, or less busy transport or patient care workload in comparison to other points in time for either group. Findings can only be implied based upon the longitudinal time period in which data collection for this specific study occurred. Although both the experimental and control groups were selected for their comparable rest and readiness policies and procedures, analogous purpose, proximal geographic location, and shift length, subsequent studies may be advanced through the exploration and coordination of parallel unit-based medical transport teams comparing rest and readiness policies and procedures and may consider incorporating stand-alone and dedicated medical transport teams.

## Conclusions

Results of this exploratory pilot study suggest initial evidence that the provision of bedside patient care between OOH medical transport missions may negatively impact the rest and readiness of unit-based SCPT clinicians. We feel that this study provides an ethically responsive, positive initial insight toward phenomena of essential relevance. Results should spark a catalyst of attention and concern among unit-based SCPT clinicians and administrators regarding rest and readiness policies and procedures. Further research is warranted.

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# The Benefits of Inhaled Nitric Oxide in the Transport of Newborns

Chris Campbell

Imagine how difficult it is for a clinical team to treat a newborn with a rare medical condition like persistent pulmonary hypertension of the newborn (PPHN) in a hospital setting. Now imagine the logistical and safety challenges involved with PPHN during an interhospital transport. That transport just pushes the risks even higher for the infant and increases the challenges for the medical team. A new review, however, highlights transport-friendly equipment that has received new US FDA approval that can facilitate treatment during transport from the moment of departure to the moment of arrival.

The published review, authored by Natalie Mitchell, Robert E. Newmyer, Mary Cominek, Rupa Crite, Heloisa Georgiev and Charles V. Pollack, sums up an advisory board event held in October 2020 and hosted by VERO Biotech, the company that makes the GENOSYL DS device that received the FDA approval. This written summary reflects the key elements and learnings of the discussion that included respiratory therapists, flight nurses, and an air transport physician.

## Dealing with PPHN

PPHN is a condition that carries with it great risks, the authors write in their introduction. “The incidence of persistent pulmonary hypertension of the newborn (PPHN) in infants  $\geq 34$  weeks gestational age without congenital heart disease, is approximately 0.2% in the United States.<sup>1</sup> A high-risk diagnosis that carries a one-year mortality rate of 7-8% and is often associated with serious congenital anomalies of the respiratory tract (in which patients one-year mortality may exceed 30%),<sup>1</sup> PPHN requires intensive cardiopulmonary care. In severe cases or in those patients who fail to respond to supportive measures and specific treatment of associated lung disease, further interventions include the use of inhaled nitric oxide (iNO), a selective pulmonary vasodilator that reduces the ratio of pulmonary to systemic vascular resistance (PVR/SVR). With iNO, oxygenation improves as vessels are dilated in better-ventilated parts of the lung, and the need for extracorporeal membrane oxygenation (ECMO) to provide adequate tissue oxygenation is diminished.<sup>2-3</sup>”

## Transportation Challenges

The authors wrote about how certain hospitals need to transport infants because they don't have the capacity to handle the specialized, intensive care required by PPHN, saying that “30-40% of newborns with severe hypoxemia due to pulmonary

hypertension who show a suboptimal or nonsustained response to iNO<sup>4</sup> must be transported with advanced life support (ALS) capability and ongoing administration of iNO from one hospital to an ECMO-capable center. Abrupt discontinuation of iNO therapy before transport in patients who have not improved oxygenation and hemodynamics can be harmful because of acute deterioration with severe hypoxemia (‘rebound’ pulmonary hypertension). Therefore, the standard of care is to transport such patients while continuing iNO treatment. In fact, initiation of iNO therapy at the referring hospital is associated with decreased length of hospitalization in those infants not ultimately requiring ECMO.<sup>5</sup> While not part of the labeled indication for iNO, therapy may also be initiated prior to transport in the management of other illness accompanied by pulmonary hypertension, including bronchopulmonary dysplasia, meconium aspiration, pulmonary hemorrhage, pulmonary hypoplasia, tracheoesophageal fistula, transposition of the great vessels or other congenital heart defects, or sepsis with respiratory failure.<sup>4,7</sup>”

Standards for interhospital transport of patients on iNO are set out by the Association of Critical Care Transport<sup>6</sup> and include blending gas capability including supplemental oxygen and room air; proper administration device that integrates with the ventilator used in transport; sufficient iNO capacity for the maximum duration of transport, plus a 30-minute reserve; and temperature stabilization for the nitric oxide.

“These standards are in addition to special controls set forth by the FDA in a guidance document entitled ‘Pre-market Notification Submissions for Nitric Oxide Delivery Apparatus, Nitric Oxide Analyzer and Nitrogen Dioxide Analyzer,’” the authors write. “The apparatus must allow reliable maintenance of an approximately constant concentration of iNO during inspiration, regardless of variation in flow rates, as set typically in the range of 0 to 80 parts per million (ppm). It must include a pressure regulator and connectors with fittings which are specific for nitric oxide gas cylinders, and must be designed to limit the time that NO is mixed with oxygen, thus minimizing the production of NO<sub>2</sub> ... The Commission on Accreditation of Medical Transport Systems (CAMTS) standards require that teams providing interfacility transport have the capability to deliver out-of-hospital care at a specialty or subspecialty level (eg, comparable to that of a tertiary or quaternary such as an ICU, PICU, NICU, or tertiary perinatal center). This includes the capability to provide blended gases, specifically citing iNO.<sup>7</sup>”

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## Logistical Challenges

The authors cite several logistical challenges, including the higher costs associated with using multiple types of ventilators and nitric oxide delivery systems (NODS), from different manufacturers.

“This approach also creates more regular and intensive training requirements in order to keep staff credentialed on and comfortable with two or more NODS, including in the transport setting where working space is severely limited and when there are substantial differences regarding set-up and manual resuscitation process for different devices,” the authors write. “This scenario increases the likelihood for error to occur in the transport of a critically ill patient. On the contrary, the potential to improve the quality of care associated with continuity of equipment use across the entire care path for the delivery of iNO via any conventional or high frequency ventilator during neonatal transports would streamline and improve this process. In addition to that, training on multiple types of equipment for the current transport process necessitates that the team overcome important and frequently encountered logistical obstacles. With variable flow modes, for example, potentially wide fluctuations in flow require adjustment from breath to breath. Space restrictions occur in both ground and air transport vehicles, especially if additional support is needed for the patient, or if bagging is required. Bagging with currently used equipment requires a second NO tank with a specialized regulator. Use of other types of tank-based equipment requires reconfiguration of the transport apparatus; the patient must be bagged with an iNO blender, which must itself be mounted along with the delivery system monitor onto the transporter.”

The authors also detail issues involving the current transport systems that increase costs for hospitals, increase the training requirements for staff and increase the chances of errors during the transport of critically ill patients.

“Using multiple types of ventilators and NODS, from different manufacturers, results in an increase in costs to the hospital,” the authors write. “This approach also creates more regular and intensive training requirements in order to keep staff credentialed on and comfortable with two or more NODS, including in the transport setting where working space is severely limited and when there are substantial differences regarding set-up and manual resuscitation process for different devices. This scenario increases the likelihood for error to occur in the transport of a critically ill patient. On the contrary, the potential to improve the quality of care associated with continuity of equipment use across the entire care path for the delivery of iNO via any conventional or high frequency ventilator during neonatal transports would streamline and improve this process.”

The authors also detail more logistical “obstacles” of dealing with multiple types of equipment for the “current” transport process. These include having additional tanks or the need to remove tanks to accommodate the iNO tank; a lack of gas supplies in some transport modes to accommodate the vent or long distance transport; the heavier weight and how that impacts fuel consumption during warmer months; the need for back-up injector modules with tank-based systems which can impact the accuracy of gas delivery without it; and a pre-use check which requires purging, leading to more prep time prior to transport.

“With variable flow modes, for example, potentially wide fluctuations in flow require adjustment from breath to breath,” the authors write. “Space restrictions occur in both ground and air transport vehicles, especially if additional support is needed for the patient, or if bagging is required. Bagging with currently used equipment requires a second NO tank with a specialized regulator. Use of other types of tank-based equipment requires reconfiguration of the transport apparatus; the patient must be bagged with an iNO blender, which must itself be mounted along with the delivery system monitor onto the transporter. Both current systems require an additional tank to be added to the transporter configuration, or another tank must be removed for the iNO tank to be added. This can be an issue if ambulance or helicopter does not have onboard gas supplies for the ventilator and during long distance transports. In addition, weight is an issue for neonatal transports; the isolette itself weighs 300 lbs or more before the NODS is added. This total weight makes it more difficult, particularly during the summer months/warmer areas for the flight crew to ensure there is enough fuel for the transport, equipment, and personnel traveling with the patient. With some tank-based systems there is a need for a back-up injector module; accurate electronic gas delivery may not be available without it. Finally, a pre-use checkout which includes a purge procedure is required prior to transport with typical tank-based systems, requiring an additional 10 minutes prior to transport. A tankless system does not have these requirements and therefore can be much lighter in weight. Using other equipment off-label may require the addition of costly proprietary parts and pieces, and special training for respiratory therapist use on that improvised combination. A system approved by FDA and consistent with FAA regulations would be a valuable asset in transport on iNO.”

## Significance of FDA Approval of the GENOSYL Delivery System

The authors wrote about how clinicians for 30 years have used devices “off-label” that were not approved by the FDA.

But now arrives the GENOSYL DS, the first tankless NODS, supplying iNO from 16-ounce cassettes instead of two six-pound D-cylinder tanks.<sup>8</sup> The device was granted FDA approval on December 14, 2020.

“The approval reflects rigorous testing and a careful design process,” the authors write. “The VERO engineering team worked with key opinion leaders and transport experts in the field to design a transport mount that would reduce the overall system weight and footprint as much as possible. The mount was designed to contour to the console geometry with minimal size and weight increase. A strap is utilized to allow easy console removal and replacement for set up. Helical mounts connected to the base of the transport mount provide shock and vibration dampening to allow the console to dose without disruption.

Applicable standards for crash safety, EMI/EMC, shock, and vibration were tested to ensure that the GENOSYL DS and transport mount assembly can withstand the environments of ground, fixed-wing, and rotary-wing intrahospital transport.”

The authors wrote that having an “on-label” device is an important step. “First, the indication means that the FDA has evaluated the safety and efficacy of the product for that specific use and found it appropriate for use in patients who have specific treatment needs. It does not mean uses outside the

# The Only Tankless Nitric Oxide Delivery System and the Broadest Transport Indication in the Acute Care Setting

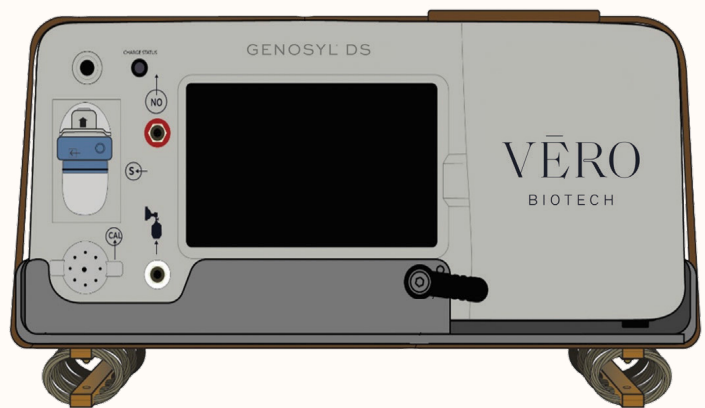
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for the administration of  
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Shock and Vibration



**INDICATION & IMPORTANT SAFETY INFORMATION:** GENOSYL<sup>®</sup> 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.

**GENOSYL is contraindicated in the treatment of neonates dependent on right-to-left shunting of blood.**

- Abrupt discontinuation of GENOSYL (nitric oxide) gas, for inhalation may lead to worsening oxygenation and increasing pulmonary artery pressure.
- Nitric oxide donor compounds may have an additive effect with GENOSYL on the risk of developing methemoglobinemia.
- Methemoglobin, NO<sub>2</sub>, and PaO<sub>2</sub> should be monitored during nitric oxide administration.
- GENOSYL must be administered using a calibrated GENOSYL Delivery System. Only validated ventilator systems or nasal cannulas should be used in conjunction with GENOSYL.
- In patients with pre-existing left ventricular dysfunction, GENOSYL may increase pulmonary capillary wedge pressure leading to pulmonary edema.
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approved labeling are not safe, it simply provides assurance that the overall approved use has been reviewed specifically by the FDA. Secondly, as alluded to above, it provides guidance and ‘guard rails’ within which that safety and efficacy are assured. This is particularly beneficial for the inexperienced or only occasional user, to have one process or one dosing regimen approved and explained. Third, it offers consistent information on any monitoring that should be applied when the patient is using the device or drug. Finally, a FDA labeled indication offers a potential pathway to reimbursement for use, so that uninsured, underinsured, and insured patients can all have access to the drug or device, and providers such as hospitals or transport companies do not have to absorb the cost of the therapy. FDA approval of the VERO transport NODS offers a streamlined approach to iNO use in acute care and in various transport settings. For those facilities that have adopted the GENOSYL system, advantages include no need for training on new devices, the reassurance and time-saving of using an approved configuration, and an improved focus on patient safety for these vulnerable neonates as they are transported to higher levels of care.”

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*News...continued from page 18*

to become severely ill with COVID-19, require hospitalization, intensive care or ventilation—and may be at increased risk for adverse pregnancy outcomes. The team also compared vaccination-induced antibody levels to those induced by natural infection with COVID-19 in pregnancy, and found significantly higher levels of antibodies from vaccination. Vaccine-generated antibodies were also present in all umbilical cord blood and breast milk samples taken from the study, showing the transfer of antibodies from mothers to newborns.

## Injured Purkinje Cells Implicated in Premies’ Locomotor Learning Deficits

Injury to Purkinje cells during fetal and early postnatal life is likely responsible for locomotor learning deficits in very premature infants, researchers say. “Using an animal model of neonatal brain injury that captures the major hallmarks of the injury seen in human newborns, our work uncovers how injury during this early period affects the function of neurons that control adaptive or anticipatory movement, namely the Purkinje cells,” Dr Aaron Sathyanesan of Children’s National Hospital in Washington, DC said. “The main technical advance in our paper is that we devised a method to monitor the activity of Purkinje cells in animals that were performing a locomotor learning task,” he said. “Since our animal model aims to mimic injury in human newborns, which is often a brain-wide injury, we wanted to know how specific the behavioral changes were to alterations in Purkinje cell function during the early neonatal period,” he explained. “We used a method to artificially silence Purkinje cell firing during the neonatal period in mice that were not exposed to the injury paradigm,” he continued. “The results were quite striking. Both the long-term behavioral measurement and the physiological responses of the Purkinje cells during learning were quite similar to what we observed in animals that were exposed to the injury paradigm.” “This indicates that Purkinje cell activity during the neonatal period is critical for normal behavior in the long-term,” he concluded. Specifically, the researchers measured neural circuit function in the mouse model by pairing GcaMP6f fiber photometry, which measures neuronal activity during movement, with an Erasmus Ladder, which tests motor learning and performance. They introduced obstacles to movement and observed how quickly the mice learned to avoid the obstacle, according to the study published in *Proceedings of the National Academy of Sciences of the USA*. A series of learning trials plus brain monitoring comparing brain-injured and normal animal models enabled the team to quantify cerebellum-dependent locomotor learning and adaptive behavior. Further, as Dr Sathyanesan noted, they found that Purkinje cell dysfunction in the brain-injured model specifically interfered with adapted learning, and that switching these cells off (chemogenetic inhibition) in normal models mimicked the effects of perinatal cerebellar injury. The authors state, “Our results uncover a direct link between perinatal cerebellar injury and activity-dependent maturation of cerebellar cortex.”

## Newborns Could Develop Fetal Inflammatory Syndrome From Mothers With COVID-19

Throughout the pandemic, doctors have found that pregnant women who contract COVID-19 may be able to pass the infection to their babies. In a new case study, doctors report that newborns could develop a fetal inflammatory response syndrome associated with the virus. In more than 95% of cases, if the mother gets infected, she does well and the baby does

*Continued on page 40...*

# Experiences From the Nursery: Supporting Moms and Babies During the COVID-19 Pandemic

Lori Wood, MSN, CNS, RNC-NIC, IBCLC

The Coronavirus pandemic and worldwide experience of COVID-19 infections, lockdowns, and social distancing prompted sudden and wide-swinging changes in birthing babies and breastfeeding support. The serious nature of this pandemic and unknown behavior of the Coronavirus led to hasty decisions meant to protect infants from illness. Many of the ideas that drove practice in the early weeks of the COVID-19 Pandemic were well intended, but fear based, leading to a reduction in face to face support for moms and babies. Moms and babies were separated at birth to prevent the transmission of COVID-19 disease to infants. With reduced maternal family support in hospitals, social distancing and separation from family once discharged home, breastfeeding and mother infant bonding were left at risk. The experiences of hospitals and maternal child staff were varied and changing with the release and sharing of knowledge. The struggle to protect both mother infant dyads and healthcare staff while providing positive encounters resulted in many stressful days stretched to home life for those trying to do their best. These experiences, coupled with evidence, are shared in this paper.

The early period of the pandemic left hospitals, community support, doctors, and lactation providers scrambling to decide what was best, and how to provide high quality professional guidance. Suggestions to separate baby from a positive or suspected positive mom was the initial move as the extent of transmission of infection to infants was unknown. This action was counter intuitive to those who support breastfeeding as it is well known that early skin to skin care, early breastfeeding, continued, in person help and support are vital components to initiation and continuation of breastfeeding.<sup>1</sup> Maternal positivity and the reduction of postpartum depression during the first months following birth is also dependent on supportive networks and continuing contact.<sup>2</sup>

The World Health Organization published a recommendation to keep mother infant pairs together following birth. The promotion of infection control measures such as good hand washing, wearing a mask, and continued breastfeeding for COVID positive mothers giving birth were part of this statement.<sup>3</sup> These recommendations were not initially followed, but over time, birthing centers and hospitals began to adopt this

practice. Early separations of mom and baby created stress for families trying to cope during already trying times. As a switch to a shared decision model between mothers and healthcare providers became standard, promotion of cares supporting breastfeeding once again became the expectation. Our hospital experienced these barriers, but due to heavy recommendations from pediatricians, a shared decision model between mom and the healthcare team was adopted. Positive conversations created an environment amenable to answering questions and creating a plan to meet individual goals.

## Reality Of Fear

One of the biggest obstacles to everyday nursing work and caring for patients and families was fear. Fear on behalf of families and fear on behalf of our staff. COVID-19 was a completely new and unknown virus. There was no comfort to be had in similarities to previous diseases, treatment, or outcomes. This unknown component of the SARS-CoV2 virus made every person medical or not fearful. Fearful of the probability of contracting the virus, fear of bringing it home to vulnerable family members, fear of what that would mean for their personal piece of the world.

Fear of fighting an unknown virus, fear of coming to work day after day, questioning practices, personal protective equipment (PPE), visitors and how safe each family member was once they left the Neonatal Intensive Care Unit (NICU); these were all negative factors working against our ability as a team to effectively care for our patients. It was a fear each individual had to deal with but something our leadership team had to tackle each and every day. Thankfully for our strong team, we banded together to take each question and need and work to create a COVID care guideline specific to our Maternal Child departments. This guideline then had to be updated sometimes weekly and sometimes within a few days to be current on recommendations and new information; a necessary job, but also stressful to the person tasked. Our COVID guideline update person became affectionately known as The COVID Queen.

Some days were spent tirelessly researching and developing protocols and guidelines for care. Algorithms for admitting a laboring mom, testing and isolating were created and updated as needed. Staff were continuously educated on practices to admit known or suspected positive moms and how to notify the NICU of a possible admission. We set up a negative pressure admitting area for moms and babies, specific warmers for the care of these babies. The ability to resuscitate and provide immediate post birth cares to infants in the room with the mom was

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maintained while following distancing recommendations at the beginning of this pandemic. We began bedside education, person to person, offering the opportunity to discuss the procedures, answer questions and receive feedback to continually improve our practice. Staff were eager to learn and participate, practice deliveries and walk through transports of potentially positive infants. Our educators and Clinical Nurse Specialist came in night and day to provide these opportunities.

Some days were spent answering questions and listening to fearful nurses, respiratory therapists, doctors, housekeepers and secretaries. People who are strong members of our team, yet felt vulnerable and overwhelmed at times. Sometimes the questions were regarding new recommendations from the Centers for Disease Control and Prevention (CDC), information on the spread of the disease, news clips seen, or the rising number of cases and deaths attributed to this virus. As the number of cases and deaths from Italy continued to pour in night after night at the beginning of this pandemic, staff and families would become more worried. Often the days of a leadership member would be spent consoling a crying staff person as they tried to talk and ask, but ended up by breaking down. The first few months of the pandemic of 2020 were trying and stressful indeed.

### Visitation

Visitation was another big issue during the early days and months of the pandemic. With constant information coming in regarding the spread of the virus and infection of people in contact, the constant coming and going of people in the hospital was of concern. Lockdown was initiated in other countries first battling the virus and our country was struggling from state to state to discern what was best. The question of who to allow in to visit was one that each state dealt with. New York was hard hit with COVID infections and deaths and adopted a no support person for laboring women. Laboring and birthing a baby in solitude, with no support, is definitely not what is natural or desired. A few people in our hospital suggested that perhaps we should follow suit to reduce the number of people in our unit and protect staff and other patients. Thanks to a very dedicated and strong nursing leader, and several supporting staff, we were able to stand by a one support person for each laboring mom and work to develop protocols for screening and safe visitation. Our visitation standards also allowed for the presence of a labor coach or doula.

In the NICU, we had to reduce visitation to the parents or mom and one other support person if father was not visiting. Our NICU is an open bay design with three rows and two negative pressure isolation rooms. The isolation rooms were designated for COVID-19 positive patients or persons under investigation (PUI) infants. Due to the setup of our unit, we were only able to accommodate one parent in the unit at a time to maintain distancing. Parents were very understanding and accommodating. With the reduced number of people in the hospital due to no visitation in the other areas, we were able to provide spaces for the remaining parent to wait while one parent was in the NICU.

### Donor Milk Concerns

Early in the pandemic, we knew nothing about the virus or its effect on mom and baby, either while pregnant or after delivery. There didn't appear to be any signs of vertical transmission, but because of concern and panic coupled with few facts, concern for our moms and babies was far reaching. In the first

weeks of the pandemic, a decision was made, late in the day, by our corporate office, to stop the use of donor milk due to apprehension that the virus could be transmitted through the milk.

A concerted effort had already been made at our hospital to contact our state's Human Milk Bank Association of North America (HMBANA) milk bank as well as another source of our acquired human milk to ensure that pasteurization processes were continuing as normal. Our hospital felt it was completely safe to continue to use donor milk and that it would be preferred to use donor and of course mom's expressed milk due to the numerous positive outcomes associated with an exclusively human milk diet. Hours were spent right there, on the spot, to draft a letter to our leadership extolling the benefits of breast milk and our reasons to consider continuation despite the pandemic. The very next day, the decision to stop was rescinded and we continued to use our pasteurized donor milk; an appreciated victory.

Our hospital had already created a policy and process for attaining and storing the milk of a mother suspected or confirmed of having coronavirus. This process included coming to the curb to retrieve milk if a mother was positive and couldn't come in the hospital. If the mother was in a negative pressure room sick with COVID, the pumped milk was passed out of the room, bottles cleaned, and the milk stored for use. Every priority was made to use mom's milk and value its use.

### Protective Qualities Of Mom's Own Milk

We also suspected that mom's pumped milk would be shown to have antibodies specific to this Coronavirus based on what is known about the enteromammary pathway and specific antibodies being made according to mom's exposure. Mother's milk is unique, and specific; colostrum and future milk is tailor made for her baby. It is well known that immunoglobulin A (IgA) is produced in the secretory cells of the mother's breast. When antigens are ingested by the mother and recognized in the intestine, lymphocytes are primed, migrate to the breast and IgA is secreted into milk.<sup>4</sup>

As early as April of 2020, information was shared regarding research on the presence of antibodies specific for the SARS-CoV2 virus found in the milk of mothers diagnosed with COVID-19. Dr Rebecca Powell reported on her ongoing study in March of 2021 that milk from lactating mothers who were previously infected with COVID-19 contains long-lasting COVID-19 antibodies capable of blocking virus infection. Nearly all women involved in Dr Powell's study are shown to produce an extremely potent IgA SARS-CoV2 antibody in their breast milk. This antibody is long lasting, demonstrating the ability to live in the infant's mouth and digestive tract and is detected 7-10 months post maternal infection. Further study is hoped to be able to demonstrate the ability to use these antibodies as a treatment for children or adults with severe COVID-19 disease.<sup>5</sup>

Another interesting line of study in reference to SARS-CoV2 antibodies in breast milk is their presence in milk after vaccination. Several studies are tying the vaccination and development of antibodies in mom's blood plasma to a growing number of antibodies in her breast milk. Pregnant and breastfeeding women were excluded from the original vaccination trials which negated this at risk population from an early inclusion in vaccination. Many mothers were left



wondering if they should forgo the vaccine to continue breast feeding or stop breastfeeding to participate in vaccination. This was a difficult decision for many given the serious nature of this pandemic coupled with the known benefits of breastfeeding.

A Registered Nurse in our NICU was in this exact situation. Working in a hospital, a newer baby at home and nursing, and a 4 year old, and a husband, this family was concerned about being exposed and bringing the virus home to the family. Wanting to continue breastfeeding the newborn was also a priority. The nurse, an International Board Certified Lactation Consultant (I.B.C.L.C.), and our Clinical Nurse Specialist/International Board Certified Lactation Consultant had a discussion and began to research and write to experts. Most of the responses were, as expected, in doubt of how to answer. The nurse wrote to the developer of the Pfizer vaccine in December 2020 to inquire about any new knowledge and was told that the half-life of the vaccine was 30 hours. With this information, our nurse was able to decide to pursue her vaccination. For the 30 hours following the vaccination, she decided to feed her newborn, milk she had previously pumped. She pumped and stored the “vaccinated” milk for the future. Pending further study, our nurse was considering giving the pumped “vaccinated milk” to her four year old to provide protection.

Studies are reporting the demonstrated existence of anti-SARS-CoV-2 antibodies in women who were never ill with COVID-19, but have been vaccinated. Both Pfizer-BioNTech® and Moderna® mRNA vaccines were studied. The efficacy of these antibodies against infant COVID-19 infection remains a focus of future study, but are thought to protect baby from infection. Currently, studies are showing antibodies in the breast milk of mRNA-vaccinated women developed after the first vaccination and increasing after the second. SARS-CoV-2 antibody numbers in the mom’s breast milk, correlate with developing titers in the blood serum of these breast fed infants.<sup>6,7</sup>

The presence of SARS-CoV-2 specific antibodies in breast milk is of no surprise to those who study and know the importance of the enteromammary pathway and the exquisite provision of immunity and protection between mother and baby. The decision of our nurse to pump her milk and save it for possible future use proved wise and informed.

While the stressors of the pandemic have been difficult on healthcare staff and moms and families, many valuable lessons can be gleaned by the astute. Science, evidence, and the passion of many committed to excellence hold the final say. Moms, babies, and families hold a special place in the heart of most, and because of this, our staff and researches have prevailed during this past trying year. We have learned as nurses, doctors, researchers, lactation consultants, therapists, social workers, secretaries, and environmental staff that our fears could be abated with understanding, science, careful attention to detail, and teamwork. The virus has been a dreaded opponent, but will not win. Continued attention to research and education, support, and love to our patients will provide the pathway to victory. #byecovid.

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For your patients with a rare and devastating genetic disorder<sup>1,2</sup>

# With MoCD Type A, waiting is not an option<sup>1,2</sup>

Introducing NULIBRY, an FDA-approved therapy for patients with MoCD Type A to reduce the risk of mortality.<sup>1</sup> MoCD Type A, the most common form of MoCD, is a rare and devastating inborn error of metabolism (IEM) that presents shortly after birth, progresses rapidly, causes irreparable damage, and often leads to an early death (median survival age is 4 years).<sup>1,2</sup>

NULIBRY is a cyclic pyranopterin monophosphate (cPMP), replacing a critical component the body needs to make molybdenum cofactor (MoCo). NULIBRY is administered as a daily intravenous (IV) infusion after reconstitution. Dosing is individualized based on the patient's actual weight. NULIBRY is a cold chain product and comes as a powder or cake in a single-dose, clear glass vial.<sup>1</sup>

**As soon as MoCD Type A is suspected, consider NULIBRY.<sup>1\*</sup>**

## INDICATION

NULIBRY is indicated to reduce the risk of mortality in patients with molybdenum cofactor deficiency (MoCD) Type A.

## IMPORTANT SAFETY INFORMATION

### WARNINGS AND PRECAUTIONS

#### Potential for Photosensitivity

NULIBRY can make the patient oversensitive to sunlight. NULIBRY-treated patients or their caregivers are advised to avoid or minimize patient exposure to sunlight and artificial UV light and adopt precautionary measures when exposed to the sun, including wearing protective clothing and sunglasses, and use broad-spectrum sunscreen with high SPF in patients 6 months of age and older. If photosensitivity occurs, caregivers/patients are advised to seek medical attention immediately and consider a dermatological evaluation.

### ADVERSE REACTIONS

The most common adverse reactions in NULIBRY-treated patients were infusion catheter-related complications (89%), pyrexia (fever) (78%), viral infection (56%), pneumonia (44%), otitis media (ear infection) (44%), vomiting (44%), and cough/sneezing (44%). Adverse reactions for rcPMP-treated patients were similar to the NULIBRY-treated patients.

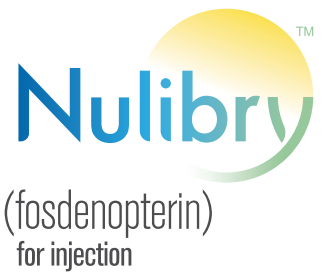
### PATIENT COUNSELING INFORMATION

Please read the FDA-approved NULIBRY Prescribing Information and Instructions for Use and follow the instructions on how to prepare and administer NULIBRY.

NULIBRY has a potential for photosensitivity; see Warnings and Precautions. Seek medical attention immediately if the patient develops a rash or if they notice symptoms of photosensitivity reactions (redness, burning sensation of the skin, blisters).

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit [www.fda.gov/medwatch](http://www.fda.gov/medwatch), or call 1-800-FDA-1088.

You may also call BridgeBio at 1-844-550-BBIO (2246).



**Nulibry**<sup>™</sup>  
(fosdenopterin)  
for injection



## In children with MoCD Type A, NULIBRY (or recombinant cPMP [rcPMP]) was shown to<sup>1</sup>:

- Improve overall survival vs untreated, genotype-matched natural history controls<sup>1</sup>
- Reduce and maintain reductions of toxic S-sulfocysteine (SSC)<sup>1</sup>

\*Discontinue NULIBRY if the MoCD Type A diagnosis is not confirmed by genetic testing.

Visit [NULIBRY.com](https://www.nulibry.com) to learn how you can give patients with MoCD Type A a fighting chance<sup>1</sup>

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**Please see accompanying Brief Summary.**

### [NULIBRY.com](https://www.nulibry.com)

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origin  
a bridgebio company

## NULIBRY™ (fosdenopterin) for injection

**BRIEF SUMMARY:** For full prescribing information, see package insert.

### 1 INDICATIONS AND USAGE

NULIBRY is cyclic pyranopterin monophosphate (cPMP) indicated to reduce the risk of mortality in patients with molybdenum cofactor deficiency (MoCD) Type A.

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Patient Selection

Start NULIBRY if the patient has a diagnosis or presumptive diagnosis of MoCD Type A.

In patients with presumptive diagnosis of MoCD Type A, confirm the diagnosis of MoCD Type A immediately after initiation of NULIBRY treatment. In such patients, discontinue NULIBRY if the MoCD Type A diagnosis is not confirmed by genetic testing.

#### 2.2 Important Administration Information

- NULIBRY is intended for administration by a healthcare provider. If deemed appropriate by a healthcare provider, NULIBRY may be administered at home by the patient's caregiver. If NULIBRY can be administered by a caregiver/patient, advise them to read the detailed instructions on the preparation, administration, storage, and disposal of NULIBRY for caregivers [see *Instructions for Use*].
- NULIBRY is for intravenous infusion only. Administer with non-DEHP tubing with a 0.2 micron filter. Do not mix NULIBRY with other drugs (note NULIBRY is reconstituted with Sterile Water for Injection, USP). Do not administer as an infusion with other drugs.
- NULIBRY is given through an infusion pump at a rate of 1.5 mL per minute.
- Dose volumes below 2 mL may require syringe administration through slow intravenous push.
- Administration of NULIBRY must be completed within 4 hours of reconstitution [see *Dosage and Administration (2.5)*].

#### 2.3 Recommended Dosage and Administration

Recommended Dosage and Administration in Patients Less Than One Year of Age (by gestational age)

The recommended dosage regimen of NULIBRY in patients less than one year of age (by gestational age) is based on actual body weight as shown in Table 1.

**Table 1 Recommended Initial Dosage and Titration Schedule of NULIBRY for Patients Less Than One Year of Age by Gestational Age**

Titration Schedule	Preterm Neonates (Gestational Age Less than 37 Weeks)	Term Neonates (Gestational Age 37 Weeks and Above)
Initial Dosage	0.4 mg/kg once daily	0.55 mg/kg once daily
Dosage at Month 1	0.7 mg/kg once daily	0.75 mg/kg once daily
Dosage at Month 3	0.9 mg/kg once daily	0.9 mg/kg once daily

Recommended Dosage and Administration in Patients One Year of Age or Older

For patients one year of age or older, the recommended dosage of NULIBRY is 0.9 mg/kg (based on actual body weight) administered as an intravenous infusion once daily.

#### Recommendations for a Missed Dose

If a NULIBRY dose is missed, administer the missed dose as soon as possible. Administer the next scheduled dose at least 6 hours after the administration of the missed dose.

#### 2.4 Preparation and Administration Instructions

NULIBRY must be reconstituted prior to use. Use aseptic technique during preparation and follow these instructions:

- Determine the total dose, number of vials needed, and total reconstituted dose volume based on the patient's weight and prescribed dose.
- Remove the required number of vials from the freezer to allow them to reach room temperature (by hand warming for 3 to 5 minutes or exposing to ambient air for approximately 30 minutes).
- Reconstitute each required NULIBRY vial with 5 mL of Sterile Water for Injection, USP. Gently swirl the vial continuously until the powder is completely dissolved. DO NOT shake. After reconstitution, the final concentration of NULIBRY reconstituted solution is 9.5 mg/5 mL (1.9 mg/mL).
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Reconstituted NULIBRY is a clear and colorless to pale yellow solution. Do not use if there are particles present or if the solution is discolored.
- Administer the total reconstituted dose.

#### 2.5 Storage of Reconstituted Solution

Reconstituted NULIBRY may be stored at room temperature [15°C to 25°C (59°F to 77°F)] or refrigerated [2°C to 8°C (36°F to 46°F)] for up to 4 hours including infusion time. If reconstituted NULIBRY is refrigerated, allow it to come to room temperature (by hand warming for 3 to 5 minutes or exposing to ambient air for approximately 30 minutes) before administration. Do not heat. Do not re-freeze NULIBRY after reconstitution. Do not shake.

Discard all unused reconstituted NULIBRY solution 4 hours after reconstitution.

### 3 DOSAGE FORMS AND STRENGTHS

For injection: 9.5 mg of fosdenopterin, as a white to pale yellow lyophilized powder or cake in a single-dose vial for reconstitution.

### 4 CONTRAINDICATIONS

None.

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Photosensitivity

Animal studies have identified that NULIBRY has phototoxic potential [see *Nonclinical Toxicology (13.2)*].

Advise NULIBRY-treated patients or their caregivers to avoid or minimize patient exposure to direct sunlight and artificial UV light exposure (i.e., UVA or UVB phototherapy) and adopt precautionary measures (e.g., have the patient wear protective clothing and hats, use broad spectrum sunscreen with high sun protection factor (SPF) in patients 6 months of age and older, and wear sunglasses when exposed to the sun). If photosensitivity occurs, advise caregivers/patients to seek medical attention immediately and consider a dermatological evaluation.

## 6 ADVERSE REACTIONS

### 6.1 Clinical Trials Experience

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.

#### Overview of Safety Evaluation

The safety of NULIBRY was assessed in 37 pediatric patients and healthy adults who received at least one intravenous infusion of NULIBRY or an *E. coli* derived non-salt, anhydrous form of cPMP (recombinant cPMP or rcPMP, which has the same active moiety and therefore the same biologic activity as NULIBRY). Of these 37 patients/healthy adults, 13 were pediatric patients with MoCD Type A in Studies 1, 2, and 3 [see *Clinical Studies (14)*], 6 were pediatric patients with presumptive MoCD Type A but who were later confirmed to not have MoCD Type A, and 18 were healthy adults (without MoCD Type A) in a Phase 1 study.

#### Adverse Reactions

Assessment of adverse reactions for NULIBRY is based on data from two open-label, single-arm studies, Study 1 (n=8) and Study 2 (n=1), in patients with a confirmed diagnosis of MoCD Type A (8 of the 9 patients were previously treated with rcPMP). In these studies, patients received a daily intravenous infusion of NULIBRY. The median exposure to NULIBRY was 4.3 years and ranged from 8 days to 5.6 years [see *Clinical Studies (14)*]. In these studies, 44% of patients were males and 56% were females, 67% were White and 33% were Asian. The mean age was 14 days and ranged from 1 day to 69 days at time of first infusion.

Table 2 presents the most common adverse reactions that occurred in NULIBRY-treated patients in Studies 1 and 2.

**Table 2 Common Adverse Reactions Reported in Two or More NULIBRY-Treated Patients with MoCD Type A (Studies 1 and 2)**

Adverse Reactions	NULIBRY-Treated Patients (N=9) n (%)
Catheter-related complications <sup>1</sup>	8 (89%)
Pyrexia	7 (78%)
Viral infection	5 (56%)
Pneumonia	4 (44%)
Otitis Media	4 (44%)
Vomiting	4 (44%)
Cough/Sneezing	4 (44%)
Upper viral respiratory infection	3 (33%)
Gastroenteritis	3 (33%)
Diarrhea	3 (33%)
Bacteremia	3 (33%)
Abdominal pain	2 (22%)
Influenza	2 (22%)
Lower respiratory tract infection	2 (22%)

Adverse Reactions	NULIBRY-Treated Patients (N=9) n (%)
Viral tonsillitis	2 (22%)
Oropharyngeal pain	2 (22%)
Rash maculo-papular	2 (22%)
Anemia	2 (22%)
Eye swelling	2 (22%)
Seizure	2 (22%)
Agitation	2 (22%)

Abbreviations: MoCD = molybdenum cofactor deficiency

<sup>1</sup> Catheter-related complications included complication associated with device, catheter site abscess, catheter site discharge, catheter site extravasation, catheter site pain, catheter site infection, catheter site inflammation, device dislocation, device leakage, device occlusion, and vascular device infection.

Safety data are also available from 10 patients with MoCD Type A who received rcPMP in Study 3 (an observational study) [see *Clinical Studies (14)*]. The median time on rcPMP treatment was 1.5 years and ranged from 6 days to 4.4 years. In Study 3, the patient population was evenly distributed between males and females with a mean age of 18 days (range 1, 69) at time of first infusion, 70% were white, and 30% were Asian.

In Study 3, one patient died of necrotizing enterocolitis. Adverse reactions for the rcPMP-treated patients were similar to the NULIBRY-treated patients, except for the following additional adverse reactions that were reported in more than one patient: sepsis, oral candidiasis, varicella, fungal skin infection, and eczema.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

There are no available data on NULIBRY use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Animal reproduction toxicology studies have not been conducted with NULIBRY.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2% to 4% and 15% to 20%, respectively.

### 8.2 Lactation

#### Risk Summary

There are no human or animal data available to assess the presence of NULIBRY or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production for the mother.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NULIBRY and any potential adverse effects on the breastfed infant from NULIBRY or from the underlying maternal condition.

#### 8.4 Pediatric Use

Safety and effectiveness of NULIBRY for the treatment of MoCD Type A have been established in pediatric patients starting from birth. Use of NULIBRY for this indication is supported by evidence from two open-label studies (Studies 1 and 2) and one observational study (Study 3), in which 13 pediatric patients aged birth to 6 years of age were treated with NULIBRY or rcPMP. Pediatric use information is discussed throughout the labeling.

Animal studies have identified that NULIBRY has phototoxic potential. Advise NULIBRY-treated patients or their caregivers to avoid patient exposure to direct sunlight and artificial UV light exposure (i.e., UVA or UVB phototherapy) and adopt precautionary measures [see *Warnings and Precautions (5.1) and Nonclinical Toxicology (13.2)*].

#### 8.5 Geriatric Use

MoCD Type A is largely a disease of pediatric patients. Clinical studies of NULIBRY did not include patients 65 years of age and older.

### DRUG INTERACTION STUDIES

#### *In Vitro Studies*

Fosdenopterin does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5. Fosdenopterin does not induce CYP1A2, CYP2B6, or CYP3A4.

Fosdenopterin is a weak inhibitor of MATE2-K and OAT1, but does not exhibit P-gp, BCRP, OATP1B1, OATP1B3, OCT2, OAT3, and MATE1.

Fosdenopterin is a weak substrate for MATE1, but is not a substrate of P-gp, BCRP, OATP1B1, OATP1B3, OCT2, OAT1, OAT3, or MATE2-K.

### 13 NONCLINICAL TOXICOLOGY

#### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with fosdenopterin.

Fosdenopterin was not genotoxic in a standard battery of in vitro (bacterial reverse mutation and human lymphocyte chromosomal aberration) and in vivo (rodent bone marrow micronucleus) assays.

Fertility studies have not been conducted with fosdenopterin.

#### 13.2 Animal Toxicology and/or Pharmacology

Fosdenopterin has demonstrated phototoxic potential in an animal study at doses equal to and greater than 4.5 times the maximum recommended human dose (based on human equivalent dose comparison). In this study, which was conducted in pigmented rats, intravenous (bolus) administration of fosdenopterin for three consecutive days followed by ultraviolet radiation (UVR) exposure resulted in dose-dependent cutaneous skin reactions (erythema, edema, flaking, and eschar) and ophthalmic and histopathologic changes indicative of phototoxicity [see *Warnings and Precautions (5.1)*].

### 17 PATIENT COUNSELING INFORMATION

Advise patients/caregivers to read the FDA-approved patient labeling (Instructions for Use) and complete the treatment logs as appropriate.

#### Photosensitivity

Advise patients and/or caregivers of the potential for photosensitivity reactions and to ensure that the patient avoids or minimizes exposure to sunlight and artificial UV light exposure (i.e., UVA or UVB phototherapy) during use of NULIBRY, uses broad spectrum sunscreen with high sun protection factor (patients 6 months of age and older), and wears clothing, a hat, and sunglasses that protects against sun exposure. Instruct patients/caregivers to seek medical attention immediately if the patient develops a rash or if they notice symptoms of photosensitivity reactions (redness, burning sensation of the skin, blisters) [see *Warnings and Precautions (5.1) and Nonclinical Toxicology (13.2)*].

To report SUSPECTED ADVERSE REACTIONS, contact Origin Biosciences, Inc. at 1-888-55BRIDGE (1-888-552-7434) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

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# New Technology That May Help Reduce Unplanned Extubations and Optimize Suctioning Practice in the NICU

Adrian J D'Angelo MSN, RN, FNP

## Introduction

Neonatal patients in respiratory distress are frequently intubated and require an endotracheal tube (ETT). Keeping an ETT in place can be challenging in neonates as they are not typically paralyzed and experience movement.<sup>1</sup> Movement can lead to migration of the ETT, which can lead to dislodgement or an unplanned extubation. The presence of an ETT can also stimulate mucus production and impair clearance of secretions. ETT suctioning is then necessary and, although required, the timing and frequency varies from patient to patient.<sup>2,3</sup> This paper will address the risks associated with endotracheal tube movement and obstruction in the neonate and explore the ways a new technology can be used to optimize care.

## Unplanned Extubations

Unplanned extubations (UEs) are a significant safety concern for neonates and are defined as any dislodgement of an endotracheal tube from the trachea that is not intentional or ordered by a health care professional.<sup>7</sup> UEs are the most common adverse event during mechanical ventilation in the neonatal intensive care unit (NICU).<sup>4,7</sup> The risk of UEs in neonates is higher when compared to other populations. This is likely due to several factors, such as neonates have a longer duration of intubation, they have a shorter trachea, use of uncuffed ETTs, and skin to skin contact with a parent is encouraged. UEs often result in an emergent reintubation and may cause cardiovascular collapse, leading to an increase in hospital length of stay and costs.<sup>6,7</sup>

## Costs

In a retrospective matched cohort study, Hatch et al evaluated the clinical outcomes and costs in very low birth weight infants. In the primary cohort they found that UEs were associated with a one week increase in mechanical ventilation, a ten day increase in length of stay, and a nearly \$50,000 increase in total hospital costs.<sup>7</sup>

## Prevention Bundles

To address this issue, a multicenter quality improvement initiative was implemented utilizing a bundled care method recommended by the Children's Hospitals Solutions for Patient Safety (SPS). In this study Klugman et al suggested a widely accepted benchmark of 1 UE per 100 vent days. The bundle

included several recommendations including the use of two licensed clinicians for procedures such as repositioning and for bedside imaging. The study found that the bundle reduced NICU UEs by 17.6% from 1.55 UE per 100 vent days to 1.282 UE per 100 vent days. Although the NICU bundle did not reach the set benchmark, they concluded that all ICUs should strive for rates at or near zero.<sup>5</sup>

Despite the implementation of prevention bundles, UE rates have been found to initially decline and then plateau at a rate greater than zero. This suggests that there is a need for additional interventions to reduce UEs to acceptable rates. One intervention that is commonly used directs clinicians to focus on the placement of the endotracheal tube tip. The current widely used method to confirm EET tip placement is through chest radiograph or X-ray. Although this procedure helps identify ETT placement it may not be routinely prescribed to avoid radiation exposure in patients that have prolonged intubations.<sup>8</sup>

By measuring the location of the endotracheal tube tip within the trachea, the SonarMed™ airway monitoring system can improve a clinician's ability to manage a patient's airway. The device provides continuous, real-time monitoring of the ETT tip position and can also assist in identifying obstructions, which can help optimize suctioning practices.<sup>9</sup>

## Suctioning

Endotracheal tube suction is one of the most common procedures in the NICU. Suction practices are associated with significant risks including hypoxemia, bradycardia, hypotension, changes in cerebral blood flow, and changes in lung volume. Recent literature suggested that ETT suction guidelines may use evidence that is outdated or from adult and animal studies. Often suction practices are performed based on the health care providers personal experience and recognition of clinical finding such as decreased breath sounds on auscultation.<sup>2,3</sup>

## New Technology

The SonarMed™ airway monitoring system is a Food and Drug Administration (FDA) cleared technology that has been proven to be a complementary method for the assessment of ETT migration and obstruction.<sup>9</sup> The SonarMed™ airway monitoring system uses acoustic reflectometry to emit sound waves through the ETT and measures them as they return to the sensor. The system analyzes the timing and amplitude of the echoes to estimate the position and integrity of the ETT. Immediate audible alerts then inform clinicians when movement or obstructions

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are detected. This unique technology assists in verifying ETT movement, position, and patency during ventilation.

## Conclusion

Through application of the SonarMed™ airway monitoring system, healthcare providers can mitigate some of the risks associated with endotracheal tube movement and obstruction, optimizing the care of the neonatal patient.

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well, too. In the case report, pediatricians describe a case of fetal inflammatory response syndrome, or FIRS. The 32-year-old mother, who went into labor prematurely at 34 weeks, showed up at the hospital with COVID-19 symptoms and tested positive for the virus. She also had severe preeclampsia. The baby was delivered quickly and required mechanical ventilation. He had a fever, neonatal respiratory distress syndrome and elevated levels of several inflammatory markers. He tested negative for COVID-19 twice, as well as other infectious diseases. The baby received an antibiotic for seven days and a platelet transfusion for low platelet counts. Ventilation was removed after the fifth day, and he began recovering at the hospital. He was discharged after 22 days with no follow-up required beyond standard prematurity care. FIRS has been documented in premature births, and this case lacked some of the typical abnormalities such as umbilical cord inflammation or placental insufficiency. However, the high inflammatory levels indicated some vascular damage and multi-organ issues, which the authors attribute to exposure to the mother's COVID-19 infection during pregnancy. The fetal inflammatory response appeared similar to the hyperinflammatory syndrome seen in children during the pandemic, which has been called multisystem inflammatory syndrome in children, or MIS-C. The low platelet counts, in particular, could indicate an inflammatory response associated with COVID-19, the authors write. Several blood and platelet abnormalities have been documented in COVID-19 cases and MIS-C. As the pandemic continues, doctors should monitor platelet counts in newborns with inflammation, the authors suggest, especially if they may have been exposed to COVID-19. In this case, platelet counts stabilized after a transfusion.

## Preterm Infant Supine Sleep Positioning Becoming More Common

Although supine sleep positioning of preterm infants is becoming more common, racial disparities remain, according to a retrospective analysis involving more than 66,000 mothers. Non-Hispanic Black preterm infants were 39%-56% less likely to sleep on their backs than were non-Hispanic White preterm infants, reported lead author Sunah S. Hwang, MD, MPH, of the University Colorado, Aurora, and colleagues. According to the investigators, these findings may explain, in part, why the risk of sudden unexpected infant death (SUID) is more than twofold higher among non-Hispanic Black preterm infants than non-Hispanic White preterm infants. "During the first year of life, one of the most effective and modifiable parental behaviors that may reduce the risk for SUID is adhering to safe infant sleep practices, including supine sleep positioning or back-sleeping," wrote Dr Hwang and colleagues. The report is in the *Journal of Pediatrics*. "For the healthy-term population, research on the racial/ethnic disparity in adherence to safe sleep practices is robust, but for preterm infants who are at much higher risk for SUID, less is known." To address this knowledge gap, the investigators conducted a retrospective study using data from the Pregnancy Risk Assessment Monitoring System (PRAMS), a population-based perinatal surveillance system. The final dataset involved 66,131 mothers who gave birth to preterm infants in 16 states between 2000 and 2015. The sample size was weighted to 1,020,986 mothers. The investigators evaluated annual marginal prevalence of supine sleep positioning among two cohorts: early preterm infants (gestational age less than 34 weeks) and late preterm infants (gestational age 34-36 weeks). The primary outcome was rate of supine sleep positioning, a practice

*Continued on page 48...*



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# When Given the Tools to Thrive: Neonates, Infants, and Pediatrics

Gabriela Ortiz, BSRT, RCP

Questions often arise about the quality of life for a child who is born with birth defects and abnormalities. Some children are born with multiple co-morbidities, such as extremely low birth weight, congenital and chromosomal anomalies, musculoskeletal, neurological, and respiratory disorders (Kurata et al., 2019). Having these types of medical diagnoses and complications from birth lead down a path requiring many medical interventions, which may also affect the emotional and psychological state. Often these diagnoses require a tracheostomy tube to support ventilation, to provide access for an airway, or to allow a direct passageway for secretion management. Having an invasive surgical procedure is a difficult process for parents to absorb, and they rely on the guidance of the physicians and other healthcare professionals to assist them in understanding the process. Though a tracheostomy may aid in providing support and stability of care, it may also come with complications. Common causes of death in children due to tracheostomy are tube obstruction, tube misplacement, and accidental decannulation (Watters, 2017).

Many questions come with the decision for a tracheotomy, at times, the only alternative as a lifesaving modality. A major concern that often arises with a tracheostomy tube is what impact it will have on the ability to vocalize and communicate. Parents also often ask about the impact on speech and language development. Parents rely on the education and guidance of the physicians and clinical staff as it relates to understanding the challenges that will occur with a tracheostomy.

A tracheostomy may not be permanent, but when it is in place, the following complications may arise (Passy-Muir, Inc., 2021):

- Loss of taste and smell.
- Reduced vocal fold closure.
- Reduction in subglottic pressure.
- Decreased laryngeal and pharyngeal sensation, which may alter secretion management.
- Increased pooling of secretions.
- Reduced cough effectiveness.

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Gabriela Ortiz has been in the field of respiratory care since 2006. She lives in Southern California and has worked in clinical education and sales roles, using knowledge gained from her clinical experience in critical care ventilation products for the ICU, PICU within acute and subacute hospitals. Gabriela is an invited guest speaker at schools, Better Breather's Group meetings, and ALS support groups. She currently is a full-time clinical specialist with Passy-Muir, Inc.

## Why Would a Newborn Require a Tracheostomy Tube?

While considering tracheostomies in infants, more procedures are performed in the first year of life with the average age of an infant being around 4.5 months of age (French et al., 2007; Akangier et al., 2020), and in children it is three years and eight months (Butnaru et al., 2006). Indications for a tracheostomy tube will depend on the child's weight, their gestational age, comorbid conditions, congenital abnormalities, complications, and potential outcomes. One initial consideration is the APGAR score (1 to 10 scale) taken at birth. This assessment tool is a good indicator of deficiencies in appearance, pulse, grimace, activity, and respirations. If the child presents with an APGAR score of less than seven, clinicians will continue therapies to increase the score. If not successful, ongoing assessment is conducted. The baby could present with a normal to midrange score at first but demonstrate decline rapidly, presenting with such symptoms as shallow breathing, apnea, duskiness, and oxygen saturation between 70 and 80%. This type of presentation often requires non-invasive or invasive support.

## Does a Tracheostomy Affect Normal Growth?

Some consider that there are five stages of child development: newborn, infant, toddler, preschool, and school age (RISE, 2021). During the first month of life, newborns demonstrate automatic responses to external stimuli, like breathing, sucking, feeding and swallowing, and sucking (including non-nutritive sucking with a pacifier). Infants develop new abilities quickly throughout the first three years of life.

Neurological and respiratory disorders that prevent the body from working as it should, can impede and prevent the child from reaching milestones that correlate to their age. Deficits or delays may occur in any of the following milestone areas:

- Speech and language.
- Physical – gross and fine motor development.
- Cognitive skills – including alertness, attention, memory, new learning, problem solving, and reasoning.
- Emotional development.
- Social and pragmatic skills.

These milestone areas are a part of the natural process of growth and development but may not be met on the normal trajectory, if an infant or child receives a tracheostomy. These developmental milestones are all impacted by the pressurized system, which is the human body. Pressure assists with Postural control and trunk support which are precursors to being able to sit up, crawl,

walk, and completion of such skills as normal toileting, if this pressurized system is disrupted, such as by a tracheostomy, then typical development, may not be possible (Massery, 2013). With a tracheostomy, most of the airflow is only passing in and out of the tracheostomy tube, with little to no airflow up through the vocal folds and upper airway, causing a decrease in positive airway pressures.

Communication begins with the first cry and develops as the child identifies responses from his surroundings, leading to early communication attempts. When an infant or toddler is unable to produce vocalizations, the quality of the caregiver-child interaction may be compromised (Torres & Sirbegovic, 2004). For example, caregivers may be less responsive to a child who is incapable of crying to obtain attention or unable to respond to social interactions vocally. Thus, restoration of phonation in the newborn and young child can play a crucial role in promoting early caregiver-child bonding experiences at a time when children are typically attaining first words and developing early expressive vocabulary.

Yi et al. (2019) studied the effects of oral feeding on the development of swallowing function in children with tracheostomies who aspirated as there has been little previous research on the topic. To qualify for the study, the child had to be under age seven years and aspirating liquids. They were then divided into two groups—an oral feeding group and a non-oral feeding group. Significant differences were found between the groups for return to full oral feeding. The group receiving oral feeding for the year had 37% return to full oral diets and 53% to partial oral diets, contrasted with only one child in the non-oral group returning to full oral feeding and 29% to partial. There was no significant difference in the incidence of pneumonia between the groups. Oral feeding was aggressively trialed with suctioning to attempt removal of aspirates through the tracheostomy; however, many of the participants were said to cough food and liquid out through the tracheostomy tube. The authors hypothesized that swallowing function could improve over time even if infants or young children continue oral feeding in the presence of aspiration and before the aero-digestive centers were fully established.

### **Quality of Life Improved with Restoration of the Pressurized System**

The body functions as a pressurized system, being negatively impacted by a tracheotomy with the tracheostomy tube reducing positive end expiratory pressure (PEEP), subglottic pressure, and intrathoracic pressures. Studies have shown that placement of a no-leak speaking Valve helps restore the pressurized system; therefore, strength in body core and stability may be restored compared to those with an open tracheostomy tube (Massery, 2013). Those with restoration of intrathoracic pressure may show improvement and benefit during physical and occupational therapy, during tasks such as transferring and toileting maneuvers.

Brooks et al. (2019) noted that the use of the no-leak Passy-Muir® Valve (PMV®) has been underutilized with infants and children who are medically fragile either on mechanical ventilation or tracheostomy collar. The authors describe the predictors of success for use of the PMV which were determined by measurements and observations of Transtracheal Pressure (TTP), tracheostomy tube size, presence of voicing, and mechanical ventilator settings.

A PMV functions by keeping its bias-closed position (no movement of the diaphragm without any airflow), no-leak design; therefore, redirecting airflow to the upper airway. The process of assessment for use of the Valve is easy, if a patient meets a few selection guidelines to be sure they are a good candidate.

Research and studies have indicated that application of the no-leak Valve not only restores voicing but will help restore laryngeal and pharyngeal sensation, assisting with swallowing or coughing to mobilize material or liquid that may go the wrong way in the throat or pool around the airway (O'Connor et al., 2019). The change in airflow with a PMV also assists with improving sensation which may restore some more natural airway protection. An effective physiological mechanism will decrease the need of mechanical assistance, like suction machines, that are used to clear the airway. Secretion management is crucial to oxygenation, ventilation, and prevention of aspiration that may lead to respiratory infections.

Sutt and Fraser (2015) conducted a study to determine if lung recruitment would decrease with deflation of the cuff in adult patients on mechanical ventilation. During the study, the researchers used electrical impedance tomography to measure muscle activity and lung volume. They compared patients with cuff deflation, Valve in place, and patients with the cuff inflated and no speaking Valve. The patients with the cuff deflated and Valve in place were found to have increased lung recruitment, improvement in diaphragmatic function for better lung mechanics, return of voice and weaning from mechanical ventilation much more quickly.

### **Quality of Life Improved for a Child with Congenital Heart Defect: Case Review**

As a homecare respiratory therapist, patients of varying ages and diagnoses are seen. When a child is born with Hypoplastic Left Heart Syndrome (HLHS), they are not expected to live long but with assessment, monitoring and using available technology, the quality of life and overall development may be improved. If they are discharged home on mechanical ventilation with a tracheostomy tube, the homecare respiratory therapist plays a key role in addressing their needs.

Since HLHS involves several abnormalities of the heart and great blood vessels and is a congenital (present at birth) syndrome, the infant with HLHS may not live long without surgical intervention, especially if other organs are affected. Despite the obstacles faced from HLHS, this case review is about a child who was followed by homecare respiratory therapy and continued to thrive. Ventilation and oxygenation needs were met with mechanical ventilation and feeding provided with a g-tube. With guidance and education from a physical therapist (PT), the parents were able to provide exercise movements and range of motion exercises to assist with development. Since the child lacked the ability to manage secretions, had poor trunk control, had difficulty maintaining PEEP for oxygenation, and had poor voicing, this child was at risk for a negative impact on development. However, using a Valve allowed for restoration of a closed system and the beginning of the developmental stages.

Since the child was placed on hospice, the one desire the parents shared, was to hear the never heard voice of their baby. The primary goal for introducing the Valve was to allow the parents to hear their child's voice, but using a Valve also assisted with restoring much more. Timely initiation of the speaking Valve

helped restore verbal communication and improved secretion management. This initial success sparked the interest of the multidisciplinary team to incorporate further therapies, changing the potential outcomes for this child.

Though the child was behind on growth and development, with restored therapies and use of the Valve, milestones were reached—walking at 18-20 months, weaning from mechanical ventilation at two to three years of age, and decannulation at four years of age. This child is now 10 years old and living a vivacious life.

### **Quality of Life Considerations for a Child with Congenital Central Hypoventilation Syndrome (CCHS): Case Review**

CCHS is also known as Ondine's curse, which is a rare disorder of decreased respiratory function and impaired autonomic regulation. It is a lifelong and life-threatening disease, typically occurring in newborns, yet does have a milder, later-onset presentation in children and adults (Weese-Mayer et al., 2014). This disease affects normal breathing and causes the individual to hypoventilate.

After six months in acute care, a child with CCHS discharges home based upon the availability of homecare, parent involvement, and accessibility to mechanical ventilation. In addition, with the inability to manage secretions, swallow, or maintain oxygenation, the need for several pieces of equipment to sustain life were placed in his room. The family and homecare providers were able to manage the condition through the support of invasive and later, non-invasive breathing devices.

Methods used included (Ortiz, 2021):

- Mechanical Ventilation with positive pressure via the tracheostomy.
- Non-invasive Bi-level positive airway pressure ventilation via masks.
- Diaphragm pacing, a minimally invasive process that stimulates the phrenic nerve enabling more natural breathing.

Growth and development continued; therefore, eating, practicing phonation, and speech with use of a PMV helped with communication and assisted with progress towards developmental milestones. At around seven years of age and with overall medical stability, invasive ventilation was downgraded to a non-invasive mask ventilation along with diaphragmatic pacing to assure adequate respiration. Now at 14 years of age, the tracheostomy tube is still in place but is capped and awaiting decannulation.

### **Born Too Soon Hinder Milestones**

Higher rates of aspiration and dysphagia are discovered in children with prematurity, upper aerodigestive tract anomalies, central nervous system malformations, neurodevelopmental delays, and craniofacial syndromes (Raol et al., 2018).

Complications of prematurity are the global leading cause of death in children younger than five years of age. Almost 15 million children are born prematurely worldwide each year (Galindo-Sevilla et al., 2019). Many complications arise when a child is born preterm, for some meeting developmental milestones within the artificial environment of a hospital. Being born too early can involve short-term and long-term complications. Again, recognizing insufficiencies in body core strength and posture, feeding, swallowing, and maintenance of

physiological PEEP due to a tracheostomy tube in place are key to assisting with development.

With normal growth, the child will eventually catch up, reaching milestones apparent for their true age. But those with complicated outcomes may encounter obstacles that prevent or prolong growth and development; perhaps, being linked to the tracheostomy tube becoming permanent. In some instances, typical speech and language may not be achieved, but the tracheostomy tube may serve as the best option for secretion management and an open airway for oxygenation purposes.

Multidisciplinary teams will work with a child to collaborate on how to improve quality of life. A speech-language pathologist and respiratory therapist may work together, recommending interventions, such as use of a PMV, to allow the child laryngeal and pharyngeal sensation and to learn how to manage secretions and protect their airway. If a child reaches school-age, use of a PMV offers many benefits beyond just speaking, as it assists with restoring cough, throat clear, secretion management, taste and smell, and pressures. All these functions may assist with airway protection and overall gross and fine motor development through increasing pressure for trunk support and postural control. Personal experiences have shown how the child with HLHS was able to accomplish mobility and wean from mechanical ventilation due to an improvement in lung mechanics. The child with CCHS has learned to live with his life-long disease, but with medical interventions is making the best of his life.

### **Thriving When Given the Right Tool for Improving Quality of Life**

Freeman-Sanderson et al. (2016) studied improvement in quality of life for adult patients with tracheostomy and mechanical ventilation in the ICU. Eligibility criteria included participants who had a tracheostomy placed for at least 48 hours. The researchers looked at use of the PMV, communication, and overall quality of life. They found that patients were had less anxiety and stress when using a speaking valve to restore their ability to communicate again. This positive outcome also presented as improvement in patient's self-esteem which led to improved mood and finding this to be a significant factor in improvement of rehabilitation.

Due to a lack of evidence in the pediatric population with medically complex infants and children, it is challenging to find consensus related to PMV application in children (Brooks et al, 2019; Zabih et al., 2017). There are many patients who may be a candidate for PMV placement but are not receiving this intervention due to physician concern when a higher risk population. Brooks et al. (2019) found certain factors predicted success, such as age and Valve use, and reported earlier improvements in those children using a PMV.

Because of the paucity of research in pediatrics, often the studies and research done in adults are used as evidence to support use in children. While more research is needed, clinicians are trialing Valve use more in pediatric patients, offering them the ability to improve their quality of life. Just because an infant cannot talk yet, does not mean that a speaking Valve is not for them. While vocalization has a strong impact on development of speech and language and impacts parental or caregiver bonding, the other benefits assist with progressing through tracheostomy use and leading to weaning and decannulation, not to mention the impacts on gross and fine motor development. So,

when considering the time for intervention, ask—what about vocalization, laryngeal and pharyngeal sensation, swallowing, and positive pressure, for posture and body core strength? All these functions impact quality of life, even in infants and young children.

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# Are You 'Flying Blind' with NIV Pressures?

Greg Spratt BS RRT CPFT

## Introduction

Noninvasive Ventilation (NIV) has become an increasingly utilized tool for ventilatory support in neonates with two primary goals: 1) preventing intubation in a newborn requiring increasing ventilatory support due to evolving respiratory failure, and 2) continued ventilatory support to avoid reintubation after extubation. The potential benefits of avoiding endotracheal intubation or reintubation and the accompanying trauma and negative sequelae from the ventilation via endotracheal tube placement are evident.<sup>1-3</sup>

As with any form of ventilatory support, settings optimized to the patient's needs are critical for a successful outcome. Clinicians typically use NIV settings for peak inspiratory pressure (PIP) and positive end-expiratory pressure (PEEP) similar to those used during intubated ventilation, assuming that these settings will deliver a relatively similar level of ventilatory support using a non-invasive interface compared to use while intubated.<sup>4</sup>

**Evidence presented below shows that this is a poor assumption which may lead to unnecessary intubation or reintubation due to an overestimation of the true level of support being provided.**



In fact, the pressure readings on the ventilator may dramatically misrepresent the pressure (and consequently ventilatory support) truly being delivered to the airway. Not only may it misrepresent the true airway pressure, the degree of error can be highly variable based on two factors: 1) added resistance from the non-invasive interface being used and 2) leak at the

patient interface. As different interfaces have different levels of resistance and leak, the level of pressure reduction is highly variable and difficult to predict when transitioning from one interface type or size to another.

During the routine, pre-use check, ventilators typically auto-calibrate to the breathing circuit characteristics so that during ventilation, the monitored PIP and PEEP values accurately represent what is measured at the patient connection port of the circuit. However, when you add a NIV interface to the circuit, the resistance and compliance of the breathing circuit change. Depending on the amount of resistance added, pressures applied to the patient may be significantly lower than the displayed values. Added resistance is primarily created by the small openings in the non-invasive interface.

Let me illustrate with a simple analogy. If you blow out forcefully through a large tube (say one inch in diameter), the pressure inside your mouth will not be appreciably different to the pressure inside of the tube. However, how would that change if you blew with the same force into a very small tube, like a coffee straw? Your cheeks would puff out and significant back pressure would be created inside of your mouth, much higher than the actual pressure inside the distal end of the straw.

The ventilator is displaying pressures for PIP and PEEP based on the pressure in the ventilator circuit (in our analogy, inside the mouth). When increased resistance is introduced with the NIV interface (in our analogy, the coffee straw), this significantly affects the pressure reading inside the ventilator circuit proximal to the restriction compared to the actual pressure distal to the restriction (ie, at the interface). The resistance may be dramatically increased because of the small diameter of the non-invasive interface ports (eg, the nasal prongs). Poiseuille's law teaches us that decreasing the diameter of the tubing by half creates a 16-fold increase in resistance (and thus a reciprocal decrease in the true airflow to the patient).<sup>5</sup>

Secondly, some level of leak is expected from these systems as the interface is typically not fully sealed to the infant's airway (ie, nose, face) and due to open-mouth leaks intrinsic to nasal interfaces. For example, a properly fitted RAM cannula is suggested to create ~70% occlusion of the nares allowing for a significant leak even when properly fitted.<sup>6</sup> Movement of the infant may also result in additional leak due to partial and variable dislodgement of the interface from the infant's face.

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Greg Spratt is a Respiratory Therapist with 40 years experience including 10 years working as a marketing and clinical science director at Medtronic, now retired and working as an independent consultant when not traveling with his wife Pam, woodworking, gardening, or visiting his 2 grandsons. Greg was compensated by Medtronic for his time in writing this article. Questions may be forwarded to [gspratt59@gmail.com](mailto:gspratt59@gmail.com).

These two factors can result in significant and highly variable dampening of the interface pressure at the patient when compared to the set pressures on the ventilator, in essence causing clinicians to be ‘flying blind’ when it comes to the actual pressures being provided to the patient as demonstrated in the studies below.

### Evidence Demonstrating Errors in PIP and PEEP Displays

In an observational study by Owens et al, median delivered PIP (ie, interface pressure) was about 80% (15.9 cmH<sub>2</sub>O) of the set PIP when set at 20 cmH<sub>2</sub>O. More than a third of all inflations (ie, ‘breaths’) were delivered at least 5 cmH<sub>2</sub>O below the set PIP. In infants with PIP set at 25 cmH<sub>2</sub>O, the error was even higher with only 69% of the pressure being delivered at the interface (median PIP of 17.2 cmH<sub>2</sub>O). When viewing breath by breath, 83% of inflations were delivered at least 5 cmH<sub>2</sub>O below the set PIP.<sup>7</sup>

In a simulated neonatal lung model, Iyer et al explored pressure transmission using the small caliber nasal RAM cannula. Using a leak within manufacturer guidelines (30%), there was a 25-37% reduction of peak airway pressure and 10-30% reduction of PEEP transmitted across the nasal interface compared to the ventilator settings. During a 50% leak (ie, ‘worst-case scenario’), there was a much higher 92% reduction in delivery of peak airway pressure and PEEP.<sup>6</sup>

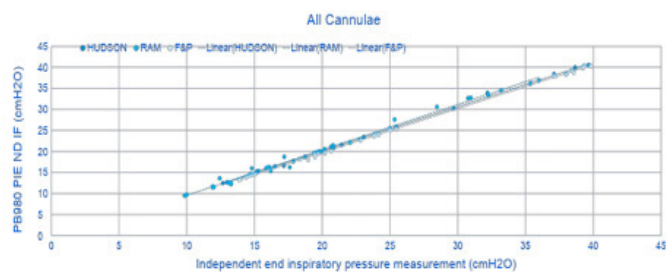
Also using a simulated neonatal lung model comparing the short binasal prongs (SBP) interface with the small caliber nasal cannula (RAM) interface, Mukerji et al found significant decrease in the interface pressure compared to ventilator settings and high variability between the effect of the two devices tested. When measured at the lung level of the model, the transmitted pressure dampening was even greater with the fraction of operator-set pressure that was transmitted to the lung being significantly lower with the RAM cannula (only 2.8% of set pressure transmitted), as compared with the SBP interface (still only 11.9% of set pressure transmitted). Carbon dioxide elimination, also measured in the model, was directly proportional to delivered PIP level, and better preserved by the SBP interface where pressure dampening of PIP was less than with RAM. Pursuant to the earlier discussion of the impact of resistance, the resistance of the smallest (‘preterm’) RAM cannula was 400% higher when compared with the SBP interface.<sup>4</sup>

In bench testing, Gerdes et al looked at the impact of the RAM cannula on nasal CPAP levels between four and eight cmH<sub>2</sub>O. Using varying nasal occlusion levels, prong depth insertion, and mouth leakage, mean airway pressure (MAP) decreased progressively with decreasing nares occlusion (ie, increasing leak). The simulated open-mouth condition (additional leak) resulted in significantly lower MAPs to < 1.7 cmH<sub>2</sub>O. The one-half prong insertion depth condition, with closed mouth, yielded MAPs approximately 35 ± 9% less than full insertion pressures (P<0.001). They concluded that in their testing, the RAM interface failed to deliver set CPAP levels when applied using the manufacturer recommended 60–80% nares occlusion, even with closed-mouth and full nasal prong insertion conditions.<sup>8</sup>

### How do I know what pressure I’m truly delivering?

An optimal method would be to actually measure true delivery pressures on the patient side of the interface or within the airways. While this may be possible in research situations or in simulated models, the specialized and invasive equipment required simply isn’t practical for everyday practice.

A new release by one manufacturer (Medtronic) is attempting to take the impact of resistance and leak into account. The NIV+™ software<sup>9</sup> option on the Puritan Bennett 980™ ventilator calibrates to the specific neonatal NIV interface in use, thereby enabling the monitoring of two additional data values: 1) interface end-inspiratory pressure and 2) interface end-expiratory pressure. By calibrating based on the resistance of the individual circuit and type/size of interface being used, these two new measurements provide a more representative reading of the true pressures being delivered to the patient.<sup>10</sup> Bench testing with three popular interfaces: 1) Fisher & Paykel Healthcare™ Infant Nasal Prongs, 2) Hudson RCI™ Infant Nasal Prongs, and 3) Neotech™ RAM Cannula, showed very high correlation between the new values displayed by the software on the ventilator and measured values using an independent manometer at the patient interface (R<sup>2</sup> – 0.992, 0.9925, and 0.9989 respectively) (See Figure 1). An R<sup>2</sup> of 1.0 represents a ‘perfect’ correlation. Any change in the type or size of the interface being used would require a new calibration.<sup>11,12,13</sup>



**Figure 1.** Agreement of PB980 End-Inspiratory Pressure at the Patient Interface (P<sub>END IF</sub>) Displayed Value & Independent Measurement by Manometer at Patient Interface.

Test setup with NIV+ in use with physiological model of neonatal patient nares and lungs. Independent pressure gauge connected to the physiological model shows end inspiratory pressure experienced by the “patient.”

### Summary

Increased resistance and leaks inherent to noninvasive interfaces frequently lead to significant misrepresentation of true delivery pressures at the patient compared to the settings on the ventilator. This makes it difficult for the clinician to know what PIP and PEEP pressures are truly being transmitted to the patient. Recent product developments may enable clinicians to better understand what level of ventilatory support is being delivered, thus potentially increasing the chances of a favorable outcome.

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that must have been followed consistently, excluding other positions (i.e. prone or side). Mothers were grouped by race/ethnicity into four categories: non-Hispanic Black, non-Hispanic White, Hispanic, and other. Several other maternal and infant characteristics were recorded, including marital status, maternal age, education, insurance prior to birth, history of previous live birth, insurance, method of delivery, birth weight, and sex. From 2000 to 2015, the overall adjusted odds of supine sleep positioning increased by 8.5% in the early preterm group and 5.2% in the late preterm group. This intergroup difference may be due to disparate levels of in-hospital education, the investigators suggested. “Perhaps the longer NICU hospitalization for early preterm infants compared with late preterm infants affords greater opportunities for parental education and engagement about safe sleep practices,” they wrote. Among early preterm infants, odds percentages increased by 7.3%, 7.7%, and 10.0% for non-Hispanic Black, Hispanic, and non-Hispanic White mothers, respectively. For late preterm infants, respective rates increased by 5.9%, 4.8%, and 5.8% for non-Hispanic Black, Hispanic, and non-Hispanic White mothers. Despite these improvements, racial disparities were still observed. Non-Hispanic Black mothers reported lower rates of supine sleep positioning for both early preterm infants (odds ratio [OR], 0.61; *P* less than .0001) and late preterm infants (OR, 0.44; *P* less than .0001) compared with non-Hispanic White mothers. These disparities seem “to be in line with racial/ethnic disparity trends in infant mortality and in SUID rates that have persisted for decades among infants,” the investigators wrote.

### **Baby Born to Partially Vaccinated Mom Has COVID-19 Antibodies**

A baby girl born three weeks after her mom got the first dose of Moderna’s COVID-19 vaccine has antibodies against the virus, a February pre-print paper reported. After getting the shot, the mom, a healthcare worker in Florida, developed COVID-19 antibodies. Testing revealed those antibodies passed through the placenta to offer some potential protection to her future child, according to the authors at Florida Atlantic University. While past reports have shown how moms who’ve had COVID-19 can deliver babies with antibodies, the authors believe theirs is the first to record how vaccines during pregnancy may do the same. Authors Dr Paul Gilbert and Dr Chad Rudnick called their report a lucky “opportunity study,” since they were able to find, and follow, a pregnant person who never tested positive for COVID but got the vaccine late in pregnancy and early in the rollout. When the baby — “a vigorous, healthy, full-term girl,” according to the paper — was born, the doctors tested her cord blood for antibodies made from the vaccine, along with conducting other typical tests like for blood type. They were able to detect COVID-19 IgG antibodies (the type that indicate recovery), suggesting the baby has some protection against the virus, though how much or how long it lasts isn’t clear. Future research should illuminate if there’s an ideal time for a pregnant person to get vaccinated to maximize protection against the virus for her child. The authors say their results were expected based on what’s known about how the vaccine, and others recommended during pregnancy like the flu vaccine, work.

### **Preterm Birth Rate Drops During COVID-19 Pandemic in Tennessee**

Statewide stay-at-home orders put in place as Tennessee fought to control the spread of coronavirus last March were associated  
*Continued on page 56...*



# Jenné Johns: A Pioneer in NICU Racial & Health Equity Education

Deb Discenza

In the neonatal intensive care community you find a few people along the way that are real powerhouses of change. They see beyond trendy topics and generic slide decks to focus on transformative structural change and work hard to create it with incredible success. Enter Jenné Johns, MPH, President of the non-profit Once Upon A Premie (<https://onceuponapremie.com>), author the book of the same name as well as the Founder and President of the Once Upon A Premie Academy (<https://www.onceuponapremieacademy.com/>). I asked Jenné to tell me about her beginnings, her initiatives and her passion behind it.

**Deb Discenza (DD): Your entire education and career has been focused on health and racial equity within healthcare, yes? Tell me about it.**

**Jenné Johns (JJ):** Growing up as a child in the inner city of Philadelphia, PA, I observed first hand the devastating effects of differences in healthcare and health outcomes. I witnessed low income African American families dying much younger and at alarming rates compared to my White friends who I went to elementary and High School with. Members in my immediate community and family died early of diabetes, heart disease, and cancer. This bothered me, and I wanted to understand why. I entered college with questions I wanted answers to such as, why are there less grocery stores in my community vs. liquor stores? Why do we have doctors who don't listen when we tell them what bothers us medically or clinically? Why is my community overlooked and misunderstood?

As an undergraduate student, I studied Nutrition as an opportunity to help my community through food, diet, and behavior change. Little did I know, this would inspire me to look beyond the individual, and look more broadly at policies, systems, and opportunities to advocate for the voiceless. My undergraduate research experience, while focused on adult and childhood obesity, I examined the racial and ethnic differences. This was a theme of all of my research and career efforts moving forward. Fast forward to completing my graduate studies in Public Health, I only sought careers that would allow me to further my understanding, advocacy, and areas to impact

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Deb Discenza runs PremieWorld.com, an educational products company full of free items for educating families. PremieWorld's flagship product, The Premie Parent's Survival Guide just published its second edition and is on sale at PremieWorld.com. In addition, Mrs Discenza is the founder of the 15+ year old global Inspire Premie Community, free for parents at <https://premie.inspire.com>.

health improvements for any population whose outcomes were different from the norm.

Throughout my career, working at the nation's largest healthcare philanthropy, and even as I transitioned to working in Medicaid Managed Care, I continued to advocate for programs and services to close healthcare gaps based on race and ethnicity. At this stage of my career, addressing health and racial equity is more than a professional interest, it is my life calling.

**DD: Why the NICU/preemie space focus though?**

**JJ:** While advocating for the food, nutrition, and healthcare access needs for low income communities, I birthed my son prematurely. I became a part of the negative birth outcome statistics plaguing African American women during our most precious and sacred time in life. While I was shocked and confused by this experience, it is a part of my life story that served as the catalyst for creating *Once Upon A Premie*. *Once Upon A Premie* is my self-published book, which at the time was the first and only children's book written for parents of preemies who needed encouragement and motivation during their NICU journey. I wrote this book because during our NICU stay, we did not have a lullaby to read to our son, that was unique and specific to our hospital based introduction to parenthood. In addition to self-publishing *Once Upon A Premie*, I joined several organizations to begin advocating for the needs of Black Premie families, as my NICU journey was less than ideal as an African American healthcare professional. I personally experienced implicit bias and that was the exact opposite of what any NICU family should experience. In addition, this negative experience was the exact opposite of what I spent my career advocating to prevent. I knew I needed to transition some of my general health and racial career experience to focus on the neonatal space.

**DD: What makes the Once Upon A Premie Academy different from the generic programs out there regarding implicit bias on the job and/or specifically in healthcare? What can NICU/preemie pros expect from your courses?**

**JJ:** Once Upon A Premie Academy is a virtual health and racial equity training program designed specifically for perinatal and neonatal healthcare professionals. Our trademarked curriculum offers real time solutions and action steps professionals can take to address implicit bias, patient satisfaction, and improved health outcomes. These courses are unique as we take a two part approach to delivering high quality and engaging content. First, we engage perinatal and neonatal professionals who have first hand experience leading or implementing strategies, programs,

or interventions that reduce disparities in the NICU. Next, we engage Premie parents who have lived experience in the NICU, and who have taken action around their NICU experience. Collectively, these professional and personal experiences make a powerful impact of insights, and recommendations for the healthcare community. We offer continuing education credits for any professional serving NICU families. Lastly, all of our training content is rooted and grounded in addressing inequities for Black NICU families.

**DD: Numbers do not lie and that was definitely the case for your launch in November 2020 (Prematurity Awareness Month). Tell me about it.**

**JJ:** The Once Upon A Premie Academy officially launched November 2020 during Prematurity Awareness Month. We hosted nearly 900 professionals across four live virtual training events. Our goal was to reach 50 professionals, so these numbers were a pleasant and welcomed surprise. We received extremely positive feedback from each participant. 65% of registered attendees reported seeing challenges around health and racial equity in the NICU, and 60% reported plans to make changes around equity within 30-60 days of attending our training programs. We look forward to continuing to expand our educational training opportunities for this community.

**DD: As I said, numbers do not lie. That is seriously impressive. So, what's next?**

**JJ:** This summer (2021), we are relaunching the Once Upon A Premie Academy with four e-learning modules. Healthcare professionals serving Premie families will have access to our training courses on an on-demand basis. They will also have access to obtaining 1 CEU per course completed. In addition to relaunching our expanded training courses, we will also host two live webinars this November during Prematurity Awareness Month. We hope that you will join us on our journey to improve health equity for NICU families. For more information please visit us at: [www.onceuponapremieacademy.com](http://www.onceuponapremieacademy.com)

**DD: And your *Once Upon A Premie* book?**

**JJ:** We are also seeking sponsors to help us donate *Once Upon A Premie* books to NICU's in low income communities. If you are interested in giving the gift of early literacy and preemie parent/child bonding, please purchase a book in your name that will be donated this November. For more information, visit [www.onceuponapremie.com](http://www.onceuponapremie.com)

**DD: Thank you, Jenné.**

Any organization in this space is likely going through self-reflection right now as racial and health equity has risen to the top of the list in global conversation. To be clear, this is not a moment. It is a movement and I believe every NICU, every hospital needs a Jenné Johns in their corner either in providing the academy curriculum in a public or private session or requesting her time to help 'do the work.' Because time and again, our society stepped up only to think that it's a checklist item. It's not. It is *ongoing work*. So...get to work.

**About Jenné:** *Jenné Johns, MPH is President of Once Upon A Premie, Founder of Once Upon A Premie Academy, mother of a micro preemie, author, speaker, advocate, and national senior health equity leader. Once Upon A Premie is a non-profit organization with a two-part mission: 1.) to donate Once Upon A Premie books to NICU families in under resourced communities, and 2.) lead virtual health and*

*racial ethnic training programs and solutions to the neonatal and perinatal community through the Once Upon A Premie Academy. Jenné provides speaking, strategic planning and consultation services for fortune 500 companies focused on preemie parent needs from a cultural lens and reading as a tool for growth, development, and bonding. Jenné is also a national senior health equity thought leader and has led solutions-oriented health equity and quality improvement portfolios for the nations' largest health insurance and managed care companies.*

# Not All Donor Milk Is Equal: Impact of Processing Methods on Bioactive Compounds

Diane L Spatz, PhD, RN-BC, FAAN and Kelley Baumgartel, PhD, RN

## Background

The importance of human milk for both healthy and vulnerable infants in order to improve health and developmental outcomes in infancy, throughout childhood, and into adulthood has been well documented, yet breastfeeding rates remain suboptimal.<sup>1</sup> Parents need to receive evidence-based care, assistance and education in order to both make an informed feeding choice and effectively initiate and maintain milk supply.<sup>2,3</sup> The Spatz 10 step model for human milk and breastfeeding has been effectively implemented in hospitals both in the United States and globally with improved initiation rates and improved human milk rates at discharge and beyond.<sup>2,6</sup> Unfortunately, the use of human milk and breastfeeding has not been universally prioritized and there remain persistent health disparities and barriers to achieve global breastfeeding recommendations for initiation, exclusivity and duration.<sup>1</sup> Therefore, many infants are exposed to infant formula early in life. This is particularly concerning given the amount of research that exists on the benefits of human milk for vulnerable infants. See Table 1.

Without enough mother's own milk, it is important to prioritize the use of Pasteurized Donor Human Milk (PDHM) as a bridge. In both the United States and worldwide more milk banks are being established. There has been an increase in both non-profit and for-profit milk banks. Despite the 2017 American Academy of Pediatrics (AAP) position statement focusing on the quality and safety of Pasteurized Donor Human Milk (PDHM) and more hospitals using PDHM, there remain persistent disparities in the use of PDHM.<sup>7,8</sup>

## Types of Donor Milk

In addition to the increased interest and use in PDHM, there are several for profit companies that have opened and are aggressively marketing and selling retort sterilized milk. Unlike pasteurization, the purpose of retort processing is sterilization which destroys many protective human milk compounds. In contrast, the purpose of pasteurization is to kill harmful organisms. There are two types of pasteurization, vat and Holder. This article aims to help readers understand that not all "donor milk" is equal. The different ways in which milk is processed is not well understood by most clinicians, nor do they understand the impact of the different methods on the bioactive components of human milk. Table 2 details the various methods of processing.

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Nurses in particular have voiced concerns regarding changes in practice when their hospital changed from PDHM to commercially sterile milk.<sup>9</sup> In particular, nurses verbalized anger and frustration because they were not involved in the decision-making processes.<sup>9</sup> Furthermore, most nurses believed the change was made to save money and this was viewed negatively.<sup>9</sup> Nurses also voiced confidence in the use of PDHM but were uncertain about commercially sterile milk.<sup>9</sup> Nurses strongly wanted evidence to support a practice change from the use of PDHM to commercially sterile milk but felt they had to go along with the change because there were barriers to obtaining the necessary evidence.<sup>9</sup>

## Fortifiers for Human Milk

In addition to the expansion of PDHM, there has also been an increase in the use of human milk-based fortifiers for preterm or other critically ill infants. Human milk-based fortifiers are used primarily to improve growth. Traditional fortifiers are made from bovine products. ProLacta Bioscience is the single manufacturer of human milk-based fortifiers which have been in use in the United States since 2006. These human milk-based fortifiers are processed using the vat pasteurization process, therefore many of the bioactive components of human milk are maintained and exposure to bovine products is prevented.

Research reports that extremely premature infants who receive diets devoid of bovine products have lower rates of morbidity and mortality.<sup>10</sup> Additionally, Hair & colleagues report improved growth for infants under 1250 grams for those who received an exclusive human milk diet (with human milk fortifiers) compared to a prior cohort of infants.<sup>11</sup>

## Milk Processing & Bioactive Components of Human Milk

Human milk is a highly complex biological system with variable composition that is influenced by many factors. Vat pasteurization and retort sterilization methods have varying effects on bioactive human milk compounds. Overall, vat pasteurization of donor milk and human-milk based fortifiers results in the protection of many such bioactive compounds. For example, immunoglobulins provide passive immunity by way of human milk to the preterm infant who has an underdeveloped immune system. Secretory IgA helps to establish the intestinal microbiome,<sup>12-14</sup> with robust antimicrobial,<sup>15</sup> and anti-inflammatory components.<sup>14</sup>

**Table 1.** Benefits of Human Milk for Hospitalized Infants\*

Decrease in mortality and morbidity
Reduction in incidence and severity of Necrotizing Enterocolitis
Decrease incidence of sepsis
Improved feeding tolerance, enhanced advancement of feeds, less days of total parental nutrition
Reduction in bronchopulmonary dysplasia
Reduction in retinopathy of prematurity
Improved brain development and developmental outcomes
Decrease in hospital costs

\*Table developed from position statements from the National Association of Neonatal Nurses and the Society for Pediatric Nurses National Association of Neonatal Nurses. The use of human milk and breastfeeding in the neonatal intensive care unit: NANN position statement #3052. *Adv Neonatal Care.* 2012;12(1):56-60. doi:10.1097/ANC.0b013e31823b5362

Spatz DL. SPN position statement: The role of pediatric nurses in the promotion and protection of human milk and breastfeeding. *J Pediatr Nurs.* 2017;37:136-139. doi:10.1016/j.pedn.2017.08.031

IgM, also found in human milk, prevents the activation of the complement system.<sup>16</sup> IgG is transferred to the infant circulation via human milk and acts directly on the bacteria found within the intestine. This immunoglobulin establishes bacterial colonization<sup>12</sup> by way of opsonization, which prevents acute inflammatory responses.<sup>14</sup> All immunoglobulins are vulnerable to decreased activity secondary to heat; however, different processing techniques result in varying immunoglobulin concentration. Vat pasteurization results in higher immunoglobulin amount and activity when compared with retort sterilization. Specifically, retort sterilization has a significantly negative impact on sIgA, resulting in 90% less sIgA and significantly decreased bioactivity.<sup>17</sup> IgM is also impacted by heat, with levels higher in vat pasteurized milk when compared with retort sterilization. Similarly, milk IgG is higher after vat pasteurization when compared with retort sterilization.<sup>18</sup>

Lysozyme is an antimicrobial enzyme that degrades bacteria and eliminates stimuli that lead to acute inflammatory responses.<sup>14</sup> Lysozyme works together with lactoferrin to reduce and eliminate pathogenic microbes. To do this, lactoferrin binds with iron, thereby eliminating it from the circulation for bacterial use.<sup>12</sup> Lactoferrin also prevents biofilm formation in the gastrointestinal tract and induces macrophage activity.<sup>12</sup> Lysosomal activity is absent following retort sterilization. Vat pasteurization results in higher milk levels of both lysozyme<sup>17</sup> and lactoferrin.<sup>18</sup>

Additional bioactive protein concentration and activity levels are also greatly impacted by different processing methods. Alpha-lactalbumin binds and assists with antibiotic uptake, thereby inhibiting bacterial reproduction<sup>18</sup> during times of gastrointestinal inflammation and potential pathology. Alpha-antitrypsin also prevents bacterial-induced pathology by limiting the ability of pathogens to enter the body,<sup>14</sup> as well as limiting local inflammation. Osteopontin, is a highly bioactive milk compound that promotes optimal immune and gastrointestinal environments. Significant to preterm infants, osteopontin supports brain development.<sup>19</sup> Working together with these proteins, casein, which represents more than half of milk protein content, contributes to the overall antimicrobial activity of human milk.<sup>18</sup> Human milk levels of alpha-lactalbumin, alpha-antitrypsin, osteopontin, and casein, are all higher when vat pasteurization is used, when compared with the retort sterilization method.

**Table 2.** Pasteurized Donor Human Milk Methods

Processing Type	Method	Organization/Country
Vat pasteurization	66°C 30 minutes	ProLacta Bioscience
Retort sterilization	121°C 5 minutes	MedoLac NiQ
Holder pasteurization	62.5°C 30 minutes	HMBANA Milk Banks EMBA Milk Banks
UV-C	Irradiation	United Kingdom

HMBANA = Human Milk Banking Association of North America

EMBA = European Milk Banking Association

UV = Ultraviolet

Human milk oligosaccharides (HMOs) are a critical bioactive component in human milk, as they greatly contribute to the microbial establishment of commensal bacteria. They often act as a decoy for pathogens,<sup>14</sup> which inhibits their ability to adhere to the gastrointestinal wall.<sup>15</sup> When compared with retort sterilization, vat pasteurization results in higher levels of HMOs. This is highly relevant to preterm infant health, as the milk microbiome is depleted with any other processing method which uses heat. The conservation of HMOs provides vulnerable infants with a robust and diverse gastrointestinal microbiome. HMOs are significantly higher in concentration following vat pasteurization versus retort sterilization.<sup>18</sup> Table 3 details the various bioactive components of milk and their biological functions.

Donor milk processing is highly relevant to clinical practice, as varying levels of bioactive compounds may contribute to disparate clinical outcomes. For example, infants who receive human milk with higher levels of HMOs have lower risks of gastroenteritis, diarrhea, and respiratory tract infections.<sup>20</sup> Additionally, preterm infants who receive exclusive human milk feedings, including fortification, have improved growth rates<sup>11</sup> and a lower risk for necrotizing enterocolitis.<sup>21</sup> In addition, an exclusive human milk diet also protects against mortality and other morbidities such as sepsis and retinopathy of prematurity.<sup>22</sup> Donor human milk is not uniform, as compositional variability has clinical implications.

A major limitation of the evidence presented is that the Meredith-Davis (2018) research is only based on 9 milk samples.<sup>18</sup> There is tremendous need for research with larger sample sizes that are collected in a standardized format to account for the complex intrinsic milk matrix variability.

**Table 3.** Bioactive Compounds Between Pasteurization Methods

Bioactive Component	Function
IgA	Protects mucous membranes
IgM	Complement activation Agglutination
IgG	Key role in humoral response and phagocyte opsonization
Lysozyme	Degrades bacterial proteoglycan matrix membrane
Lactoferrin	Antimicrobial Antioxidant Anti-inflammatory
Alpha-antitrypsin	Protection against inflammatory cell enzymes
Osteopontin	Intestinal maturation Brain myelination Neurodevelopment
Casein	Most abundant milk protein Nutritive function Provides essential minerals and amino acids

Note: Vat pasteurization yields higher levels of all bioactive compounds listed above when compared with Retort sterilization.

## Conclusions

Clinicians need to understand the impact of various milk processing techniques on the quality and bioactive components of donor milk. Overall, there is limited literature on how/if milk compositional variability contributes to disparate neonatal outcomes. Additional studies are needed that specifically examine whether milk processing methods influence neonatal clinical outcomes. Current clinical evidence for improved neonatal outcomes is based on products using vat and/or Holder pasteurization. Because of the abundant differences noted in milk composition, it is unclear whether products undergoing retort sterilization can be expected to result in any similar outcomes.

If an institution is considering implementing a donor human milk program or changing the type of donor milk they use, it is critical for all members of the interdisciplinary team (physicians, nurses, dietitians, etc.) to understand that not all donor milk is equal. We would recommend that hospital staff read the research and understand the impact of processing methods on the milk and share the research with all members of the team so that informed decisions are being made. We also firmly believe that hospital administrators should not be making decisions about what type of “donor milk” they purchase based on cost of the product alone.

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# Technology for Communication in the NICU

Robert D White, MD

## Introduction

At the beginning of the 21st Century, physician-parent communication in the NICU was usually a once-a-day occurrence at best. Families were typically prohibited from the NICU except during “visiting hours” and nearly always excluded from medical rounds. Parents would get a verbal report from their baby’s physician or nurse when they were present and occasionally by phone call if they could not be at the hospital; the content of this report was usually problem-oriented and brief.

In the ensuing two decades, many things have changed. Families are often encouraged to be present with their babies; they are now welcomed 24 hours a day in many NICUs. Their participation in the care of their baby is likewise encouraged and, in many units, actively facilitated.<sup>1,2</sup> Parent support groups have multiplied, empowering parents to be more proactive about their role in the NICU.<sup>3,4</sup> As a result, both the availability of and need for ongoing parent-caregiver communication have increased significantly. Fortunately, the proliferation of electronic communication options have increased just as dramatically, providing many new strategies for optimal communication between caregivers and family, especially when it is difficult for the family to be present in the NICU for extended periods.

## Parent-Caregiver Interaction

Even in NICUs where it is encouraged, parents are often unable to be physically present for rounds due to obligations outside of the hospital setting. Innovative NICUs have utilized telephone or video links to allow parents to be virtually present during rounds, and the same devices can be used for updates at any time of the day. Some devices now allow a physician or other care team members to record an update and relay it to the parents for viewing at their convenience or to provide similar information through a text message when real-time conversations are not an

option. It is possible to imagine additional strategies to enhance communication for parents who are unable to be present at the bedside, such as providing online access to information or educational resources from a hospital’s library or digital content providers. These resources also cater to different learning styles and languages that have been barriers to parent-caregiver interactions in the past.

## Parent-Infant Interaction

Bedside camera systems are now available that allow parents, family members, and friends of their choosing to view their infant continuously, as well as to facilitate some of the parent-caregiver interactions noted above. Many NICUs also utilize devices that use recordings of a parent’s voice, singing, or heartbeat to play at the bedside.

## The Future of Communication Devices in the NICU

It is reasonable to expect that these technological communication aids in the NICU setting are just in their infancy. What opportunities can we anticipate in the future?

## “Continuous Rounding”

Continuous readouts of vital signs have been available in the NICU for a generation now, but therapeutic responses to those values have remained chiefly episodic. An incubator or radiant warmer’s heat output can be servo-controlled to maintain a constant body temperature for an infant, but the capability to servo-control oxygen intake to respond to minute-to-minute changes in oxygen saturation, vasopressor dosing to changes in blood pressure, or glucose infusion dosing to changes in blood sugar remains unavailable. It is likely and optimal that responding to rapid changes in the tenuous condition of a critically ill infant will be achieved by artificial intelligence (AI)-driven devices, shifting the focus of medical rounds to adjustment of the parameters for AI to respond to rather than on making intermittent changes based on historical data, at least in the most critically ill infant.

What implications will this have for caregiver and family communication? First, it has the potential to provide more information to the family, depending on how transparent the process is. A recent law in the United States now requires access to any patient’s medical records; it is too soon to know how this will be implemented in terms of these real-time data points, but providers should prepare to no longer be the sole gatekeepers of a patient’s information. With more medical record information available, parents will know more and



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To this end he has written many papers, and co-founded the Consensus Committee to Establish Recommended Standards for Newborn ICU Design, the Gravens Conference on the Physical and Developmental Environment of the Newborn, and the International Newborn Brain Conference.

will ask more questions. This is already being encountered as families become more present at the bedside and active in care; these technological and data sharing advances will further bring families into the center of the caregiving and decision-making process. Clinicians will need to proactively provide families with tools to help them understand the additional information they have access to. Existing devices, such as camera systems with information-sharing capabilities and smartphone apps, are logical platforms on which to provide this kind of information in a way that will allow healthcare professionals to direct families to the most useful and reliable resources. By providing access to additional vetted resources, families will become more engaged, empowered, and confident in their understanding of their child's care.

### Developmental Care

Today's NICU environment of care is far more nurturing than it was a generation ago, but many infants, especially in the United States, spend most of their days without positive developmental stimuli. In utero, the fetus received almost constant multisensory input from the mother during this period of crucial brain growth and development;<sup>5,6</sup> however, in the NICU, the input is typically sporadic and often limited to a single form of stimulus—e.g., sound or touch. While there is no equivalent to extended, intimate, multisensory interaction with another human, opportunities to provide beneficial stimuli should be explored when human contact is limited. Are there ways technology can be harnessed to bring some elements of the parent-infant interaction to the bedside when the parents cannot do that in person? A more speculative question may be whether a bedside camera can itself become a visual monitoring system of neurological activity, analogous to a continuous EEG, but providing more clinically relevant data.

### Parent Education

As parents become more engaged in the active care and decision-making for their infants, their need for educational resources will grow. There is a large and intimidating body of information on the internet, ranging from authoritative to speculative and dubious. There is an urgent need for these resources to be curated for family consumption so that they do not provide a mixed message when compared to the medical team's proposed plan. One desirable way to accomplish this is to add appropriate resources, both web-based and locally produced, to a web

camera solution already being used by the family. This process can be learner-driven to allow families who want more extensive information to easily find helpful resources and make parents more prepared to engage in the discussions surrounding care decisions for their infant. Many priorities, such as the importance of breastfeeding or developmental support for an infant, might receive too little emphasis during medical rounds. However, families can still learn the roles these priorities play in their infant's care through access to electronic resources.

### Summary

The exchange of information from baby to clinician, baby to parent, and between clinicians and parents is

accelerating. Identifying one or more electronic platforms that support this communication should be a priority for every NICU team to provide optimal care for our patients and their families.

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with a 14% lower rate of preterm birth, according to a research letter published today in *JAMA Pediatrics*. Preterm infants have higher morbidity and mortality risks than babies born at term. Senior author Stephen Patrick, MD, director of the Vanderbilt Center for Child Health Policy and a neonatologist at the Monroe Carell Jr. Children's Hospital at Vanderbilt, and his colleagues had observed in March that there appeared to be fewer infants than usual in the NICU at the children's hospital. Along with colleagues at the Tennessee Department of Health and the Centers for Disease Control and Prevention, the team aimed to test if these anecdotal observations were related to the statewide lockdown order. The study is the first in the United States to confirm the trend that more persons staying at home, essentially on forced bed rest, reduced the number of late preterm infants (34-35 weeks). "Preterm birth affects 1-in-10 infants nationwide, taking a substantial toll on children, families and communities," Patrick said. "Our study, coupled with similar studies from Europe, provide initial evidence that COVID-19 stay at home orders were associated with reductions in spontaneous preterm birth. While encouraging, we need to ensure other pregnancy complications, like stillbirth, did not increase during this time period." Statewide stay-at-home orders in Tennessee were announced March 22 and expired on April 30. Researchers from Vanderbilt University Medical Center, the Tennessee Department of Health and the CDC collaborated to determine if the odds of pre-term birth during the stay-at-home orders in Tennessee were lower as compared with the same periods in 2015-2019 in Tennessee. There were 49,845 births among Tennessee residents during the study period. The preterm birth rate during the 2020 stay-at-home order was lower than rates in previous years (10.2% vs. 11.3%); late preterm (35-36 weeks gestation) birth rates were also lower (5.8% vs. 6.5%). "The overall decrease in preterm birth we saw during Tennessee COVID-19 stay-at-home order was driven by reductions among infants born late preterm, 35-36 weeks gestation," said lead author Elizabeth Harvey, PhD, MPH, Maternal and Child Health Epidemiologist at CDC Division of Reproductive Health. "Although we saw less infants born preterm, we also saw infants born during this time required more respiratory assistance at birth, which may suggest they were sicker and warrants further investigation," she added. Future research could explore whether other US states observed similar reductions, Patrick said, and how obstetric interventions for fetal and maternal complications, or lack thereof, may have contributed.

**Hospital Working to Close Health Inequity Gaps**

Sinai Chicago is working to close the health inequity gap for its most fragile patient population: premature infants. Sinai Chicago's neonatal intensive care unit (NICU) has adopted Prolacta Bioscience's nutritional products as part of an Exclusive Human Milk Diet (EHMD) to deliver the high quality neonatal nutrition to the communities it serves. Sinai Chicago's implementation of an EHMD is a result of Illinois House Bill 3509, which provides that pasteurized donated human breastmilk and breastmilk-based fortifiers shall be covered under health insurance and the medical assistance program under the Illinois Public Aid Code for premature and at-risk infants. Sinai Chicago is the first system in Illinois to implement both an EHMD and these nutritional products since the legislation went into effect. "As Chicago's largest private safety net health system, we serve a high percentage of low-income, minority patients, many of whom are Black women who would not otherwise have access

*Continued on page 59...*



# Benefits of an On-Unit NICU MRI System

## Introduction

MRIs offer many benefits for newborns in the Neonatal Intensive Care Unit (NICU), but performing off-unit MRIs is incredibly complex and creates many risks for this vulnerable population. On-unit MRI options for NICU patients greatly reduce these risks and can lead to significant benefits that make them cost-effective and clinically superior to off-unit MRIs.

## Background

Magnetic resonance imaging (MRI) is one of the most thorough and in-depth forms of imaging technology, allowing high quality, three-dimensional visualization of internal structures. MRIs provide superior soft tissue contrast compared to computed tomography (CT) scans and are better at differentiating between different types of soft tissues (US Food and Drug Administration, 2017). MRI technology can provide valuable diagnostic information that can be used to predict neurodevelopmental outcomes in neonates and infants (Cheong & Miller, 2018).

## Difficulties of Utilizing MRI Technology with a NICU Population

While MRI technology provides an invaluable resource for treating neonates and infants in a NICU, there are several barriers that make use of this technology suboptimal for these fragile patient populations. The potential risks caused by transporting a NICU patient to the MRI and back is one of the most dangerous of these barriers.

NICU patients are more compromised and less adaptable to changes in their environment than adult patients. NICU patients almost never physically leave the controlled environment of the NICU, with travel for off-unit MRI scans being one of the most notable exceptions. The MRI room is often on another floor of the hospital, requiring the neonate, the neonate's equipment, and the neonate's nurse to transport this compromised patient through hospital hallways and elevators. In one study, the average time off the NICU for an MRI was 121 minutes, even though the scan only took 46 minutes on average, meaning that transporting the patient made the process three times longer than the scan itself. (Coughlin, 2020).

## Negative Effects of MRI Transportation on NICU Patients

When compromised NICU patients are transported outside the unit there are several ways that they are likely to be negatively affected. These include:

- **Impaired Patient Safety**—NICU patients are more susceptible to hypothermia (Bastug et al., 2016); transporting the patient outside of the controlled NICU environment increases this risk due to decreased ability to control the ambient temperatures. While in the MRI scanner, monitoring the patient is also both more complex and less effective. Many of the monitoring and advanced treatment devices used in the NICU are not suited to use an MRI environment. MRI specific equipment is made for adult patients and therefore is inadequate or inappropriate for neonates. Patient safety is further affected by the limited resources in the MRI area and by the limited experience and knowledge of MRI staff in the care of critically-ill, newborn patients.
- **Infection Risk**—Infections are a great concern for NICU patients, especially central line-associated bloodstream



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infections (CLABSIs). Transporting a vulnerable neonate through a hospital and into the MRI environment exposes their underdeveloped immune systems to potential bacteria and viruses that thrive in hospitals (Ilyas et al., 2019). MRIs may also require line extensions to permit the use of IV medications while in an MRI. Accessing a central line outside of the controlled NICU environment can increase the risk of CLABSI.

- **Lack of Family-Centered Care**—Removing the patient from the NICU environment removes them from their family, which can cause distress for the patient and for the patient’s family.
- **Staffing Strains**—The compromised condition of NICU patients often requires that they be accompanied by at least one RN and a respiratory therapist during transport. This causes staffing strains on the NICU for the duration of the time that the patient is off the floor, which can be three times longer than the time spent doing the scan itself (Coughlin, 2020). Having staff off the floor can lead to extra labor expenses to meet the regulated staffing needs of the floor or can lead to lower nurse-to-patient ratios, resulting in lower quality of care for the duration of the MRI, and increased stress for the staff.
- **Expense Considerations**—Many of the negative effects caused by transporting a NICU patient to an off-unit MRI result in increased costs. These include the costs incurred with complications from impairments to patient safety, infections such as CLABSIs, and increased staffing needs.

The numerous negative effects that can result from transporting NICU patients to off-unit MRIs factor into providers’ risk-benefit considerations. This can result in fewer MRIs being ordered and performed, leading to potential delays in recognition of problems that could be treated to avoid permanent disability or other negative outcomes. MRIs that are ordered may also be delayed due to the logistical complications of obtaining one and the safety and staffing concerns outlined above.

### Embrace® Neonatal MRI System

The Embrace® Neonatal MRI System is a solution designed specifically for the neonatal population, tailored to meeting imaging needs specific to these patients. This unique MRI system is designed to be installed directly in the NICU, allowing on-unit NICU MRI imaging and eliminating the need for off-unit transportation. This system has cutting-edge shielding technology that prevents the magnetic field from reaching outside the scanner, making the scanner safer and easier to position in a small space.

The customized design of the Embrace® MRI provides special accommodations for the use of complex monitoring and treatment devices that most NICU patients depend on. This MRI system also allows for visualization of the patient, easy accessibility of the patient and on-unit resources, and control of the temperature of the patient’s environment throughout the scan through the incorporated thermo-controlled patient bed.

### Positive Effects of Implementing the Embrace® Neonatal MRI System in the NICU

The Embrace® Neonatal MRI System offers NICU patients many benefits compared to off-unit MRI systems. These benefits improve many components of care, including:

- **Patient safety**—The Embrace® Neonatal MRI provides continuous temperature control, reducing the likelihood of hypothermia. This system is also specifically designed to allow use of complex monitoring equipment and permits



visualization of the newborn during the scan, further ensuring their well-being and reducing the need for sedation.

- **Infection Prevention**—Use of an on-unit MRI system reduces exposure of NICU patients to other parts of the hospital environment. This greatly reduces the likelihood of exposure to pathogens that could be encountered during transport and in the MRI environment (Shen et al., 2020). On-unit MRIs also reduce the exposure of newborn patients to staff who are not uniquely trained in the care of neonatal patients and who may not be familiar with the best practices for infection prevention for this patient population.
- **Patient & Family Centered Care**—The Embrace® Neonatal MRI allows for visualization of the newborn during the scan and allows them to stay on the unit. Both of these factors ensure the patient is not separated from their family for extended periods of time, reducing potential distress for the patient and their family.
- **Staffing Effectiveness**—Off-unit MRI transport is a personnel-intensive exercise. The on-unit capabilities of the Embrace® Neonatal MRI remove the additional staffing strains of having NICU staff off of the NICU floor for prolonged periods of time. An on-unit MRI also helps to alleviate some of staffing strain associated with off-hours imaging, when the NICU medical staff may not be as accessible as they would be during the day.
- **Cost Considerations**—The on-unit capabilities of the Embrace® Neonatal MRI avoid the many potential costs that may be incurred with the complications associated with off-unit MRIs. A NICU-specific MRI can also allow greater use of an existing MRI and the revenue it generates.

Overall, the primary benefit of adopting the Embrace® Neonatal MRI is the unparalleled access to the critical data only available from MRI which can direct care with the goal of improving neurodevelopmental outcomes of neonatal patients, in a safe, patient-focused workflow within the NICU. With easy access to MRIs that represent less patient risks, less workflow complexity

and are more convenient, clinicians are more likely to take advantage of the benefits that MRIs can offer their patients and order MRIs more frequently.

This can lead to quicker recognition and treatment of potential problems, ultimately leading to better outcomes and healthier lives for these vulnerable newborns.

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to this standard of neonatal nutrition that their premature infants need to survive and develop,” said Karen Teitelbaum, president and CEO of Sinai Chicago. “We’re addressing this problem head-on by making an EHMD accessible to underserved families.” Proven to reduce complications and improve health, Sinai Chicago will be using nutritional fortifiers that are 100% human milk-based as opposed to cow milk-based. Studies have shown cow milk-based fortifiers can trigger feeding intolerance and increase mortality in premature infants due to the risk of severe complications. When it comes to preterm birth, there are several racial and socioeconomic disparities that need to be addressed. While 1 in 10 babies are born prematurely each year, the preterm birth rate for Black women is 50% higher than for all other women in the US, and prematurity is the leading cause of death among Black infants. Premature infants are at an increased risk for problems with the lungs, brain, eyes, and other organs, as well as long-term intellectual and developmental disabilities. “Offering these products as part of an EHMD in our NICU is a monumental step forward for the premature babies born here at Sinai each year,” said Brandee Grenda, clinical nutrition manager at Sinai Chicago. “For these vulnerable babies, access to an EHMD may be the difference between life and death. Not only will this give them the best chance to survive prematurity, but also to go on to thrive as healthy infants, children, and adults.” Premature infants require 20% to 40% more calories and protein than a full-term baby to make up for the growth they missed in the third trimester. To provide this extra nutrition, NICUs often add a fortifier to mother’s own milk or donor breastmilk. However, clinical studies show a direct correlation between the use of cow milk-based fortifiers and the development of devastating, and potentially terminal complications, including necrotizing enterocolitis (NEC), a disease of the intestines. In contrast, preterm infants who receive Prolacta’s products as part of an EHMD, which comprises mother’s own milk and/or donor milk with Prolacta’s 100% human milk-based fortifiers, have fewer complications and better growth outcomes, which have been linked with healthy neurodevelopment in these fragile infants, giving them the best possible chance in life. “The health disparities in the NICU are based on a variety of factors, including race, ethnicity, and income level, among others, and we are committed to ensuring that all premature infants have access to the highest standard of care available,” Teitelbaum said. Sinai Chicago offers high-quality OB/GYN services—including Level III neonatal intensive care and maternity care recognized by the Illinois Perinatal Collaborative for Excellence as well as Blue Cross Blue Shield’s “Blue Distinction” awards—at its north campus located at Mount Sinai Hospital. Its Level III NICU provides the highest level of care available for newborns just steps from the delivery room.

# Newborn Avoids Surgery With Stanford Medicine's Unique Treatment for a Small Jaw

Erin Digitale

**Stanford Children's Health is the only place in North America to offer the non-invasive, orthodontic approach to Pierre Robin sequence.**

In her first few weeks of life, Alianna Cervantes struggled to eat and breathe. When her parents tried to coax her to drink from a bottle, she would wheeze and tire after just a few minutes.

She was born in July 2020 with a cleft palate and an unusually small jaw, a condition known as Pierre Robin sequence. Her tongue was crowded into a cumbersome position that made it hard for her to swallow and often impaired her breathing. Karina Medina Moya and Jonathan Cervantes, Alianna's parents, wondered if their firstborn would need jaw surgery.

Experts at Stanford Children's Health offered something better: Alianna received an orthodontic device that immediately repositioned her tongue and gradually stimulated her jaw to grow to a healthy size without surgery. The Stanford Children's Health Cleft and Craniofacial Center is the only team in North America to use this approach, which they have offered since 2020.

"The most important thing about this treatment is that babies are able to breathe comfortably right away without surgery," said HyeRan Choo, DDS, director of craniofacial and airway orthodontics at Stanford Children's Health. The retainer-like device used in the treatment is custom-made for each patient, said Dr. Choo, who began caring for Alianna when she was a few weeks old. "It immediately opens the airway and keeps the baby's tongue out of the way."

## A rare diagnosis

When Alianna was two days old, a nurse at the hospital where she was born realized she had a cleft palate, a gap in the roof of her mouth. Cleft palate, which affects about 1 in every 1,700 U.S. births, makes it difficult for infants to generate enough suction to nurse or drink from a standard baby bottle. Some affected babies can use a special bottle that allows the caregiver to control the flow of milk.

But it didn't help Alianna — she required a feeding tube that ran from her nose into her stomach. Her parents were told she could leave the hospital once she learned to eat by mouth. Because she continued to have problems, she was transferred

"When you push the tongue — which is a huge muscle — forward and downward, bone remodeling in the temporomandibular joint area is very activated."

— Dr. Choo, referring to the joint where the jaw joins the skull

to the neonatal intensive care unit at Lucile Packard Children's Hospital Stanford, where caregivers noted her small jaw and diagnosed her with a much rarer condition that sometimes occurs with cleft palate. Called Pierre Robin sequence, it affects 1 in 3,500 to 8,500 births.

In Pierre Robin sequence, because the baby's mouth is so small, it's common for the tongue to fall backward toward the throat, blocking the airway. In other cases, including Alianna's, babies hold their tongues inside the cleft on the roof of the mouth. Although this helped Alianna breathe, it got in the way of feeding.

"Many babies with this condition have feeding difficulties," said Dr. Choo. "Breathing and swallowing are always paired in the suck-swallow-breathe mechanism, and when the airway is disturbed, this three-step mechanism is also disturbed."

Alianna's parents had read online about jaw distraction surgery for infants with Pierre Robin sequence. In the surgery, the baby's jawbone is cut in two places and braced by separating hardware, with the ends of the bone a few millimeters apart. New bone grows in the gaps, gradually enlarging the jaw.

Dr. Choo encouraged Karina and Jonathan to consider the retainer instead. Developed in Germany, where it has been used for decades, this non-invasive approach avoids the risks of surgery and can be started more quickly. The retainer fits against the roof of the mouth and extends in back to the base of the baby's tongue. It pushes the tongue forward and downward, keeping the air passage from the nose to the back of the throat clear so the baby can breathe consistently. This allows the baby to learn to eat by mouth.

Jaw surgery can't be performed until a baby is a few months old, whereas a retainer can be fitted for a newborn. The retainer also takes advantage of babies' enormous natural capacity for growth.

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“When you push the tongue — which is a huge muscle — forward and downward, bone remodeling in the temporomandibular joint area is very activated,” said Dr. Choo, referring to the joint where the jaw joins the skull. Wearing a retainer during the first three to six months of life, when growth rates peak, stimulates jaw enlargement. This makes room in the mouth for the baby’s tongue and permanently stabilizes the new jaw position.

### **Help to breathe, eat and grow**

When Dr. Choo suggested the retainer, Jonathan was enthusiastic about the non-invasive treatment, but Karina felt nervous. Dr. Choo arranged for her to speak with another mother whose child had received a retainer, helping her feel reassured about what to expect for Alianna. Dr. Choo also explained that if Alianna’s jaw needed more expansion after using the retainer, surgery would still be an option later.

A retainer was custom-made for Alianna using a dental impression of her mouth. Soon after the device was fitted, her parents noticed a difference in her oral feeding sessions.

“With the retainer, she drank a lot more comfortably,” Karina said, adding that after a few weeks, Alianna was consistently able to coordinate sucking, swallowing and breathing. “It was amazing. That’s when I began to trust the process and knew it was going to be worth it.”

Alianna stayed in the hospital for about three weeks after receiving the retainer, until she was breathing easily and steadily gaining weight, and her parents were comfortable removing the device for daily cleanings.

“Dr. Choo was there for my husband and me, during every cleaning and every time the retainer was taken in and out,” said Karina. “She was very supportive. To me, that meant a lot.”

Close collaboration between ear, nose and throat specialists; neonatologists; and craniofacial orthodontists is required for the orthodontic airway plate treatment to be offered, Dr. Choo noted. She recently published a scientific journal article about her results to encourage other experts in North America to consider the treatment, which currently is mostly used in Europe.

“Many hospitals don’t have a craniofacial orthodontist at all,” she said. “We’re fortunate to be able to offer this option at Stanford Children’s Health.”

Alianna wore the retainer until she outgrew it, which took about four months. Her jaw growth caught up to the rest of her face and is expected to continue on a normal trajectory, so she won’t need jaw surgery. She will receive surgical repair of her cleft palate after she turns 1 year old.

Best of all, according to Karina and Jonathan, 8-month-old Alianna is now crawling, trying to stand up and meeting all her developmental milestones. She loves when her parents sing her favorite songs, the ABCs and “Twinkle, Twinkle, Little Star.”

“This treatment made a huge change in my daughter’s life,” said Jonathan. “She’s a very happy baby, very energetic,” Karina added. “We’re very happy we took this route. It’s amazing seeing her grow.”

# Role of Umbilical Cord C-Peptide Levels in Early Prediction of Hypoglycemia In Infants of Diabetic Mothers

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## Abstract

**Background:** Until now, diabetes during pregnancy has been associated with a high risk of maternal, fetal, and neonatal morbidities and mortalities. The main aim of this study was to evaluate the risk factors of hypoglycemia in infants of diabetic mothers (IDMs) and to study the relationship between umbilical cord (UC) C peptide levels and the risk of developing hypoglycemia.

**Material and methods:** UC blood C-peptide and serial serum blood glucose measurements were done for all included singleton newborns born to diabetic mothers during the study period. Maternal and neonatal data such as gestational age, maternal age, maternal weight, types of diabetics and its control, maternal glycated hemoglobin (HbA1C), birth weight, Apgar score, and neonatal complete blood picture were collected.

**Results:** In total, 83 IDMs met the inclusion criteria. Fifty-four (65.06%) developed hypoglycemia and 29 (34.94%) remained normoglycemic. However, there were no significant differences between hypoglycemic and normoglycemic IDMs in terms of types of maternal diabetics ( $P$  value = 0.41), its duration ( $P$  value = 0.43). The hypoglycemia peak occurred within the first 3 h of life, with  $33.11 \pm 8.84$  mg/dl for the hypoglycemia group and  $54.10 \pm 6.66$  mg/dl for the normoglycemic group ( $P$  value < 0.0001). Most of the babies had no hypoglycemic manifestation (96.30%). Neonates with hypoglycemia their mothers had poor diabetes control in the last trimester (HbA1C  $7.09 \pm 0.96\%$ ) compared to normoglycemic babies (HbA1C  $6.11 \pm 0.38\%$ ), ( $P$ -value < 0.0001). The mean (SD) of UC C-peptide level in hypoglycemic neonates increased to  $1.73 \pm 1.07$  ng/ml compared to normoglycemic ones with  $1.08 \pm 0.81$  ng/ml ( $P$  value = 0.005).

**Conclusion:** Poor diabetes control, especially in the last trimester, is associated with neonatal hypoglycemia. Increased UC C-peptide levels could be used as an early indicator for the risk of developing neonatal hypoglycemia and a predictor for babies need neonatal admission.

**Keywords:** Infants of diabetic mothers, Umbilical cord C-peptide, Blood glucose, Full-term infant

## Introduction

Despite marked declines in neonatal mortality nowadays,<sup>1</sup> diabetes mellitus (DM) with pregnancy either gestational (GDM), type 1, or 2 is still associated with a risk of maternal, fetal, and neonatal morbidities and mortalities. Moreover, its prevalence did not decline, as GDM was about 8.74% on one cohort.<sup>2</sup> Infants of a diabetic mother (IDM) often have complications closely linked to fetal hyperglycemia and hyperinsulinemia, induced by maternal hyperglycemia.<sup>3</sup>

In the first trimester, maternal hyperglycemia can cause spontaneous abortions or major birth defects such as truncus arteriosus or aortic coarctation. In the second and third trimesters, maternal hyperglycemia can cause fetal hyperglycemia and hyperinsulinemia, which lead to post-natal neonatal hypoglycemia, hypocalcemia, polycythemia, hyperbilirubinemia, septal myocardial hypertrophy, delayed lung maturation, and macrosomia.<sup>4</sup>

Most IDMs develop asymptomatic hypoglycemia in the first postnatal hours, as after delivery, the transplacental supply of high glucose is stopped. Hyperinsulinemic hypoglycemia is a major risk factor for brain injury and subsequent neurodevelopmental impairments; therefore, rapid identification and prompt management of the newborn with hypoglycemia are essential to avoid brain damage.<sup>5</sup> In this context, early detection of babies at high risk of hypoglycemia is important.

Human C-peptide is a 31-amino acid chain secreted from the beta cells of the pancreas in equimolar ratio with the insulin level. It was chosen over insulin to estimate neonatal hyperinsulinemia, as C-peptide has a long half-life and is unaffected by several blood processing conditions such as hemolysis.<sup>6,7</sup>

Maternal control during pregnancy mainly depends on diet and insulin control. The degree of control can be increased by serial measurements of blood glucose (BG) and glycated hemoglobin (HbA1C). However, HbA1C, now the current gold standard marker for glycemic control, reflects the BG level over the previous 2–3 months. It is a strong predictor of diabetic complications, and the cut-off used is 6.5% to diagnose diabetes.<sup>8</sup>

Therefore, the main aim of this study is to evaluate the risk factors of hypoglycemia in IDM and its relation to maternal DM control in the last trimester. Furthermore, the relationship between UC C peptide and the risk of developing hypoglycemia was evaluated.

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## Material and methods

### Design

The current clinical study was performed at the neonatal intensive care unit (NICU) in the Pediatrics Department, in cooperation with the Department of Obstetrics and Gynecology, Egypt, during the period from June 2018 to June 2019. Local ethical approval for the study was obtained from the Research Committee of the Faculty of Medicine at Sohag University (No. 321, 2018), and written informed consent was obtained from all parents of the children.

We included all singleton newborns born to diabetic mothers. Exclusion criteria included IDMs with preterm delivery, major congenital malformation at birth, severe perinatal asphyxia, twins, or erythroblastosis fetalis.

Eighty-three full-term singleton IDM newborns met the inclusion criteria and were enrolled in the study. The case group in this study consisted of any newborn infants delivered to DM mothers and who developed hypoglycemia within the first 24 h of life (BG less than 47 mg/dl), other IDMs maintaining normoglycemic during the study period served as controls. Both the cases and the controls groups were drawn from the same population characteristics.

Maternal data such as maternal age, gestational age, maternal weight, type and duration of DM, maternal drugs for the control of DM, maternal diseases such as pre-eclampsia, premature rupture of membranes (PROM), mode of delivery, and the presence of meconium in the amniotic fluid were recorded. Maternal HbA1C was performed. Neonatal data such as gender,

neonatal weight, Apgar score at 1 min and at 5 min, causes of admission to NICU, if indicated, birth injuries, and detailed systemic examination were recorded. Observation for any hypoglycemia manifestations as (irritability, jitteriness, and convulsions) were done during NICU admission or in the nursery until babies discharged from hospital. Furthermore, BG measurements (Roche HITACHI Cobas C-311 Auto-Analyzer System) were performed at birth, after 30 min, and after 1, 3, 6, 12, 18, and 24 h; follow-up BG evaluations were performed until BG was normalized. We also determined complete blood count (Cell Dyn 3700, automated cell counter, Abbott Diagnostics, USA), electrolytes, CRP, and blood group. Neonatal outcome for neonates admitted to NICU were recorded. Echocardiography study were done before discharge for all IDM newborns met the inclusion criteria and were enrolled in the study.

Approximately 3 mL of UC blood were drawn immediately after delivery from all infants who met the inclusion criteria. The blood was chilled to 4°C, centrifuged as soon as possible, and stored at -84 °C. UC serum C-peptide was measured using a third-generation enzyme-linked immunosorbent assay (ELISA) (Modular Analytics E170, Roche Diagnostics, Singapore).

### Data analysis

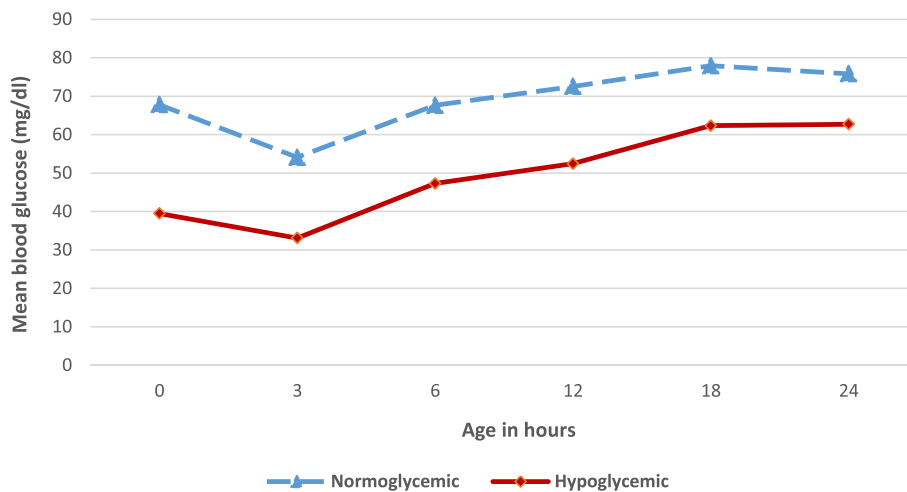
Data were analyzed using STATA version 14.2 (Stata Statistical Software: Release 14.2 College Station, TX: Stata Corp LP.). Quantitative data were represented as mean, standard deviation, median, and range. Data were subjected to student t-test to compare means of two groups. When the data were not normally distributed, Mann-Whitney's test was applied. Qualitative data were presented as number and percentage and compared

**Table 1** Comparison between normoglycemic and hypoglycemic infant according to maternal characteristics

Variable	Normoglycemic N = 29	Hypoglycemic N = 54	P value
Maternal age (years)			
Mean ± SD	36.03 ± 6.93	35.22 ± 4.35	0.51
Maternal weight (kg)			
Mean ± SD	77.76 ± 8.60	79.54 ± 7.90	0.35
Preeclampsia			
Yes	9 (31.03%)	21 (38.89%)	0.18
PROM > 18 h			
Yes	2 (6.89)	4 (7.41%)	0.69
Mode of delivery			
CS	24 (82.75%)	44 (81.48%)	0.25
NVD	5 (17.24%)	10 (18.51%)	
Type of DM			
Gestational DM	12 (41.38%)	23 (42.59%)	0.41
Type 1	0	3 (5.56%)	
Type 2	17 (58.62%)	28 (51.85%)	
Duration of DM (years)			
Mean ± SD	2.21 ± 2.18	3.18 ± 4.3	0.43
Type of treatment of DM			
Diet	1 (3.45%)	5 (9.26%)	0.62
Insulin	23 (79.31%)	40 (74.07%)	
Oral/Insulin	5 (17.24%)	9 (16.67%)	

**Table 2** Comparison between normoglycemic and hypoglycemic infant according to Neonatal characteristics

Variable	Normoglycemic N = 29	Hypoglycemic N = 54	P value
Gestational age (weeks)			
Mean ± SD	38.28 ± 2.59	38.98 ± 2.01	0.11
Gender			
Female	20 (68.97%)	30 (55.56%)	0.23
Male	9 (31.03%)	24 (44.44%)	
Neonatal weight (kg)			
Mean ± SD	3.78 ± 0.49	3.90 ± 0.81	0.07
APGAR score 1 Min			
Median (range)	8 (7–9)	8 (6–9)	0.44
APGAR score 5 Min			
Median (range)	10 (7–10)	10(8–10)	0.45
Hct (%)			
Mean ± SD	53.22 ± 3.59	51.59 ± 4.20	0.08
WBCs (thousands)			
Mean ± SD	11.07 ± 1.81	12.06 ± 3.47	0.16
Platelets (thousands)			
Mean ± SD	221.69 ± 37.10	213.91 ± 45.37	0.43
Serum total Ca (mg/dl)			
Mean ± SD	8.5 ± 0.71	8.32 ± 0.39	0.13
Ventricular septal hypertrophy (≥ 6 mm)			
Number (%)	10 (34.48%)	21 (38.89%)	0.3



**Fig. 1** Comparison between normoglycemic and hypoglycemic IDM according to blood glucose during the first 24 h of life

using either the Chi square test or Fisher's exact test. Graphs were generated using the software packages Excel or STAT; differences were considered significant at a P value below 0.05.

## Results

### Patient characteristics

In total, 83 IDM met the inclusion criteria and were included in this study. Of these, 54 (65.06%), developed hypoglycemia and 29 (34.94%) remained normoglycemic. However, there were no significant different maternal or neonatal differences between hypoglycemic and normoglycemic IDMs, even for types of maternal diabetics (P value = 0.41), its duration (P value = 0.43), or measurements used for control of diabetes (P value = 0.62), as shown in Tables 1 and 2. Furthermore, IDM with hypoglycemia had higher birth weights ( $3.90 \pm 0.81$  kg) when compared to IDM with normoglycemia ( $3.78 \pm 0.49$  kg), although this difference was not statistically significant (P-value = 0.07). As regard the echocardiographic finding, ventricular septal hypertrophy ( $\geq 6$  mm) were found in 21 (38.89%) IDM with hypoglycemia compared to 10 (34.48%) IDM with normoglycemia (P-value = 0.3).

### Blood glucose measurements

In the hypoglycemic group, the peak of hypoglycemia occurred at the first 3 h of life, with  $33.11 \pm 8.84$  mg/dl for the hypoglycemia group and  $54.10 \pm$  mg/dl for the normoglycemic group (P = 0.0001; Fig. 1). Furthermore, of a total 54 patients developing hypoglycemia, most of the babies had no hypoglycemic manifestation (96.30%), and only two patients had manifestation one, with lethargy and poor suckling (3.70%).

### Glycated hemoglobin (HbA1C) measurements

As shown in Fig. 2, there were a statistically significant difference between patients developing hypoglycemia and having mothers had poor diabetes control in the last trimester (HbA1C  $7.09 \pm 0.96\%$ ) compared to normoglycemic babies of mothers with good diabetes control (HbA1C  $6.11 \pm 0.38\%$ ), (P-value < 0.0001).

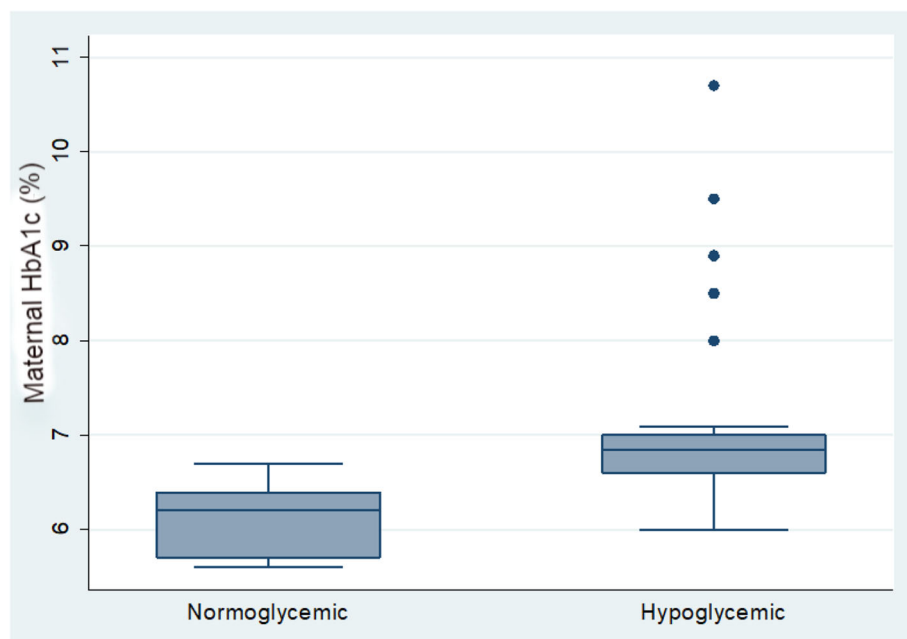
### C-peptide measurements

Moreover, as shown in Fig. 3, the mean (SD) of UC C-peptide in the case group was  $1.73 \pm 1.07$  ng/ml, ranging from 0.13 to 3.3 ng/ml, while in the control group, it was  $1.08 \pm 0.81$  ng/ml, ranging from 0.25 to 3.9 ng/ml; there was a statistically significant difference between the two studied groups (P value = 0.005).

## Discussion

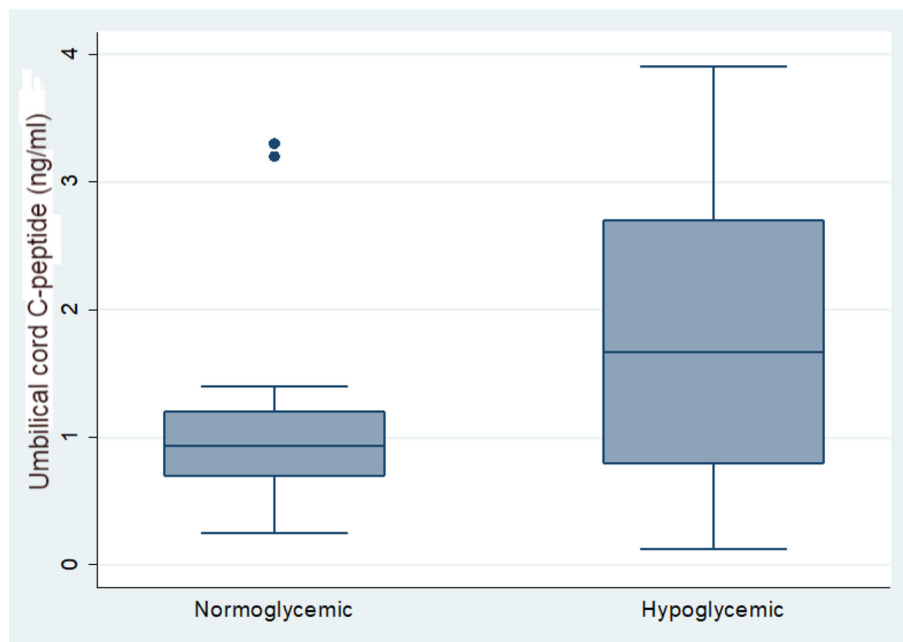
Our results show that poor diabetes control, especially in the last trimester, is associated with neonatal hypoglycemia. Furthermore, increased UC C-peptide levels could be used as an early indicator for risk of developing neonatal hypoglycemia and a predictor for babies need neonatal admission.

Major risk factors for developing GDM during pregnancy include increased maternal age, a family history of diabetes, a history of GDM in a previous pregnancy, a history of macrosomia in a previous pregnancy, and an increased pre-gravid body mass index.<sup>2</sup> In our study, 35 (42.17%) mothers had GDM, the mean  $\pm$  SD of maternal age was  $36.03 \pm 6.93$  years, and the mean  $\pm$  SD of maternal weight was  $77.76 \pm 8.60$  kg.



**Fig. 2** Comparison between normoglycemic and hypoglycemic infant according to maternal HbA1c





**Fig. 3** Comparison between normoglycemic and hypoglycemic IDM according serum level of umbilical cord C-peptide

In this study, at least one attack of hypoglycemia within the first 3 h of life developed in IDM in about 65.06% neonates. This is comparable to the findings of a study by Begum et al.,<sup>9</sup> in which the occurrence of hypoglycemia was 73.3% within the first 6 h of life, while in Agrawal et al.,<sup>10</sup> only 47% of the infants developed hypoglycemia during the first 2 h of life. In our study, of a total of 54 patients developing hypoglycemia, most cases were asymptomatic hypoglycemia (96.30%), which is in agreement with the findings of previous studies. For example, in a study by Begum et al.,<sup>9</sup> about 93.3% of the hypoglycemic babies were asymptomatic, while in Agrawal et al.<sup>10</sup> and Van Howe et al.,<sup>11</sup> 100% of the hypoglycemic babies were asymptomatic.

Hypoglycemia is the most common metabolic disorder reported in full-term and preterm infants. The definition of hypoglycemia as well as its clinical significance and optimal time at management remain controversial.<sup>12</sup> Previously, asymptomatic hypoglycemia has been considered to be of no clinical significance.<sup>13</sup> However, numerous studies have demonstrated that even asymptomatic hypoglycemia can have a poor neurodevelopmental outcome immediately after birth<sup>14</sup> and even later on up to school age.<sup>15</sup> Therefore, early detection and management of even asymptomatic hypoglycemia are critically important.

In our study, the demographic characteristics of the mothers were similar in hypoglycemic and normoglycemic groups, such as maternal age, maternal weight, and type and duration of diabetes, with similar results when compared to Begum et al.<sup>9</sup> In contrast, Agarwal et al.<sup>10</sup> who found that IDMs with hypoglycemia had significantly longer durations of maternal diabetes. In our study, infants with hypoglycemia had higher birth weights than normoglycemic babies, although this difference was not statistically significant. This is in agreement with Dawid et al.,<sup>16</sup> who found neither a correlation between birth weight and maternal fructosamine level nor between birth weight and maternal HbA1C level. In contrast, Metzger et al.<sup>17</sup> and Cooper et al.<sup>18</sup> found that infants with a higher birth weight were more likely to develop hypoglycemia and hyperinsulinemia

than the control group with a normal birth weight, suggesting physiologic relationships between maternal hyperglycemia and fetal insulin production.

We observed a statistically significant difference between infants developing hypoglycemia and having mothers with poor diabetes control in the last trimester and normoglycemic babies. This finding is in agreement with Griffiths et al.<sup>19</sup> and Fallucca et al.,<sup>20</sup> who observed a correlation between infant hypoglycemia and poor maternal diabetes control. Poor diabetes control in our cases group mainly related to poor patients compliance and/or resistance against treatment due to lack of regular ant-natal visits as most cases came to our tertiary hospital referred from primary hospitals just before delivery. In contrast, other researchers found that even in well-controlled diabetic mothers, the incidence of early hypoglycemia in infants is still high, particularly in those mothers who

had a longer duration of diabetes.<sup>10,16,21</sup> Even for some other IDM complications, we found no correlation between the presence of ventricular septal hypertrophy in IDM either with hypoglycemia or normoglycemia cases. Other research by Vela-Huerta et al.,<sup>22</sup> found no correlation between the increased prevalence of asymmetric septal hypertrophy and the state of maternal diabetic control.

Furthermore, in this study, we found a statistically significant increase in UC C-peptide levels in infants who developed hypoglycemia when compared to the control group (P value = 0.005), suggesting that C-peptide can be used as an early predictor for hypoglycemia in IDMs. This finding is comparable with other studies reporting that cord C-peptide levels were inversely related to BG concentrations in the early postnatal period.<sup>9,17,18,20</sup> Furthermore, the increased UC C-peptide level may be associated with infant macrosomia<sup>17,23</sup> and neonatal septal hypertrophic cardiomyopathy.<sup>18</sup> Therefore hyperinsulinemia is the cornerstone in the development of many complication in IDM.<sup>24</sup> However, some patients in our case group showing hypoglycemic without elevation of C-Peptide, this points needed to be discussed in further research to study the relation of C-Peptide measurements and hypoglycemia severity.

In conclusion, poor diabetes control, especially in the last trimester, is associated with neonatal hypoglycemia. Furthermore, increased UC C-peptide levels could be used as an early indicator for risk of developing neonatal hypoglycemia and a predictor for babies need neonatal admission. However, further studies with larger sample sizes are needed to determine the cost effectiveness of this relatively costly test before it can be used routinely in daily care practice.

### Abbreviations

BG: Blood glucose; DM: Diabetes mellitus; GMD: Gestational diabetes mellitus; HbA1C: Glycated hemoglobin; IDM: Infants of diabetic mothers; NICU: Neonatal intensive care unit; PROM: Premature rupture of membranes; UC: Umbilical cord

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## Authors' contributions

AMS, RAM are responsible for the study design, collection and interpretation of the data, manuscript writing. MAM study design, maternal data collection, participated drafting the manuscript. RAM, MAM performed statistical analysis, AAS responsible for study design, revised the manuscript. All authors reviewed and approved the final manuscript for publication.

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## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Ethics approval and consent to participate

The research related to human subject use complied with all the relevant national regulations and institutional policies. Local ethical approval for the study was obtained from the Research Committee of the Faculty of Medicine at Sohag University, Egypt (No. 321, 2018). Written informed consent was obtained from all parents of the children.

## Consent for publication

The authors declare that they have obtained the consent for publication from each parent's patient.

## Competing interests

The authors declare that they have no competing interests.

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