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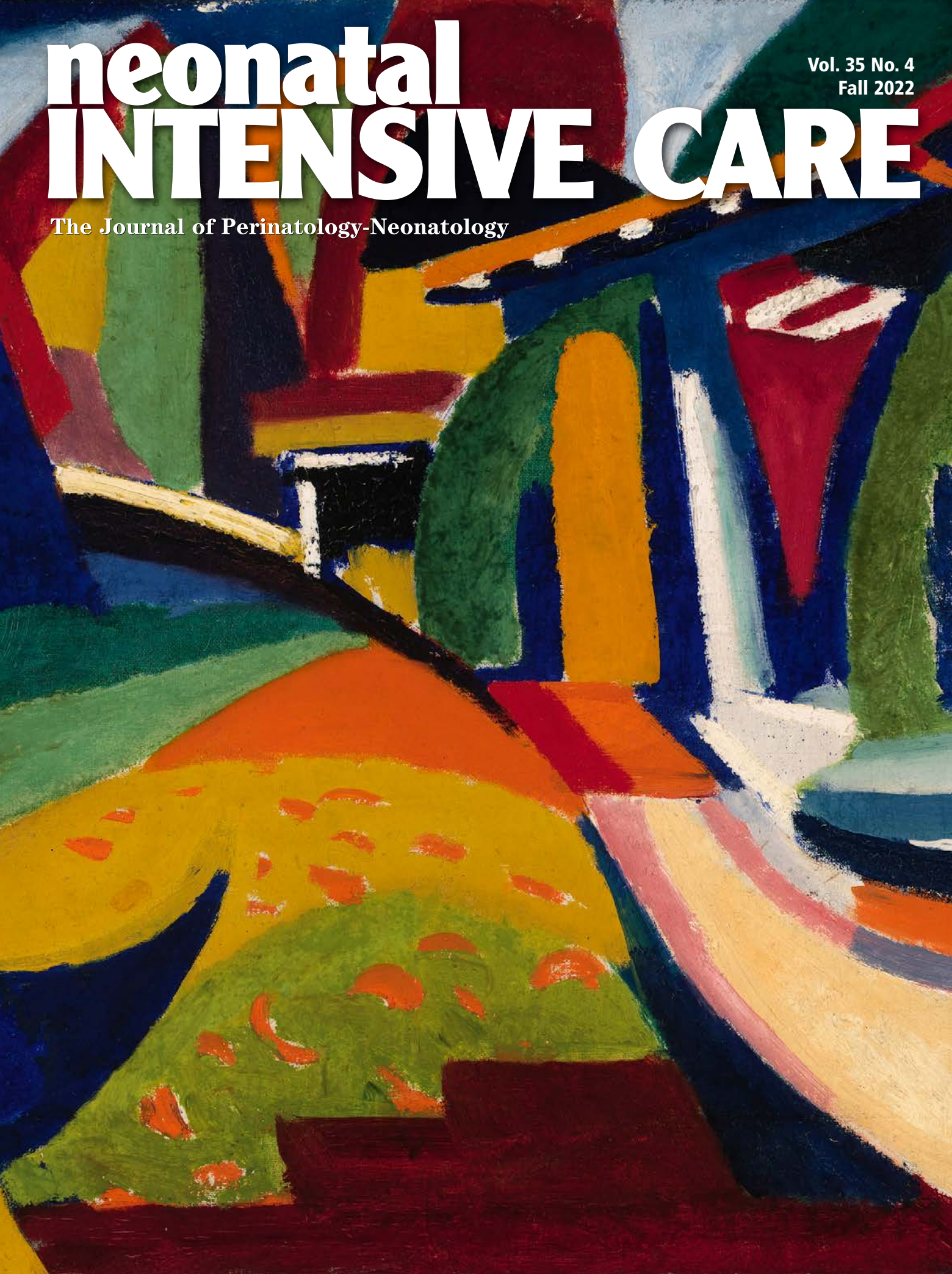

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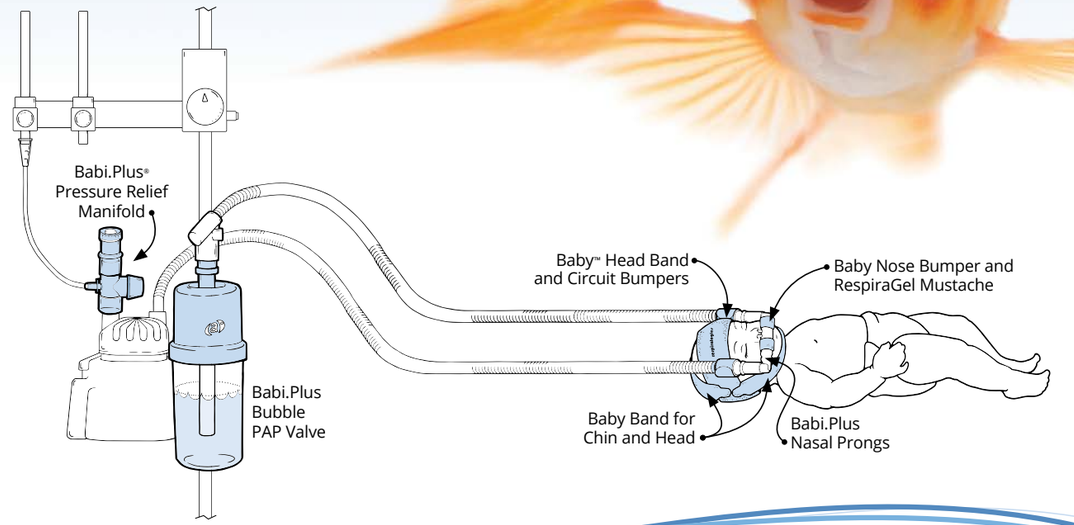

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Partnership to Enhance Neonatal Intensive Care Clinical Workflows and Patient Outcomes

Etiometry, a leader in clinical decision-support software for critical care, and Radiometer, a leading medical device company specializing in acute care testing solutions, announced a new collaboration to enhance the clinical workflows in Neonatal Intensive Care Units (NICU). The partnership pairs Etiometry's platform to create a holistic view of the patient's clinical picture empowering rapid, informed decision-making with Radiometer's Transcutaneous Monitoring (TCM) solution, focused on monitoring ventilation of neonatal patients. Integrating the Etiometry platform with Radiometer's real-time Transcutaneous Monitoring solutions will allow clinicians across the care continuum to view carbon dioxide trends with other physiologic parameters consolidated on one screen to streamline patient care management. The data will also help fuel clinical research activities by Etiometry and Radiometer aimed to demonstrate the minimization of ventilation times and improve extubation failure rates, with the goal to help reduce the time a patient needs to spend in the NICU as well as the associated costs of long NICU stays. The first phase of the partnership will validate proof of concept. "The care that neonates receive in the first hours and days of their life can have a significant impact on their quality of life," said Henrik Schimmell, President and CEO of Radiometer. "Supporting caregivers in making well-informed treatment decisions is therefore crucial, and this partnership with Etiometry has the potential to make it easier for clinicians to provide the right treatment at the right time." Etiometry's platform enables hospitals to embed their specific clinical protocols and workflows into the software, automatically screening all patients for eligibility and tracking performance once a protocol is initiated. Incorporating Radiometer's transcutaneous monitoring data into the Etiometry platform can further reduce the burden of manual protocol management. "Etiometry brings deep expertise in managing data analytics with our Clinical Decision Support platform that modernizes clinical workflow management and associated patient care activities through its customizable Clinical Management Application," said Shane Cooke, CEO of Etiometry. "This partnership with Radiometer propels our ability to serve our customers with the essential patient data they need to make informed care decisions."

In Utero COVID Exposure Tied to Neurodevelopmental Disorders at 1 Year

Infants exposed to SARS-CoV-2 in utero are at increased risk for neurodevelopmental disorders in the first year of life, new research suggests. But whether it is exposure to the pandemic or maternal exposure to the virus itself that may harm early childhood neurodevelopment is unclear, caution investigators, led by Roy Perlis, MD, MSc, with Massachusetts General Hospital, Boston. "In this analysis of 222 offspring of mothers infected with SARS-CoV-2, compared with the offspring of 7550 mothers in the control group (not infected) delivered during the same period, we observed neurodevelopmental diagnoses to be significantly more common among exposed offspring, particularly those exposed to third-trimester maternal infection," they write. The study included 7772 mostly singleton live births across six hospitals in Massachusetts between March and September 2020, including 222 (2.9%) births to mothers with SARS-CoV-2 infection confirmed by polymerase chain reaction testing during pregnancy. In all, 14 of 222 children born to SARS-CoV-2-infected mothers (6.3%) were diagnosed with a neurodevelopmental disorder in the first year of life vs 227 of 7550 unexposed offspring (3%) (unadjusted odds ratio [OR],

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Web: www.nicmag.ca

Publisher/Editor in Chief
Steve Goldstein

Managing Editor
Christopher Hiscox

Senior Editor
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2.17; 95% CI, 1.24 - 3.79; P = .006). In models adjusted for preterm delivery, as well as race, ethnicity, insurance status, child sex and maternal age, COVID-exposed offspring were significantly more likely to receive a neurodevelopmental diagnosis in the first year of life (adjusted OR, 1.86; 95% CI, 1.03 - 3.36; P = .04). The magnitude of the association with neurodevelopmental disorders was greater with third-trimester SARS-CoV-2 infection (adjusted OR, 2.34; 95% CI, 1.23 - 4.44; P = .01). The majority of these diagnoses reflected developmental disorders of motor function or speech and language.

The researchers note the finding of an association between prenatal SARS-CoV-2 exposure and neurodevelopmental diagnoses at 12 months are in line with a "large body of literature" linking maternal viral infection and maternal immune activation with offspring neurodevelopmental disorders later in life. They caution, however, that whether a definitive connection exists between prenatal SARS-CoV-2 exposure and adverse neurodevelopment in offspring is not yet known, in part because children born to women infected in the first wave of the pandemic haven't reached their second birthday—a time when neurodevelopment disorders such as autism are typically diagnosed. There is also the risk for ascertainment bias arising from greater concern for offspring of infected mothers who were ill during pregnancy. These parents may be more inclined to seek evaluation, and clinicians may be more inclined to diagnose or refer for evaluation, the researchers note.

Best Practices Award Honors Commitment to Neonatal/ Respiratory Care

Dräger, an international leader in the fields of medical and safety technology, announced that Frost & Sullivan has selected the company for its 2022 Global New Product Innovation Leadership Award in the categories of neonatal and respiratory care. Dräger was the recipient of Frost & Sullivan's Global Technology Innovation Leadership Award for mechanical ventilation in 2014, 2017, and 2020, which are consecutive evaluation periods in this specific category. It remains unmatched in achieving this level of recognition as a single company during this time-period. Frost & Sullivan's award criteria evaluate companies on their devices and the overall value they deliver to healthcare. Reflective of this year's award, Dräger's approach goes beyond its extensive expertise and best-in-class capabilities, with customer value as a strategic imperative. "Healthcare executives are looking for value beyond devices to support care delivery in the NICU and critical care environments," said President and CEO for Draeger, Inc., Lothar Thielen. "This award validates our approach of combining best-in-class products, cost-effective accessories, and service solutions that deliver unmatched value for our hospital customers." Frost & Sullivan applauded Dräger's focus on improving outcomes for a baby's neonatal intensive care unit (NICU) stay, highlighting the NICU by Dräger concept, which is designed to achieve this goal. Through this single, comprehensive solution, Dräger supports clinicians in delivering flexible, family-oriented, and patient-centric care, providing best-in-class neonatal ventilation and lung protection solutions, thermoregulation, jaundice phototherapy devices, and neonatal care accessories, along with expert NICU design and workflow consultancy. "Dräger's new and purpose-built solution suite for neonatal care sets it apart from its competitors, with superior design, reliability, and quality as its central pillars," the award text reads. In its research, Frost & Sullivan noted a key differentiator for the company; its commitment to supporting customers' paths toward clinical needs, "Unlike competitors, Dräger builds its products by collaborating closely with a range of stakeholders and partners to evolve alongside market needs and trends. It works with leading physicians leveraging its advisory board, product managers, and research and development team to interact with key opinion leaders around the globe to understand the actual customer and market demands." The award also honors Dräger's commitment to continuing education. Dräger's "A Breath Ahead" portal provides clinicians access to live and online continuing respiratory care education (CRCE) courses. Through its INSIGHTS program, Dräger shares ideas and innovations that can help hospitals achieve their goals by improving clinical outcomes, managing the cost of care, ensuring staff satisfaction, and enhancing the patient experience. "Dräger maximizes patient outcomes by improving safety, increasing the education level for clinicians, streamlining supply chain issues, and creating cost-effective and reliable biomedical solutions," said Bhaskar Vittal, industry principal for Frost & Sullivan. "Everything that makes a healthier hospital in terms of patients' safety, costs and outcomes for customers are the reasons driving Dräger's successful momentum and continuous development over decades."

Milk Allergy Frequently Overdiagnosed

Many infants in some countries are misdiagnosed with allergy to cow, sheep, or goat milk, and they're prescribed specialized formulas they don't need, according to a consensus study. "Milk allergy overdiagnosis is common in some regions and can potentially harm mothers and infants," the authors write in Clinical & Experimental Allergy. "These new consensus recommendations on the safe detection and management of milk allergy in children under 2 years aim to reduce harms associated with milk allergy overdiagnosis."

"This guidance, developed by experts without commercial ties to the formula industry, aims to reduce milk allergy overdiagnosis and [to] support…breastfeeding and less use of specialized formula, compared with current guidelines," they add. Up to 1% of European infants 2 years of age and younger are considered allergic to cow's milk. Prescriptions for specialized formula for bottle-fed infants allergic to cow's milk in Australia, England, and Norway have grown to over 10 times the expected volumes. Lead study author Hilary I. Allen, National Heart and Lung Institute, Imperial College London, United Kingdom, and her colleagues on several continents developed practical guidance for providers on safely detecting and managing milk allergy in infants. Due to lack of high-certainty research evidence in this area, they used the Delphi consensus method. The study involved two rounds of anonymous consensus-building surveys and one formal meeting in 2021. The team identified experts from diverse geographic and cultural settings by searching medical databases for the term "milk hypersensitivity." They asked those experts to recommend colleagues. The researchers also contacted experts with ties to international professional organizations, such as the International Board of Lactation Consultant Examiners, as well as societies associated with the World Allergy Organization.

PerkinElmer and Novartis Collaborate to Address the Unmet Need of Sickle Cell Disease in Sub-Saharan Africa

PerkinElmer Inc., a global leader committed to innovating for a healthier world, today announced that it is collaborating with Novartis, a leading global medicines company, to expand newborn screening for sickle cell disease (SCD) in sub-Saharan Africa. PerkinElmer together with the Novartis Africa Sickle Cell Disease program aims to expand advocacy efforts to educate patients, caregivers and communities about the importance of newborn screening and early intervention with hydroxyurea (HU) and other SCD treatments. Newborn screening for SCD and comprehensive disease management in high-income countries like the United States has reduced mortality in children under five years old by 94%[1]. Yet, in sub-Saharan Africa which bears the highest burden of the disease, no national newborn screening program exists. This collaboration aims to galvanize governments to provide universal newborn screening as part of national health programs in support of early diagnosis and comprehensive interventions such as prophylactic penicillin, a pneumococcal vaccination and therapies like HU. With effective screening and management of SCD, governments could save many precious lives. The Novartis Africa Sickle Cell Disease program was launched in Ghana in 2019 as an end-to-end effort that encompasses SCD screening, diagnosis, treatment, education, research and advocacy. Today this unique program has been expanded to Uganda, Tanzania, Kenya and Zambia, with plans to reach a total of 10 countries. Among its varied contributions to the program, PerkinElmer will work toward strengthening existing SCD programs by providing training, consultations, support and related services to health care professionals and lab technicians across participating countries in sub-Saharan Africa. The Company will also help establish new lab facilities to build capacity for SCD screening in participating countries. "As a global leader in newborn screening solutions we are pleased to be working with Novartis to assist people across sub-Saharan Africa affected by this condition," said Petra Furu, general manager, reproductive health at PerkinElmer. "By building awareness around the importance of newborn screening, our hope is that more babies receive an early diagnosis that leads to earlier treatment – ensuring they have the best possible chance of a healthy start to life." "This collaboration with PerkinElmer reaffirms our commitment to reimagining care for sickle cell disease patients, by accelerating access to national newborn screening and hydroxyurea through public-private partnerships with local governments and other organizations," said Racey Muchilwa, Country President and the Head of Novartis sub-Saharan Africa. "We will also be educating patients, caregivers and communities on the importance of newborn screening, early intervention and treatments while elevating the capacity for healthcare professionals to address the high unmet need of SCD." In an initiative announced in March 2021, PerkinElmer works alongside the American Society of Hematology and its Consortium on Newborn Screening in Africa (CONSA) to provide resources for SCD screening programs in countries throughout sub-Saharan Africa, including Ghana, Kenya, Nigeria, Uganda, Zambia, Liberia and Tanzania. Novartis announced its partnership with ASH in early June, which will advance ASH's CONSA objectives to demonstrate the benefits of newborn screening and early interventions for children with SCD and create a sustainable infrastructure for SCD newborn screening.

Vaccines in Pregnancy Reduce Infants' COVID-19 Risk

COVID-19 vaccination during pregnancy appears to lower newborns' risk of coronavirus infection, according to a study conducted in Norway. Norwegian researchers tracked 9,739 babies whose mothers received a second or third dose of a COVID-19 vaccine from Pfizer (PFE.N)/BioNTech (22UAy.DE) or Moderna (MRNA.O) while pregnant, and 11,904 babies whose mothers were not vaccinated before or during pregnancy. Overall, COVID infections were rare in the babies. But the risk of a positive COVID-19 PCR test during the first four months of life was 71% lower during the Delta era and 33% lower when Omicron was dominant for babies whose mothers got vaccinated during pregnancy compared with infants born to unvaccinated mothers, the researchers reported.

Pregnant Women With Monkeypox Advised to Have C-Section

Pregnant women with monkeypox will be advised to give birth by C-section to avoid infecting their baby during delivery, according to a new paper in Ultrasound in Obstetrics & Gynecology. The risk of monkeypox infection remains low for the general public, the authors wrote, though cases continue to grow worldwide, particularly in the UK. "We are aware infants and children are at greater risk of becoming seriously ill if they do catch monkeypox," Edward Morris, one of the authors and president of the Royal College of Obstetricians and Gynecologists, said in a statement. "Therefore, to minimize the risk of a baby contracting the virus, we recommend healthcare professionals discuss the benefits and risks of having a caesarean birth with a pregnant women or person who has or is suspected of having the virus," he said. Morris and colleagues pulled together existing evidence on monkeypox diagnosis, treatment, and recommended modes of birth for mothers and babies. "The World Health Organization states there could be adverse consequences for pregnant women and babies if they become infected, including congenital monkeypox, miscarriage, or stillbirth, which is why we have provided clear guidance for healthcare professionals in this paper," Morris said. The monkeypox virus typically spreads through direct contact, droplets, or contaminated surfaces and objects. But some limited evidence shows that the virus can be passed from a mother to a baby via the placenta, which can lead to congenital monkeypox.

Prolacta Bioscience Introduces Its First Evidence-Based Feeding Protocol for an Exclusive Human Milk Diet in the NICU

Prolacta Bioscience, the world's leading hospital provider of 100% human milk-based nutritional products for critically ill, premature infants, today announced the introduction of the first evidence-based feeding protocol for the use of an Exclusive Human Milk Diet including Prolacta's products (Prolacta's EHMD) in the neonatal intensive care unit (NICU). Prolacta's EHMD Protocol addresses the nutritional risks of late and inadequate nutrition facing low birth weight premature infants and is the first nutritional guidance issued for the use of the company's human milk-based nutritional products. Developed in conjunction with independent clinicians, registered dieticians, nurses, and neonatologists, Prolacta's EHMD Protocol is backed by 15 years of clinical experience and more than 20 clinical studies. The protocol presents additional perspective on the standard of care in NICUs that can help premature infants avoid complications and reach key growth goals. "This protocol provides best-practice guidance to members of the NICU team as we tailor nutrition to each infant's needs and risk factors," said Rangasamy Ramanathan, MD, professor of pediatrics, division chief, Division of Neonatal Medicine, LAC+USC Medical Center. "A standardized feeding approach for an EHMD with human milk-based products helps eliminate the uncertainty in meeting infants' protein goals to achieve adequate growth with fewer complications." Prolacta's EHMD Protocol supports clinicians in delivering the optimal nutrients to fragile infants at the optimal time — helping as they work to achieve better health outcomes lower hospital costs, and significantly reduce the risk of complications and feeding intolerance associated with cow milk-based fortifiers. Over the past 15 years, more than 20 clinical studies involving more than 5,000 premature infants have shown that hospitals with the best outcomes followed similar feeding practices with the use of Prolacta's fortifiers.1 Inversely, it is proven that delayed fortification leads to less-optimal results in critically ill, premature infants. An EHMD is achieved when 100% of the protein, fat, and carbohydrate in an infant's diet are derived from human milk. An EHMD with Prolacta's 100% human milk-based fortifiers, compared with the use of cow milk-based fortifiers or formula, is known to reduce the risk of severe complications and feeding intolerance in preterm infants. For years, the risks associated with cow milk-based fortifiers left healthcare professionals in the NICU cautious about starting fortification too early. With Prolacta's EHMD Protocol, clinicians can safely begin fortification as early as the first week of an infant's life, confident that issues such as feeding intolerance and other complications have been shown to be significantly reduced. "Prolacta's EHMD Protocol can reduce the incidence of comorbidities, support adequate growth, and improve mortality rates, offering groundbreaking benefits for this fragile patient population," said Melinda Elliott, MD, FAAP, and chief medical officer at Prolacta. "Even the most vulnerable infants born weighing less than 750 g have been shown to greatly benefit from an EHMD, giving them the best chance for a healthy, bright future." To help meet each patient's unique needs, Prolacta's EHMD Protocol is designed to provide flexible feeding advancement based on each premature infant's weight, clinical status, and health risk factors. Prolacta's EHMD Protocol supports adequate growth with fewer complications as measured by increases in length, head circumference, and weight. These gains lower the risk of long-term metabolic morbidities including obesity, diabetes, and cardiovascular disease. Research has shown that Prolacta's fortifiers, when used as part of an EHMD, support healthy body composition with improvements in lean body mass, normal total body fat, and adequate bone mineralization. Furthermore, for premature infants fed an EHMD, the benefits of appropriate nutrition extend to long-term neurocognitive development.

New Tool May Identify Pregnant Women With Eating Disorders

A new screening tool may help clinicians identify pregnant women with eating disorders. The 12-question instrument is intended to be a quick way to help clinicians identify women who may may need to be referred to a mental health expert for further evaluation, according to the researchers, who reported on the instrument in a study published in Archives of Women's Mental Health. "It would be most appropriate for clinical encounters so that women can get screened and referred," said Elizabeth Claydon, MD, assistant professor in the Department of Social and Behavioral Sciences at West Virginia University's School of Public Health, in Morgantown, who led the study. "If you miss it, they may carry on their eating disorder throughout their pregnancy." Pregnant women who have an eating disorder are at increased risk for gestational diabetes, premature birth, labor complications, difficulties nursing, and postpartum depression, according to the National Eating Disorders Association. Their babies are at increased risk for premature birth, low birth weight, and poor development. However, clinicians have not had an accurate way of screening pregnant women who may have an eating disorder. The American College of Obstetricians and Gynecologists offered its first clinical guidelines for managing anorexia in pregnancy in April 2022. The group's recommendations include regular monitoring of cardiac and liver function, blood pressure, and heart rate, as well as tests to monitor iron, sodium, potassium, bone density, and blood sugar levels. Anorexia, bulimia, binge eating, and subthreshold disorders — also known as other specified feeding or eating disorder — are among the most common eating disorders among

pregnant women. There are no recent data on the incidence or prevalence of eating disorders among pregnant women, according to Lauren Smolar, vice president of mission and education at the National Eating Disorders Association. "It's hard to capture the number of pregnant women affected, since it so often goes undetected," Smolar said. Existing screening tools for eating disorders ask patients whether they're currently pregnant; a questionnaire specifically tailored to pregnant women may help to better gather data on the prevalence within this group, Smolar said. For the new study, Claydon and her colleagues tested the questionnaire among more than 400 mostly White women aged 25–34 years. They found that it could reliably identify women who may have an eating disorder. The questionnaire was validated for women to take during any trimester, according to the findings. A score of 39 or above would serve as an indicator for follow-up. Women who score at least 39 were up to 16 times more likely to receive a diagnosis of an eating disorder compared to women who scored less, the researchers found.

Births Rise for First Time Since 2014

More than 3 million live births occurred in the United States in 2021, the largest increase in the nation's birth rate since 2014, according to the US Centers for Disease Control and Prevention (CDC). Provisional data showed a 1% uptick in births, to 3.66 million, after 6 years of dropping by approximately 2% per year. The gains were concentrated among birthing people ages 25 and older. Teenage births, on the other hand, are at their lowest level since the 1990s, according to the CDC. The agency reported a record 6% decrease in births for teenagers aged 15 to 19 years between 2020 and 2021. Women ages 20 to 25 years also had a record decrease in births of 4% during that period.

Brady E. Hamilton, PhD, of the CDC's National Center for Health Statistics, and the lead author of the new report, said the rise in births points to childbearing that was postponed during the pandemic. Data from 2021 showed a 4% drop in the nation's birth rate between 2019 and 2020. "The option to forgo birth is not always viable for older women, but you saw a lot of that during the pandemic," Hamilton said. "Events happened related to job security and the economy that caused people to wait to have a child." Hamilton said more data are needed to determine the full impact of increased overall birth rates on individuals. The final report, which will be released in July, will delve deeper into the influence increased birth rates had on demographics and preterm births, which Hamilton and his team found have increased by 4%.

Food Allergy Risk Not Greater in C-Section Infants

Cesarean births are not likely linked to an elevated risk of food allergy during the first year of life, an Australian study found. Published online in the Journal of Allergy and Clinical Immunology, the findings may help assess the risks and benefits of cesarean delivery and reassure women who require it that their babies are not more likely to develop food allergy, according to Rachel L. Peters, PhD, an epidemiologist at the Murdoch Child Research Institute (MCRI) in Melbourne, and colleagues. Peters' group undertook the analysis to clarify a possible association between mode of delivery and food allergy risk, which has remained unclear owing to the absence of studies with both challenge-proven food allergy outcomes and detailed information on the type and timing of cesarean delivery. "The infant immune system undergoes rapid development during the neonatal period," Peters said in an MCRI press release, and the mode of delivery may interfere with the normal development of the immune system. "Babies born by cesarean have less exposure to the bacteria from the mother's gut and vagina, which influence the composition of the baby's microbiome and immune system development. However, this doesn't appear to play a major role in the development of food allergy," she said. In the period 2007-2011, the longitudinal population-based HealthNuts cohort study enrolled 5,276 12-month-olds who underwent skin prick testing and oral food challenge for sensitization to egg, peanut, sesame, and either shellfish or cow's milk. It linked the resulting data to additional birth statistics from the Victorian Perinatal Data Collection when children turned 6. Birth data were obtained on 2,045 babies, and in this subgroup with linked data, 30% were born by cesarean – similar to the 31.7% of U.S. cesarean births in 2019 – and 12.7% of these had food allergy versus 13.2% of those delivered vaginally. Compared with vaginal birth, C-section was not associated with the risk of food allergy (adjusted odds ratio [aOR] 0.95, 95% confidence interval [CI], 0.70-0.30). Nor did the timing of the C-section have an effect. Cesarean delivery either before labor or after onset of labor was not associated with the risk of food allergy (aOR, 0.83, 95% CI, 0.55-1.23) and aOR, 1.13, 95% CI, 0.75-1.72), respectively. Compared with vaginal delivery, elective or emergency cesarean was not associated with food allergy risk (aOR, 1.05, 95% CI, 0.71-1.55, and aOR, 0.86, 95% CI, 0.56-1.31).

The Tiniest Babies: Survival Rates on the Rise

Growing numbers of extremely premature infants are getting lifesaving treatment and surviving. A pivotal study in the Journal of the American Medical Association this year, which looked at nearly 11,000 such births in a neonatal research network that is part of the National Institutes of Health, found that 30% of babies born at 22 weeks, 56% born at 23 weeks and 71% born at 24 weeks lived at least until they were healthy enough to be sent home if doctors tried to save them. Those gains happened gradually and quietly as the notion of viability got a lot more attention in the abortion arena. Viability is mentioned 36 times in the initial draft of the leaked majority opinion by the U.S. Supreme Court in a Mississippi case that would strike down Roe v. Wade. The decades-old abortion ruling says the Constitution protects a woman's right to an abortion before viability, a standard Mississippi argues is arbitrary. But viability has nothing to do with the vast majority of abortions; more than 99% of abortions occur at or before 21 weeks, according to federal statistics.

So although viability is central to abortion law, the crux of the argument around the procedure comes down to disagreement about whether and in which cases someone should have the choice to terminate a pregnancy. Meanwhile, viability is a growing real concern for those who care for premature babies as science keeps moving the line lower and lower.

Maternal Autoimmune Diseases Up Risk of Mental Illness in Children

Mental disorders were significantly more likely in children whose mothers had one of five common autoimmune diseases, a new study found. Previous research has linked both maternal and paternal autoimmune diseases and specific mental disorders, such as attention-deficit/hyperactivity disorder (ADHD), but most of these studies focused on specific conditions in relatively small populations. The new study included data on more than 2 million births, making it one of the largest efforts to date to examine the association, according to the researchers, whose findings were published in JAMA Network Open. Previous evidence of the possible association between certain maternal autoimmune diseases and mental disorders in offspring has been "scattered and limited," which "hampered an overall understanding" of the link, Fei Li, MD, the corresponding author of the study, said. Li, of Shanghai Jiao Tong University School of Medicine, in China, and her colleagues reviewed data from a Danish registry cohort of singleton births with up to 38 years of follow-up. They explored associations between a range of maternal autoimmune diseases diagnosed before childbirth and the risks of mental disorders in children in early childhood through young adulthood. The study population included 2,254,234 births and 38,916,359 person-years. Data on mental health were collected from the Psychiatric Central Research Register and the country's National Patient Register. The median age of the children at the time of assessment was 16.7 years; approximately half were male. A total of 50,863 children (2.26%) were born to mothers who had been diagnosed with autoimmune diseases before childbirth. During the follow-up period, 5460 children of mothers with autoimmune diseases and 303,092 children of mothers without autoimmune diseases were diagnosed with a mental disorder (10.73% vs 13.76%), according to the researchers. The risk of being diagnosed with a mental disorder was significantly higher among children of mothers with any autoimmune disease (hazard ratio [HR], 1.16), with an incidence of 9.38 vs 7.91 per 1000 person-years, the researchers report. The increased risk persisted when the results were classified by organ system, including connective tissue (HR, 1.11), endocrine (HR, 1.19), gastrointestinal (HR, 1.11), blood (HR, 1.10), nervous (HR, 1.17), and skin (HR, 1.19). The five autoimmune diseases in mothers that were most commonly associated mental health disorders in children were type 1 diabetes, rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, and psoriasis vulgaris. The greatest risk for children of mothers with any autoimmune

Continued on page 18…

Future of Nasal Ventilation in Preterm Infants

Shabih Manzar, MD

Nasal ventilation in preterm infants has been shown to decrease the re-intubation rates.[1-3] Ali et al[1] described the feasibility of nasal high-frequency oscillatory ventilation (NHFOV) as a prophylactic or rescue mode of non-invasive ventilation (NIV) following extubation. They reported fewer apneas without significant changes in PCO_2 or oxygen requirements with the use of NHFOV.

Recent reports have shown the promising result of neurally adjusted ventilatory assist (NAVA) as a NIV mode in preterm infants.[2,3] Benn et al[2] showed an improvement in the growth trajectory with the use of NAVA ventilation in premature infants. Piątek et al[3] studied the implementation of NAVA and its effects on pulmonary and central nervous system outcomes. By comparing pre-implementation and postimplementation cohorts, they showed an improvement in brain MRI findings and cognitive outcomes with the use of NAVA.

Image supplied

As both modes, NHFOV and NAVA, have shown to be superior to nasal cannula and continuous positive airway pressure, it would be interesting to see future trials comparing these two modes of NIV in preterm infants.

Abbreviation

NHFOV-nasal high-frequency oscillatory ventilation
NIV-non-invasive ventilation
NAVA- neurally adjusted ventilatory assist

Shabih Manzar, MD, Section of Neonatal-Perinatal Medicine, Ochsner LSU St Mary Medical Center, Shreveport, LA. Correspondence: Shabih Manzar, MD, Ochsner LSU St Mary Medical Center, St Mary Place. Shreveport, LA, 71101. Phone: 318-626-1623. Fax: 318-675-6059. Email: shabih.manzar@lsuhs.edu. Conflict of interest: None. Financial Disclosures: I have no financial disclosure.

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What To Expect When You're Not Expecting?

BM Petrikovsky, MD, PhD

Introduction

Unwanted pregnancies may result from:

1) Not using birth control (BC)
2) Inappropriate use of BC
3) Failed BC
4) Assumption that pregnancy is not possible (An example would be perimenopause)
5) Rape
6) Miscellaneous

Medical literature which addresses this topic is complicated and confusing because it attempts to explain the medical, political, financial, and socio-economical aspects of unwanted pregnancies. The rate of unintended pregnancies is around 40%.[1] Over the last decade, the prevalence of unintended pregnancy ranged from 15% to 58% in North Africa and the Middle East: 58% in Yemen, 38% in Palestine, 32% in Morocco, 31% in Syria and Algeria, and 23% in Egypt.[2] Unintended pregnancy is known to be associated with multiple complications, including poor prenatal care, preterm deliveries, substance abuse, smoking, and low birth weight, among others.[3,4] The psychological impact of an unwanted pregnancy on the mother and the family, as a whole, cannot be underestimated. It has been reported that an unwanted pregnancy is associated with an increased risk of postpartum depression, divorce, alcohol, and substance abuse.[5-7]

Material and Methods

We conducted a retrospective study on the outcomes of unintended pregnancies based on validated questionnaires and a review of medical records. The questionnaire had three sections:

A. Possible cause of unintended pregnancy
B. Maternal compliance with prenatal care and attitude towards unintended pregnancy
C. Basic pregnancy outcomes:
   1. Major complications of pregnancy
   2. Gestational age of delivery
   3. Method of delivery
   4. Apgar score and weight of newborns

Statistical analysis was performed using the SPSS software (Version 16.0. Chicago, SPSS Inc.). Univariate and multivariate logistic regression were used to detect the determinants of unintended pregnancies. Patients with desired pregnancies were used as the reference group in the logistic regression analysis.

Results

A total of 135 women who declared their pregnancy unwanted were included in this study. 128 participants fully responded to at least 70% of the questions. 135 patients who announced a desired pregnancy served as a control group. The prevalence of unwanted pregnancies was significantly higher in women over 40 years old (44.2%) or younger than 20 years old, women with 3 or more living children (36.4%), and women within 48 months of a living birth and breastfeeding. Thirty six out of 128 patients blamed failed BC for the unintended pregnancy, 12 were relying on breastfeeding as the only form of birth control, and 8 assumed they were menopausal.

The average number of prenatal visits were also lower in the study group compared to the controls (3.4 vs 7.2, $p<0.05$) with a delayed first visit in 16% of patients with a declared unwanted pregnancy. Retrospective chart review failed to detect any significant differences in pregnancy complications in both groups: preeclampsia was detected in 6.4% in the study group versus 4.3% in control, diabetes in 6.4% versus 5.3% respectively. Mean gestational age at delivery was 37 ±2.9 weeks in the study group and 38 ±6.1 in control. The rate of cesarean delivery was 37% in the study group and 41.6% in the control group. Over 25% of patients, in both groups, have had multiple cesarean sections. The mean Apgar score was 8 ±2 in the study group versus 7 ±2 in the control group. One stillbirth was detected in the study group. Most importantly, the average weight of the newborns was 3412 ±412g in the study group and 3608 ±611g in the control group (not statistically significant).

Comment

Unwanted pregnancy has numerous causes which complicate its definition, outcome analysis, socio-economic, and psychological impacts. These pregnancies are often defined as mistimed, unwanted, or unintended. One can't be sure that each of these definitions have similar significance. Our study concentrated on cases where women, despite not wanting their pregnancies, chose to continue until delivery. Our patient population largely consisted of middle-class women in the suburbs, Long Island and Brooklyn. This patient population is significantly different from one in third world countries.[8-10] Green Foster, et al,[11] studied the effects of an unwanted pregnancy on a woman's attitude and her existing children and concluded that negative or ambivalent feelings towards a pregnancy may change over the course of pregnancy and after childbirth. These authors stated that many studies of unintended pregnancy use retrospective design that are likely to lead to misclassification of an "unintended" pregnancy. Their study has overcome these challenges to detect an effect on existing children. This study shows that the effect of a birth following an unwanted pregnancy may not just affect the child born from that pregnancy, but there may also be negative effects on existing children. These findings support the legitimacy of women's concerns about the effect of carrying an unwanted pregnancy on the well-being of their existing children. Our study failed to detect any significant effect of unwanted pregnancy on its outcome, including, but not limited to the rate of prematurity, the incidence of preeclampsia and diabetes among others. These findings may reflect the demographics of our population and may not be applicable to other groups.

The limitation of the study is its retrospective nature and its reliance on the patient's response to the questionnaires.

Many important aspects of unwanted pregnancies (i.e., postpartum depression) were beyond the scope of our study. Significant findings included incomplete prenatal care as evidenced by a late first prenatal visit and decreased number of follow-up visits. Failed or non-existent contraception was the main cause of unwanted pregnancy. An unwanted pregnancy is more likely in very young women or ones approaching menopause.

BM Petrikovsky is a Director at the Prenatal Diagnostic Unit Services, New York Downtown Hospital, New York, NY. The author expresses gratitude to V. Gardner, PA, Garden OB/GYN for valuable editorial comments.

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Aerodigestive Changes and Considerations in the Neonate: a Three-Part Series

Part Two: Oral Feeding Trials, Protocols, and Troubleshooting in the Neonatal Intensive Care Unit (NICU)

Catherine S Shaker, MS/CCC-SLP, BCS-S

This article is the second in a three-part series addressing potential aerodigestive changes and considerations for preterm and sick-term infants in the neonatal intensive care unit (NICU). The first article addressed considerations related to extubation, high-flow nasal cannula, and pre-feeding skills. The prevalence of aerodigestive challenges leading to feeding and swallowing difficulties is high for sick-term and preterm infants in the NICU.[1,2] This article addresses feeding trials, protocols, and troubleshooting. Problem-solving critical decisions about developmental expectations and cautious opportunities to feed are essential to optimizing feeding outcomes after the NICU.[3] Some of the considerations for oral feeding trials, multidisciplinary approaches, and troubleshooting changes in breath sounds are discussed below as Catherine Shaker responds to frequently asked questions.

Using a Passy-Muir Valve to restore airflow to the upper airway and improve pressures for swallowing. Photo supplied.

In our NICU, there is the idea that oral feeding trials need to happen within a feeding "window" or there could be longer-term feeding issues. Any thoughts for or against this "window"? Or do we know the origin of this idea?
My conversations with neonatologists over the years suggest this paradigm is based on writings from Gesell back in the 1960s, who described a "critical window" for infants to learn to eat. At that time, NICUs were just being developed; there were no therapists as part of the neonatal team since the need for therapy support was not well understood. Many neonates did not survive, and those who did survive often had enduring developmental impairments.

Back then, NICU infants were not orally fed until term adjusted age or beyond (i.e., 40+ weeks) due to complex medical issues precluding oral feeding. Historically, during their typically prolonged hospitalization back then, neonates did not have developmental support to avert maladaptive sensory, sensory-motor, and oral-motor patterns that often evolved. Feeding techniques to "transfer volume" were common. Follow-up community Early Intervention, which today is available community-wide and immediately post-NICU discharge, was not established back then. NICU graduates and children with developmental needs often could not access therapy until 3-4 years of age and, by then, presented with longstanding feeding impairments and complex maladaptive behaviors. Parents, after discharge, had done the best they could without guidance from skilled therapists. "Not missing a window" by starting oral feeding by an arbitrary age became the "solution." That was then. This is now. Actually, the solution is providing the *right kind of feeding intervention when the infant shows readiness*.

Today, with the advent of neonatal interdisciplinary teams that include physical therapy (PT), occupational therapy (OT), and speech-language pathology (SLP), we can support readiness by *maintaining and developing* those systems for future oral feeding when co-morbidities safely permit. "Readiness" to orally feed is best determined, not based on an arbitrary date or age, but rather on clinical signs and behaviors in the context of that unique infant's gestational age (age at birth), history and co-morbidities. That can set the stage for success, by recognizing safety issues inherent with some co-morbidities and clinical presentations that should suggest caution. Parents can then learn that positive learning versus volume supports long-term success.[4]

Does the team ask them to orally feed to not "miss a critical window"? Or does the team maintain the neonate's readiness with therapy support, to optimize safety and neuroprotection, by individualizing readiness? The fact that NICU infants "eat" and "are fed" and "transferred volume" does not equate to safe or neuroprotective feeding.[5]

Can you share your feeding protocol for infants in the NICU requiring long-term ventilation via tracheostomy?
I don't follow a strict protocol as much as scaffolding – peel the layers as I go along and learn from the neonate, combining that with history and co-morbidities, asking more questions, and collaborating.

It is uncommon for a neonate in the NICU requiring long-term ventilation to be discharged as a full safe oral feeder, given typical complex co-morbidities. These indeed are often our most fragile NICU infants. Start with understanding that infant's unique co-morbidities that led to the need for long-term ventilation, such as persistent pulmonary hypertension, chronic lung disease, central hypoventilation, ventilatory muscle weakness, neuromuscular disorders, and/or lower airway obstruction, such as bronchomalacia or tracheomalacia.[6-7] They create an even higher risk for the infant to safely tolerate oral feeding.[8-9]

Multiple additional factors that should be considered include level and mode of respiratory support in the setting of that neonate's respiratory history, the prerequisite neuromotor and oral-motor integrity, ability to swallow saliva, oral-sensory processing, non-nutritive sucking, as well as physiologic stability during interventions utilized to support these prerequisites, and whether they are emerging. Once these prerequisites are established, I would likely be considering appropriateness of, and tolerance for, the PMV to establish flow into the upper airway. Restoring this airflow promotes restoration of taste, smell, and subglottic pressure, which most optimally underpins swallowing; at this juncture, the process includes working closely with the neonatologist, ENT, pulmonologist, and the RT.

For those infants with readiness skills, and who are appropriate for and tolerate an in-line PMV (with MD approval), the next steps may include using the PMV in-line while providing pacifier dips, followed by very limited trace oral feeding experiences with the therapist using interventions (developmentally-supportive positioning, a slow flow nipple, co-regulated pacing, and resting). Brief, cautious, interval motor learning is likely important to reduce artifacts in radiology. Ideally, an NICU infant's first oral feeding should not be in radiology. However, this must be carefully and cautiously balanced with that infant's risk for, and ability to tolerate, airway invasion, especially from a pulmonary perspective.

In radiology, I have seen improved swallowing physiology with the Passy-Muir Valve (PMV) in place for these complex neonates. When a tolerated PMV restores the fundamental underpinnings for swallowing, we see improved physiology for suck-swallow-breathe coordination.

We have an infant in our NICU who presents with a high-pitched sound on inhalation and congested/loud breathing on exhalation. What might be the reason?
Stridor may be iatrogenic (caused by post-extubation, post-ECMO; post PDA ligation or repair to the aortic arch; post-emergent, prolonged, or repeated intubation; or due to resulting subglottic stenosis, for example), or it may be congenital (related to a vascular ring, idiopathic occurrence at birth without explanation, laryngomalacia, pharyngomalacia, and tracheomalacia).[10] Sounds like you are describing inspiratory stridor. Inspiratory stridor can have varying etiologies, such as Extra Esophageal Reflux (EER) or Laryngopharyngeal Reflux (LPR), laryngomalacia, pharyngomalacia, or other alterations that may affect airway patency. With dynamic sucking, swallowing, and breathing, it is not uncommon for the underlying etiologies to increase risk for airway invasion during oral feeding.[11]

Stridor heard at rest may suggest a primary airway pathology and may be exacerbated with the aerobic demands of feeding, both at breast and bottle. Contrast that with stridor that occurs only during feeding, which may suggest either swallow-breathe incoordination, due to the tendency to inhale after the swallow, or perhaps attempts at airway closure in a protective maneuver due to bolus misdirection from above and/or below.[12]

Of course, as therapists, we do not diagnose airway problems. Describing what is heard, in the setting of that neonate's unique history and comorbidities, may assist the neonatologist and ENT (otolaryngologist) with their differential. It also helps the therapist consider the "whys" that may underlie the feeding and swallowing challenges that are observed.

In my experience with stridor, a clinical swallowing evaluation followed by an ENT consult and flexible scope at bedside can guide us to etiology and reinforce the benefits of a video-swallow study to objectify swallowing physiology and potential interventions. The ENT may see a reddened larynx or vocal folds or altered airway structures that may adversely affect swallowing physiology and inform our practice.

Neonates with stridor may misdirect refluxate from below or misdirect a bolus from above being swallowed. The co-occurring congestion at rest may suggest refluxate or saliva in the hypopharynx and/or laryngeal inlet. If there is onset of congestion with oral feeding, that may suggest bolus misdirection related to suck-swallow-breathe incoordination or a combination of etiologies.

What you describe as noisy breathing on exhalation may be low-pitched stridor related to tracheomalacia or bronchomalacia, or perhaps prolonged exhalation (which an infant may be using to re-open the collapsing airway, to open the alveoli, and to add positive-end expiratory pressure (PEEP), if there's indeed some level of airway obstruction). The infant may also be trying to clear the congested material off the vocal folds or out of the supraglottic space. Just hypothesizing.

Other co-morbidities, if present, need to be correlated, though this may be an "isolated," altered airway problem. There are quotes around "isolated" as ENT colleagues have taught me that truly "isolated" airway problems are rare, since it is a dynamic system. Advocating for ENT consult would elucidate the integrity of the airway to assist you in your feeding and swallowing differential.

Summary

Addressing some of the more prevalent challenges faced in the NICU as they pertain to feeding trials, protocols, and troubleshooting, this discussion provides an overview of considerations to improve the care of neonates in the NICU. With the prevalence of aerodigestive challenges leading to feeding, swallowing, and respiratory difficulties in sick term and preterm

Ms Shaker is the Senior Clinician for Feeding and Swallowing in the NICU/Pediatrics at Advent Health for Children in Orlando, Florida. She is a recognized expert in swallowing and feeding across all pediatric settings and teaches both nationally and internationally to physicians, nurses, and therapists. With almost 45 years' experience, Ms Shaker has been a part of large level III and IV NICUs since 1985. A Board-Certified Specialist in Swallowing and Swallowing Disorders, Ms Shaker's passion is infant-guided feeding and family-centered care. She is the author of several articles on NICU intervention and co-author of The Early Feeding Skills Assessment Tool for NICU Infants. She can be reached through her website: www.Shaker4SwallowingandFeeding.com.

infants in the neonatal intensive care unit (NICU), this discussion emphasized the interdisciplinary team approach with neonates which allows the systems involved in feeding, swallowing, and respiration to be addressed in a more holistic manner. Continue to follow this series as more questions related to considerations following tracheostomy and the use of speaking valves will be addressed in Part Three in the next *Neonatal Intensive Care* issue.

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disease was observed for organic conditions such as delirium (HR, 1.54), followed by obsessive-compulsive disorder (HR, 1.42), schizophrenia (HR, 1.54), and mood problems (HR, 1.12). Children of mothers with any autoimmune disorder also had a significantly increased risk of autism (HR, 1.21), intellectual disability (HR, 1.19), and ADHD (HR, 1.19).

Warning Against Increased Lingual Frenotomy in Infants

The French Academy of Medicine published an official statement calling for "more cautiousness for lingual frenotomy in newborns and infants." In January, several academic societies had already expressed concern about the abnormal increase, in France and worldwide, in lingual frenulum surgeries in children following their discharge from maternity clinics. André Chays, MD, member of the French National Academy of Medicine, and Michel Le Gall, MD, member of the French Federation of Orthodontics, have shed light on the practice "A lingual frenulum section (frenotomy) or excision (frenectomy) in newborns or infants involves surgically cutting (with scissors or a laser) a short and/or thick lingual frenulum to restore range of motion of the mobile tongue, in particular its protraction. Until recently, this rare surgical procedure has been indicated for ankyloglossia with a significant effect on function," the Academy of Medicine explained in an official statement published on April 26. Ankyloglossia limits the tongue's range of motion due to a "restrictive" very anterior and/or thick lingual frenulum. It is a congenital anomaly. "This is not a new procedure. It is old and well-known," said Chays, an ear, nose, and throat specialist and member of the French National Academy of Medicine. But what concerns the academy is "the dramatic increase, in France and worldwide, in lingual frenotomy, a procedure which, if performed very soon after discharge from the maternity clinic, supposedly then permits breastfeeding that is both effective for the newborn and infant and painless for the mother." Thus, in Australia, it found an increase of more than 420% in this procedure over a decade. "The increase has not been quantified in France," said Chays. In January 2021, several academic medical, surgical, and paramedical societies, such as the French Society of Oral Surgery, the French Association for Pediatric Otolaryngology, the French Society of Pediatric Dentistry, and the French Pediatric Society, were already troubled by the abnormal increase, in France and worldwide, in lingual frenulum surgeries in children after their discharge from maternity clinics. Thus, the academic societies pointed out that "lingual frenotomy has always been a standard, albeit quite rare, practice in the maternity clinic. They are performed to address sucking problems following a clinical evaluation and a lack of success in breastfeeding assistance measures. Their unjustified recent increase in the months following birth warrants alerting parents, early childhood experts, and institutional specialists."

Genomic Testing Services Expanded with Ultrarapid Whole Genome Sequencing

PerkinElmer, Inc., a global leader committed to innovating for a healthier world, announced the availability of ultrarapid whole genome sequencing (urWGS) through PerkinElmer Genomics. This addition to the Company's portfolio of whole genome sequencing (WGS) offerings provides physicians with comprehensive, meaningful results in five days to help inform clinical management and improve outcomes for critically ill patients in neonatal and pediatric intensive care units (NICUs and PICUs). With many genetic diseases being chronic and

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Balancing Brain and Lung Protection in the NICU with Transcutaneous CO_2 Monitoring

In this feature, Neonatal Intensive Care adapts educational webinars presented by clinicians and health-care providers for a narrative format. The webinar adapted below was presented by Brad Sexauer, BHS, RRT, previously of St Louis Children's Hospital.

Premature Birth in the US

About 12% of babies born in the US are born prematurely.[1] This is a higher rate than any other developed country. That means NICUs in the US care for a lot of small and premature babies who require a lot of attention, intensive respiratory support, and a lot of appropriate monitoring so that we can protect their brains, protect their lungs, and hopefully discharge them from the NICU in a situation where they can thrive. One parameter that is integral to the care of NICU babies, especially premature infants, is carbon dioxide.[2]

CO_2 and Its Impact on the Neonatal Brain and Lungs

Typically, the relationship that we (especially if you are a respiratory therapist) think about is: CO_2 in the lungs. But CO_2 levels also affect the brain through the relationship with cerebral blood flow, and high CO_2 causes cerebral blood flow to increase. Low CO_2 is going to decrease cerebral blood flow. All three scenarios (high CO_2, fluctuations in CO_2, prolonged periods of low CO_2), increase your incidence of intraventricular hemorrhage (IVH) in your babies.[3] Those babies weighing less than 1500 grams have a 25 to 42% incidence of IVH[4,5] and the risk of IVH is at its greatest within the first three days of life.[2] So being able to stabilize and normalize that CO_2 to stabilize that cerebral blood flow for those babies, especially those who weigh less than 1500 grams, within the first three days of life is very important.

CO_2 in Neonatal Lungs

This is typically the relationship we think about when we think about CO_2, especially if you're a respiratory therapist. We see high CO_2 levels, and we want to adjust the ventilator to normalize them. But if we can employ certain strategies, if we have a continuous reading of CO_2, that can help us optimize our invasive settings, our noninvasive settings, our high frequency settings, so that we can protect the lungs. We may be able to wean faster and hopefully get them off the ventilator.

The overall goal is to reduce chronic lung disease, try to reduce BPD, PPHN, neurodevelopmental impairment.[6] If you can employ noninvasive strategies, if you can optimize those non-invasive settings with continuous monitoring of ventilatory status and avoid endotracheal intubation altogether, you may help reduce BPD rates in your NICU.[7]

In lung-protective ventilation, we try to avoid over distension and volutrauma. If you have continuous monitoring of CO_2, you might employ a strategy of permissive hypercapnia to avoid this peak. You may allow your CO_2 to go into a little bit of a higher range if it means that you keep your plateau pressures within a reasonable range.

We also try to prevent against derecruitment and atelectasis. We want to make sure we're giving enough volume, enough PEEP; and really what helps us target that safe window is continuous monitoring of CO_2 status.

Balancing Brain and Lung Protection

A continuous CO_2 reading can help us balance these two ideas of brain protection *and* lung protection. We can consider what we're doing to the brain and at the same time, we can consider what we're doing to the lung. We're going to try to prevent against IVH and also consider what we're doing to our patients' lungs and try to prevent against ventilator induced lung injury, chronic lung disease, BPD, etc. What helps us shoot for that and helps us employ strategies that consider both of these priorities is the continuous monitoring of CO_2.

The True Cost of ABGs in the NICU

The standard for accuracy for CO_2 measurement is an arterial blood gas, or ABG. In the NICU, capillary blood gases (also referred to as CBGs or heel sticks) are commonly performed. Unfortunately, we have to draw blood to get a blood gas, and there are a lot of risk factors associated with drawing blood: blood loss, pain and stimulation, infection risk, and even time loss—since blood draws only give you information for a single point in time.

First let's consider blood loss, or how much blood is being drawn. Within the first six weeks of life, up to 30% of neonates' circulating blood volume is drawn from lab work *each week*.[8] When you are caring for a neonate and you're drawing a couple mL of blood, it may not seem like a lot, but if that neonate weighs around 500 grams, that one or two mL of blood is a substantial amount of their circulating volume.For perspective, 6-7 mL of blood from an infant weighing 1 kg is equivalent to 450 mL of blood in an adult.[9] This kind of data begs the question, "Why are we drawing all that blood in the first place?"

This content has been adapted from a previously recorded webinar with Bradley Sexauer. Content has been edited for length, and readability. If you would like to participate in this feature, as a company or healthcare provider, please contact Steve Goldstein at s.gold4@verizon.net.

One study of 50 very low birth-weight infants found that over the course of a week, an average of 140 laboratory tests were performed per infant, and the highest driver of tests, at ~57 per infant, was for pH and blood gases.[10] So if we can reduce the amount of blood gases we're doing, we should help reduce blood loss in our NICU.

Another issue we need to consider is whether all that blood is being used, with some data suggesting that up to 54% of blood drawn from NICU babies ends up as phlebotomy waste.[9] Especially with point of care machines, which don't require that much blood,it's important to pay attention to those specific amounts so that we reduce some of this phlebotomy waste.

The bigger picture here is the connection between blood draws, anemia, and transfusion in the NICU. Phlebotomy is well-established as a main cause of anemia prematurity in the NICU.[8,11] There's a direct correlation between the amount of blood that is coming out and the amount of blood that is needing to be put back into our babies. Blood draws lead to anemia. Anemia leads clinicians to want to transfuse. You may think, "*That's okay. We can just transfuse and correct a red blood cell count*" but transfusions come with their own host of risk factors.

Transfusion may as much as double the risk of your patient developing NEC,[12] 30% of NEC cases are estimated to be transfusion related.[13] And if your baby has transfusion associated necrotizing enterocolitis (NEC), these patients have higher morbidity and mortality rates.[12] Transfusions can also cause vascular overload. You might have pulmonary edema and lung injury, or other transfusion reactions.[14] If you have a baby who has a grade one or two IVH and you transfuse that baby, you're drastically increasing their overall circulating volume. You may increase that stage one or two IVH to stage three or four.[15]

What can be done to reduce blood draws?

A 2019 publication from Counsilman, et al[16] makes eight different recommendations on how to reduce blood draws in the NICU. These suggestions include delayed cord clamping, iron supplements, strict adherence to the minimum blood requirements for point of care testing, and transcutaneous monitoring to reduce blood gases.

The authors state, "decreasing the amount of phlebotomy loss is probably the area of neonatology that can be changed the quickest and have the biggest impact. This is automatically going to decrease the amount of neonatal anemia and all the complications associated with transfusions."

Painful Events in the NICU

Another risk factor associated with drawing blood is pain. In the most recent literature, we typically see anywhere from eight to 17 painful procedures per day, per infant,[17-19] which is significant. Which painful procedure is most common? Heel sticks (CBGs) have been shown to be responsible for 61 to 87% of invasive procedures performed on ill infants.[20] Rarely do we give any local anesthetic when we do heel sticks.

We also know that premature babies don't process pain very well. They don't process stimulation very well. Even when we go in with our stethoscope, take a listen to our baby, sometimes they clamp down, they bear down, we see their heart rate drop. We see their saturation drop. Sometimes we see fluctuations in their blood pressure.[19] They don't have the neurodevelopment to be able to comfort themselves.[21] They're more sensitive to pain; and pain within the first few days of life has been shown to magnify the pain response to later stimuli.[22]

Why does this matter? Of course, we don't want to hurt babies — and that's a good enough reason — but studies have also revealed adverse (and in some cases long-term) neurological outcomes in NICU patients.

One study assessed NICU babies at 40 weeks and found that a higher number of "early skin breaks" were associated with reduced or altered brain growth. This altered brain growth also correlated with lower cognitive and motor scores with those same patients at age 3.[23] Another study found that babies who experienced a higher number of skin breaks during their NICU stay had lower mental development index (MDI) scores at eight and 18 months of age.[24] A mental development index score is basically a baby IQ score.

Two different studies of ~7-year-olds who had long NICU stays found similar results: one showed poor visual perceptual abilities associated with cumulative neonatal pain,[25] and the other showed a greater number of invasive procedures associated with reduced white matter and lower IQ scores.[26]

A final study showed that eight-year-olds who experienced a lot of neonatal invasive procedures had smaller amygdalas and thalami. The amygdala is the area of the brain that processes emotion, and the thalamus sends motor and sensory signals to the brain. These smaller neurological vessels in turn related to poorer cognitive, visual-motor, and behavioral outcomes.[27]

The broad takeaway is that early experiences to painful, invasive, or otherwise stressful procedures as a neonate resulted in negative neurological outcomes in these patients, in some cases enduring long, long after they were discharged from the NICU.

Reducing Pain and Stress in the NICU

Reducing pain and stress in the NICU is possible but tricky. Analgesics have proven to be extremely complex and minimally effective for the neonatal population, so that leaves us with reducing painful procedures.[28] We accomplish some of that through touch times or care times, a way to group stressful but necessary care tasks together with the goal of long periods of calm without disruption. Anticipate laboratory testing to avoid multiple draws when one would suffice. Provide non-pharmacological comforting and soothing techniques like kangaroo care and comfort holds. Finally, utilize and leverage noninvasive monitoring such as transcutaneous CO_2 monitoring to systematically reduce the frequency of blood draws which, as we discussed previously, are the most common painful procedure performed in the NICU.

Infections From Blood Draws in the NICU

Infection is yet another risk factor of drawing blood in the NICU. For babies less than one month and those one month to 11 months of age, bloodstream infections are the most common healthcare acquired infection.[29] Heel sticks themselves can result in cellulitis, perichondritis, calcaneal osteomyelitis, and abscesses.[30] One publication on pain reduction[28] recommended a central line for patients you know will need frequent draws. However, if a central line is placed, it's important to remember that every time that central line is accessed, you're increasing the risk of contamination, the potential infection of your neonate.[31]

It is commonly known that every NICU tries to reduce central line associated bloodstream infections(CLABSI), and with good reason: CLABSIs can add up to 21 days onto a NICU length of stay[32] and are the most common cause of late onset sepsis, the leading cause of morbidity and mortality in this age group.[33]

The effort to reduce CLABSIs usually ends up restricting how often central lines can be accessed, which in turn reduces visibility to CO_2 without an alternative solution like transcutaneous monitoring.

Time Loss in the NICU from Blood Draws

Lastly, we must think about time loss. This is the amount of time that you're losing if you're just relying on point-in-time measurements like periodic ABGs, instead of a continuous parameter: you may not be reacting to changes in your patient quickly enough.

Data suggests that in the NICU anywhere between 17 and 31% of patients experience hypercapnia and about 3-4% experience hypocapnia.[34,35] As clinicians, if we're relying on ABGs, we're probably drawing blood every 4-6 hours or so. If you get a relatively normal number, you might have a false sense of security,and not respond to changes in ventilation, even though we know especially in the NICU population how quickly CO_2 can change — even in response to the act of drawing the ABG. You might not respond to those changes in ventilation until you see them clinically.

What continuous CO_2 monitoring can do is help you respond to changes in ventillation more quickly, ideally to the patient's benefit.

One study, using continuous CO_2 in the form of end-tidal, demonstrates what can happen from an outcomes perspective.[35] This study features a NICU patient population, all monitored with continuous CO_2, and two groups of clinicians — one group blinded to the CO_2 values and the other group with visibility to the continuous CO_2 information. In the blinded group, patients spent an average of 17.7% of the time outside the designated "safe ranges" of CO_2. In the monitored group, where they saw the continuous CO_2 reading, (and could make adjustments based off that reading if desired), patients spent only 7.6% of the time outside safe CO_2 ranges. What's perhaps more interesting, while dealing with very small numbers, is that in the blinded group, there was a 43% incidence of IVH compared to only 12% in the monitored group with visibility to continuous CO_2.

Methods of Continuous CO_2 Monitoring

At this point, hopefully, you've come to the conclusion that CO_2 is important enough to monitor continuously. But how will you do it? There are two different ways to monitor CO_2 continuously.

End-tidal, or capnography, is great for intubation. It's going to tell you whether or not you're in the trachea or the esophagus. It's also going to give you nice breath-to-breath wave forms. You can see if the patient has any restrictive or any obstructive issues going on. However, when it comes end tidal in the NICU, most of the time, it's pretty much infeasible to use. The tidal volumes are too small, and the respiratory rates are too high.[36] You're not getting a good enough sample of exhaled breath to give a good end tidal reading. End-tidal also adds a lot of dead space to the endotracheal tube. And, you can't use end tidal with noninvasive or high frequency modes, which we try to prioritize in the NICU because they are good for lung protection. Also, it's going to cause weight at the end of ET tube, and certainly no one wants to cause an accidental extubation in the NICU.

The other option of measuring CO_2 continuously is transcutaneous technology. Transcutaneous monitoring is compatible with patients on any type of ventilation: noninvasive, high frequency, mechanical, even bubble cPAP. There's no dead space or weight on the ET tube.

Modern transcutaneous technology operates at a lower temperature than original technology and has been shown to be safe for neonatal skin.[37] It does require routine calibration and decent local perfusion at the sensor site for the best accuracy. While you won't have a breath-to-breath measurement or be able to use it to confirm ET tube placement like you might with end tidal, transcutaneous monitoring has been shown to be more accurate especially in cases of V/Q mismatch.[2]

In closing, transcutaneous CO_2 monitoring is one tool that can help NICU teams balance the long list of priorities in the NICU: prevent IVH, protect the lungs, keep a close eye on the babies, don't overstimulate patients, stick to touch times, prevent anemia and transfusions, reduce painful procedures,[38] etc. Caring for these premature infants involves an incredible amount of tradeoffs and attention to detail, but of course it's worth it every time we get to send a patient home. Hopefully we continue to progress and evolve our care patterns and follow the data to discharge them in better and better shape with bright futures ahead.

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progressive in nature, reducing the time to reaching an accurate diagnosis can eliminate unnecessary procedures, initiate treatment and improve clinical outcomes. The PerkinElmer Genomics urWGS offering uses a dried blood spot sample to provide phenotype-driven analysis with a mean coverage of 40x of a patient's genome. Studies suggest that up to 15 percent of disease-causing genetic variants may be found in the non-coding regions of the genome, which WGS helps identify. In addition to an analysis of the mitochondrial genome, CNV detection — which identifies deletions, duplications, and other gene- and chromosomal-level events, SMA and a repeat disorders screen — the PerkinElmer urWGS offering includes a StepOne® Comprehensive Biochemical Profile. The StepOne offering screens for more than 70 inherited conditions and disorders, including the Recommended Universal Newborn Screening Panel (RUSP) and many others that may not be found in state-mandated programs. "Increasingly, whole genome sequencing is proving its value as a first-tier clinical test for many patients, especially in a NICU and PICU where timely clinical decisions are critical for timely intervention," said Madhuri Hegde, PhD, FACMG, SVP and chief scientific officer, Global Lab Services, PerkinElmer Inc. "By making services such as this urWGS combined with StepOne available to more hospital systems and physicians, our hope is that we may help shorten the diagnostic odyssey for more newborns and their families. With PerkinElmer's global leadership in newborn screening using dried blood spot card technology, we will continue to enhance urWGS with additional assays." As a result of informing and initiating changes in clinical management, rapid WGS tests have been shown to reduce healthcare costs for patients in NICUs and PICUs. Additional benefits of these testing services include the elimination of unnecessary tests and procedures, and reduced length of hospital stays. PerkinElmer Genomics is among the first commercial clinical laboratories to receive approval from the State of New York for its next generation sequencing-based method for WGS using saliva, whole blood, and dried blood spot specimens. In December 2021, the Company also launched a prenatal WGS test offering, further expanding its capabilities as a leader in this space.

Issues with Vasopressin Infusion in Neonate Born After a Significant Perinatal Event

Hilary L Tice, PharmD and Shabih Manzar, MD

Summary

We describe a case of a neonate who was delivered with a history of significant acute perinatal event. She was started on vasopressin infusion for low blood pressure. A significant fluid retention was observed after the commencement of infusion manifested by excessive weight gain and hyponatremia. The case highlights the need to practice caution while using vasopressin in neonates with acute perinatal event. Vasopressin further aggravates fluid imbalance in these neonates who are already at high risk for acute kidney injury.

Case

A preterm female infant was born via emergency cesarean section for presumed placental abruption. The infant was depressed at birth with Apgar scores of 0,0, and 0 at 1, 5 and 10 minutes respectively. Aggressive resuscitation was performed in the delivery room with multiple doses of epinephrine. The infant was then transferred to the neonatal intensive care unit and was placed on a ventilator. The infant continued to have low blood pressure despite intravenous fluid boluses for which a dopamine continuous infusion (15 microgram/kg/min) was started. A vasopressin drip was added on day 3 of life at a rate of 0.04 units/kg/hr. Following the vasopressin infusion, a drop in serum sodium with significant fluid retention was noted. Table 1 depicts the serial serum electrolyte values gained, while figure 1 shows the fluid balance in first six days of life. Infant gain 70% weight with mean urine output of 0.88 ml/kg/hour despite reduction in the total fluid intake from 142 ml/kg/day to 30 ml/kg/day. Serial neurological examinations were performed and after discussing with the family, life sustaining therapies were withdrawn on day 7 of life.

Table 1. Serial Electrolytes in the first six days of life

Day of Life	Serum Na (mmol/L)	Serum BUN (mg/dL)	Serum Creatinine (mg/dL)	BUN: Creatinine Ratio
1	138	23	1.4	16.4
2	143	35	2.20	15
3	136*	36	2.50	14.4
4	133	37	2.50	14.8
5	126	41	2.60	15.7
6	126	43	2.60	16.5

*Vasopressin started, note the trending down in serum sodium (Na) levels
BUN: Blood Urea Nitrogen

Discussion

Vasopressin acts on V1 and V2 receptors. Activation of V1 receptors located in vascular smooth muscle cells results in vasoconstriction, thereby helps in improving the blood pressure. The V2 receptors, present in the basolateral membrane of the principal cells of the renal collecting tubules and connecting tubules, mediate the osmotic effect of vasopressin, resulting in fluid retention.[1] Hyponatremia and water intoxication have been reported as adverse reactions to the use of vasopressin.[2]

The use of vasopressin in neonates has not been well established. The published studies on vasopressin in neonates are limited with 3 retrospective and only one randomized control trial. Joynt and Cheung [3] in a review concluded that due to a lack of high-quality trials there was insufficient evidence to recommend or refute the use of vasopressin. Perinatal asphyxia has been associated with possible development of inappropriate antidiuretic hormone (arginine vasopressin) secretion therefore adding continuous vasopressin infusion would further exaggerate the fluid overload.[4]

Reduced urinary output (UO) has been associated with mortality in neonates.[5] On day 2 of life, the infant had a UO of 0.45 ml/kg/hr (Figure 1) and rising serum creatinine (SCr) of 2.20 mg/dL (57% increase from the baseline of 1.4 mg/dl, Table 1). Therefore, infant could be classified as having acute kidney injury (AKI) per pRIFLE (pediatrics-risk, injury, failure, loss, end stage) and KDIGO (Kidney Disease: Improving Global Outcomes).[6,7] Although, the mean BUN: creatinine ratio of 15.4 (Table 1) was not classic of renal injury but in view of the history of acute perinatal event and need for aggressive resuscitation, high SCr and low UO, infant manifested signs of AKI. Adding vasopressin infusion in such cases would further aggravate fluid retention, as was seen in the described case.

In conclusion, as vasopressin has a potential to cause water retention and hyponatremia, it should be used with caution in neonates with history of significant acute perinatal event.

Hilary L Tice is a Clinical Assistant Professor, Faculty, University of Louisiana at Monroe, Shreveport campus. Shabih Manzar is an Associate Professor, Department of Pediatrics, School of Medicine, Louisiana State University, Health Sciences Center. Address correspondence to: Shabih Manzar, MD, 1501 Kings Highway, Shreveport, LA 71103, Telephone: 318-626-1623, Fax: 318-698-4305, Email: shabih.manzar@lsuhs.edu.

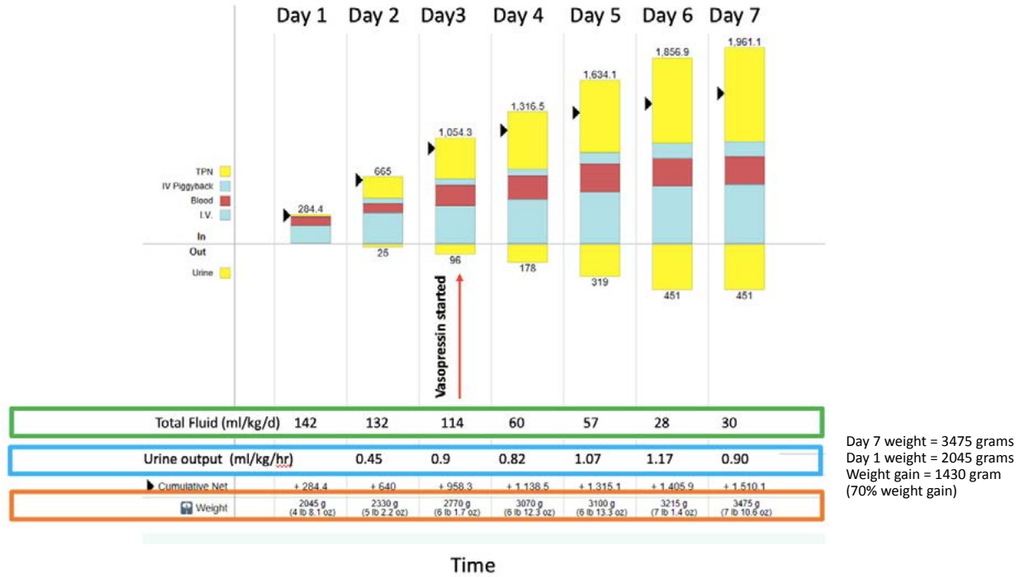

Figure 1

Day 7 weight = 3475 grams
Day 1 weight = 2045 grams
Weight gain = 1430 gram
(70% weight gain)

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Umbilical Cord Infection with Immersion Tub Bathing and Immersion Swaddle Bathing – What's the Risk?

Dana L Denton, MPT and Timothy R Wolfe, MD

Tub bathing whether by swaddle bathing or immersion bathing is superior to sponge bathing for reducing temperature loss and decreasing behavioral stress for full term and preterm infants.[1,2,3,4,5,6] Tub bathing also improves caregiver satisfaction.[1] However, traditional bathing practices commonly use sponge bathing until the umbilical cord falls off due to the notion that tub bathing can lead to an increase in umbilical cord infection. Evidence does not support this notion. In four randomized controlled trials directly comparing tub baths and sponge baths, tub bathing was not shown to cause cord infection. Tub baths do reduce temperature loss and improve infant comfort.

Bryanton[1] divided 102 healthy term infants into 2 groups, an experimental tub bathing group and a control sponge bathing group. Their aim was to compare the effects of traditional sponge bathing and tub bathing methods on healing and infection of the umbilical cord in healthy term infants. Using an umbilicus assessment scale, they found no differences in cord healing scores between the two groups. They did find, however, that the infants had significantly less temperature loss and they were significantly more content with tub bathing.

Henningsson et al[7] divided 205 infants into a bathing group (immersed in a tub and hand washed with non medicated soap) and a washing group (wiped with a wet face flannel and non medicated soap) and compared the effects on infection rate, bacterial colonization rate, body temperature, and crying. The infants were observed for infection for 5-6 days during their hospital stay. Specimens from the umbilical cords were cultured. No statistically significant differences were found between the two groups for clinical signs of infection or bacterial colonization rates. However, change in rectal body temperature was highly significant. The tub bathed infants had less temperature loss compared to the washed group.

In the study by Hylen et al[8] their aim was to compare the effects in the newborn babies of washing and bathing in regard to bacterial colonization rate, clinical infection rate, body temperature and crying. Infants from two maternity wards in Sweden were divided into two groups, 305 were bathed in a tub and 313 were washed with a washcloth. Soap was not used on either group. No differences in bacterial colonization or signs of infection were found between bathing and washing. However, temperature loss and crying were both highly significant. Bathing in a tub had less temperature loss and a decrease in crying compared to the group washed with a cloth.

Ayyildiz et al[9] separated 100 healthy full-term infants and their mothers into two groups, tub bathing and sponge bathing. They evaluated the influence of sponge and tub bathing methods on umbilical cord separation time in full term babies. They found that tub bathing delayed the separation of umbilical cord. No differences were found in cord infection rates, but the study lacked statistical power to make conclusions.

While tub bathing did not lead to increase in cord infection for clean settings, cord infection remains a concern in third world settings.[10,11,12] Approaches to prevention of cord infection in the third world need to be different and more conservative than in modern societies that have clean water, clean birthing situations, and the ability to treat infections quickly and effectively. Large antiseptic studies done in the third world show that moistening the cord with antiseptic solution does lead to a sightly longer time until cord separation. Longer time to cord separation did not lead to increase in cord infection rates or increase in death, however, as the antiseptic killed the bacteria. Bathing studies on cord separation are less conclusive and too small to be sure. The traditions of delay in cord separation and the possible infection from unclean tubs and water could fuel the reasoning for waiting for cord separation prior to bathing.

Choosing sponge bathing over tub bathing exposes the infant to its own set of risks- cold stress and behavioral stress. Hypothermia triggers increased need for oxygen consumption and glucose utilization leaving an infant at risk for hypoglycemia or respiratory compromise, both of which may require additional medical testing, lengthened stay, or transfer to a higher level of care.

Behavioral stress cues are the infant's communication. When caregivers attend to stress cues, medical procedures and caregiving practices can be transformed to less stressful experiences. Stressful experiences in the preterm infant have been shown to change the structure and function of the brain.[13,14] Increased exposure to stressors is associated with decreased brain size in the frontal and parietal regions, altered brain microstructure and function connectivity in the temporal lobes, and alterations in neurobehavior at term equivalent.[13] Negative or painful experiences have the potential for negative effects on development. Altering procedures to decrease behavioral stress has the potential to enhance the infant's long term developmental outcome.

When an infant is more content in the bath, not only does the infant experience less stress, but the family or caregiver also enjoys a more stress-free activity. An enjoyable experience can lead to increase in parent involvement and patient satisfaction.

Immersion tub bathing or swaddled immersion bathing is supported by nursing organizations. The Neonatal Skin Care Guideline published by the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN) and National Association of Neonatal Nurses (NANN) supports immersion tub bathing or swaddled immersion bathing. They determined that tub bathing did not have an association with increase in bacterial colonization of the cord, cord infection, or cord healing.[15]

The importance of infant comfort and warmth should be considered regardless of the bathing method used. If tub bathing is determined to be unsafe due to unclean water or otherwise, measures to ensure infant warmth and comfort should still be implemented. Providing containment and positional support and being mindful of behavioral communication can help the caregiver bathe without the bath becoming an infant stressor.[16]

Of the many studies investigating the differences between sponge bathing and tub bathing on hypothermia, motor stress, physiologic stress, maternal comfort, and caregiver satisfaction, none have attributed any increase in cord infection to tub bathing in modern hospitals using clean water. The event is so rare that large enough studies cannot be done to determine if either method will minimally change cord infection risk. This is not the case when evaluating temperature loss and infant comfort. The data provide clear evidence that immersion tub bathing and immersion swaddle bathing are superior for decreasing temperature loss and increasing infant comfort.

Dana Denton, MPT, is a Pediatric Physical Therapist with over 20 years of clinical experience. The last 14 years have been in the NICU. Her mission is to improve the long term functional outcomes of infants. She is a co-founder and Clinical Specialist for Catapult Products, LLC.
Timothy R Wolfe, MD is an Adjunct Associate Professor at the University of Utah School of Medicine, Salt Lake City, Utah. Correspondence requests: Timothy Wolfe, MD, 1119 E Alpine Pl, Salt lake City, UT 84105, +1-801-910-8518. timwolfe5@gmail.com.

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NOXIVENT® Indication and Important Safety Information

Indication

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

Important Safety Information

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 steadystate 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 (NO2) 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

Nitric Oxide donor compounds may increase the risk of developing methemoglobinemia.

Administration

Use only with a calibrated, FDA-cleared NOxBOXi® Nitric Oxide Delivery System (NODS). Refer to the NODS labeling for needed information on training and technical support for users of this drug product with the NODS.

Please see the full Prescribing Information for additional important Noxivent® safety and risk information.

Distributed by Praxair Distribution, Inc., a Linde Company
10 Riverview Dr. Danbury, CT 06810
Phone 844.445.4633, www.noxiventus.com

Pulse Oximetry for Term and Preterm Newborns

In this feature, Neonatal Intensive Care adapts educational webinars presented by clinicians and healthcare providers for a narrative format. The webinar adapted below was presented by Ruben Bromiker, MD, Director, NICU, Neonatology Department at Schneider Children's Medical Center of Israel.

Ruben Bromiker: We are going to speak about pulse oximetry for term and preterm newborns, different aspects.

Oxygen was discovered in 1772 by Scheele and Wiltshire. They just identified the product of a chemical reaction between potassium nitrate and sulfuric acid liberating nitrous oxide and another gas, which they called dephlogisticated air or air fire, which in 1779 was named by the famous physicist, Lavoisier, as oxygen, which is the terminology we use still nowadays.[1]

The first description of using oxygen for neonatal resuscitation was by Chaussier. The first equipment, a bladder connected to a face piece in order to deliver the gas or to the nose through the hose and even an endotracheal tube, which is probably one of the first, if not the first, described in the literature.[2]

Close to our days, between the '30s and '50s of the previous century, unrestricted oxygen was given to premature newborns. Until in the middle of the previous century, the use of oxygen in prematures was linked to retinopathy of prematurity, which was then called fibrolental retrofibroplasia.

Therefore, after this linking, oxygen use was limited. But it was unmonitored because it was not a clinical key for monitoring oxygen then. And the consequence was an increase of cerebral palsy and mortality in premature newborns.

In '66, Klaus and Meyer said that 100% FiO_2 can only be helpful in the delivery room. And there would be no contradictions for term babies. In the same year, Campbell conducted resuscitation of newborn rabbits with room air, which was successful.[2,3]

The guidelines of the American Academy of Pediatrics for Neonatal Resuscitation in 1992 stated that oxygen should be used. It's nontoxic. And there would be no reason for concern. But a few years later in 2005, they stated that room air for resuscitation may be used by some. And in 2010, the recommendation based on meta-analysis would show higher mortality for 100% oxygen.[2,3]

So, the guidance changed and said that it was best to begin resuscitation with room air. And they published target levels of oxygen over the first 10 minutes, which range from more or less 60 in the first minute up to 90 plus minus 5 by 10 minutes.[2,3]

For this, it was necessary to introduce the pulse oximeter in the delivery room, which now is common practice. But then it was not understood. It was not considered the standard of care. So, the recommendation was to start with 21%. And if needed, to increase until the target saturation was reached. And in the real world, the blender that we can see here was suggested not to be 100% but whatever is necessary, unless there was a necessity of performing chest compressions. In this case, 100% should be used until return of spontaneous circulation.

The recommendation for term babies was to stop initiating resuscitation with 100% oxygen, instead to start with room air. For premature babies above 32 weeks, similar but to move the blender as soon as possible in order to reach the target. And for less than 32 weeks, although they suggest 21% to 30%, most centers would use 30% based on further studies. And oxygen should be titrated according to saturation and heart rate.

In summary, 100% oxygen for neonatal resuscitation was introduced with no scientific evidence. For almost a quarter of a millennium, the validity was unquestioned. If oxygen had been considered as a drug, toxicity by the liberal use could have been avoided. Many blind premature neonates, for example, may not have been blind. So, oxygen is a drug. And like any other drug, the dosing must be monitored.

Speaking of premature neonates, the importance of pulse oximetry for monitoring is crucial. Hypoxia and also hyperoxia are potentially associated with damage to organs. Saturation must be monitored in all NICU patients, but especially in the most vulnerable who are the premature newborns.

This idea was the right rationale for conducting important studies. We can find three main studies which were conducted in the USA, Canada, and Australia. They included more or less 5,000 premature neonates with mean gestational age of 26 weeks.

And they were divided into two groups, low range, 85% to 89% saturation, and high range, 91% to 95% saturation. This was, of course, intention to treat. But many times, groups overlapped.[2,3,4]

After these three studies, because of the importance of the issue of determining what would be the range for given oxygen to premature neonates, the meta-analysis was conducted with all the participants. And they were analyzed together.

And the primary outcome of this meta-analysis was death or major disability composite outcome. And it was found to be nonsignificant by 18 to 24 months postmenstrual age.[7]

But there were other outcomes. The lower saturation target presented increased rate of death and necrotizing enterocolitis. On the other hand, there was a lower risk of retinopathy of prematurity requiring treatment that the composite primary outcome shows death by corrected age, 18 to 24 months, favored the high saturation group, while other secondary outcomes also, again, death was lower in the high saturation group and ROP lower in the low saturation range group. And severe necrotizing enterocolitis was lower in the high saturation group. Supplemental oxygen at postmenstrual age 36 weeks, obviously, was lower in the low saturation group because the required saturation was low. Therefore, there would be no need for oxygen supplementation. Other outcomes, especially neurodevelopmental, showed no difference, of course, among survivors. So now we know the suggested range, which in most places nowadays would be between 90% and 95%.[7]

Another use of pulse oximetry which became very popular, especially in most states of the United States, if not all, and other countries, is the use of pulse oximetry for the detection of critical congenital heart diseases in newborns, , in the normal baby nursery.

Critical congenital heart defects incidence is 2 in 1,000 live births. The gold standard for the diagnosis would be the postnatal echocardiography. But the limitation is that this method is not widely available and requires a lot of time consuming, high qualified staff, which is not everywhere and always available. The ductus arteriosus ensures adequate pulmonary and systemic perfusion over the first hours or days of life. But most obvious symptoms start with the closure of ductus and often may happen after discharge. Therefore, the early detection of ductus-dependent critical congenital heart disease is crucial to keep the ductus open before the patients come in a crisis. And, of course, initiation of prostaglandin to keep the ductus open allows the correct management of these patients.

The rationale for the screening would be that prenatal screening may miss up to 50% of these conditions or in many cases, especially in underdeveloped countries or non-well-organized, there might be no prenatal screening. Most infants with critical congenital heart disease present with hypoxemia. But many times, it's difficult to see on examination. a study in which almost 30 people were requested to say when they consider the babies to be pink. And most observers stated that they were pink when the saturations were below 80. Therefore, color is not a trustable and accurate method. Pulse oximetry is a quick, painless, noninvasive, reliable, and widely used method. And it's not expensive as well. Therefore, it's been suggested to be used. And the screening will detect most critical congenital heart disease, which were not detected by other methods before discharge. And it allows urgent cardiac intervention before onset of life-threatening collapse as we said before, for example, starting initiation of prostaglandin.

A Cochrane systematic review of 21 cross-sectional and cohort studies was conducted, including almost half a million newborns, which were screened. And their conclusions were that out of 10,000 normal newborns, six will have a critical congenital heart disease. The screening with saturation will detect five and miss one. There were also false positives. Out of 10,000, 14 newborns will be false positives, which is really not very high. And if the screening is performed in newborns after 24 hours, the false positive is even lower.[8]

It's significantly lower. And it's important to know that more than 30% of the false positive have a respiratory or infective condition requiring medical intervention. This is an added value of the screening for congenital heart disease. So, the conclusions of the Cochrane were that pulse oximetry is a highly specific and moderately sensitive test for detection of critical congenital heart disease with very low false-positive rates.

Routine screening in asymptomatic newborns before discharge is recommended.[8]

Another paper actually studied more than 40,000 normal newborns in which 90 critical congenital heart diseases were diagnosed, how they were diagnosed. So, 60% were diagnosed prenatal by prenatal ultrasound, 20% by clinical examination, 16% by pulse oximetry, and only four, which were 4% approximately, were diagnosed after discharge when they came symptomatic. There were 44 false positive from which 28 were sick, 15 with persistent pulmonary hypertension of the newborn, and 13 with sepsis. Only 12 out of 42,000 were really false positive. And they were healthy.[9]

Their recommendation, the revised algorithm actually includes the initial measurement locating the sensors of the pulse oximetry, one preductal, most popular site would be the right hand, and in one of the feet, which are postductal, by 24 hours of life or before the patients are discharged early. So, if this saturation is below or equal to 89% in either the right hand or one of the feet, it requires immediate assessment. If the saturation ranges between 90% and 94%, which means below 95% and above 90%, or there is more than 4% difference between site, the patient should be retest in one hour. And if the saturation is equal to 95% in both the right hand and foot and no difference, of course, it is considered that the test is normal. In case of retest, if after one hour the saturation is below or equal to 95% or the difference between the sensor is higher than 4%, requires immediate assessment, typically, of course, echocardiography. And if the saturation is equal or above 95% in both sides or the difference is less than 3%, the test is normal.[10]

The expected sensitivity of saturation for the most severe critical congenital is 80%. For example, for critical pulmonary stenosis, d-transposition of the great arteries, hypoplastic left heart, pulmonary atresia, total anomalous venous return, total anomalous pulmonary venous return, and truncus arteriosus. Medium for critical aortic stenosis, double-outlet right ventricle, tricuspid atresia, and Tetralogy of Fallot. And relatively low, less than 60%, for coarctation, Ebstein anomaly, interrupted aortic arch, and single ventricle.

The hyperoxia test is a relatively old test but very popular, consisted when a child was cyanotic to give 100% and seeing if the color of the baby changed.

The physiological basis for the hyperoxia test is that in cyanotic congenital heart disease, the pulmonary venous oxygenation is normal, which means that the blood which passes through the lungs is well oxygenated. The low oxygenation is due to right-to-left shunt which occurs after the blood reaches the left atrium.

Therefore, the resistance of deoxygenated blood. If FiO2 is increased, there would be an increase in PO2 in the pulmonary veins. But the effect would be minimal in the systemic circulation because of the shunt we referred to. In case of pulmonary disease, increasing the saturation would increase

the PaO2 in the pulmonary veins and also systemic. And an increase in FiO2 typically would increase the pulmonary venous oxygenation and the systemic oxygenation.

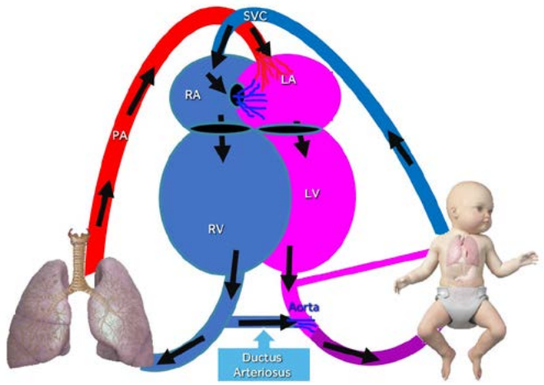
The formal hyperoxia test originally described states that a measure based on preductal PaO2 arterial should be measured. And after 10 minutes of delivering 100% FiO2, repeat it. In this case the PaO2 increases but it's less than 150 millimeters or no increase, most probably the condition would be a cyanotic heart disease. If the increasing in PaO2 is above 150 millimeters of mercury, it's most probably pulmonary disease. But PaO2 levels may differ depending on the type of congenital heart disease lesion.

So, this was the original, which is an increase in arterial PO2 when giving 100% oxygen. But this is very traumatic and might be complicated and, in many places, difficult to perform. The modified hyperoxia test would be performed by using a pulse oximetry. And saturation should reach more or less 100% or close to 100%. If not, most probably would be a congenital heart disease. But 100% saturation — in 100% saturation, the range of PaO2 maybe between 80 and 600, as we can see in this graph of the oxygen hemoglobin saturation curve. We see that with 100% saturation, the PaO2 is very valuable. And this is acknowledged by most manufacturers. Therefore, even some critical congenital heart disease may have its saturation closer to 200%. But typically, if the saturation is 100%, most probably it is a lung condition, especially when saturation increases very fast. This test is less reliable but avoids arterial puncture for blood sampling. An increase in the saturation more than 10% after 100%, most probably, will point to a pulmonary condition as a cause of cyanosis. And further evaluation is required by history, examination, chest X-rays, and such. But if the response is abnormal or equivocal in any case, echocardiography should be performed. And even if the response is normal as we explained, critical congenital heart disease is not completely excluded, but if suspected, echocardiography should be performed any way. So, this is a nice test for initial management. But it doesn't replace all other systems — all other examinations. Of course, severe lung disease and pulmonary hypertension may cause false positive to the hyperoxia test.

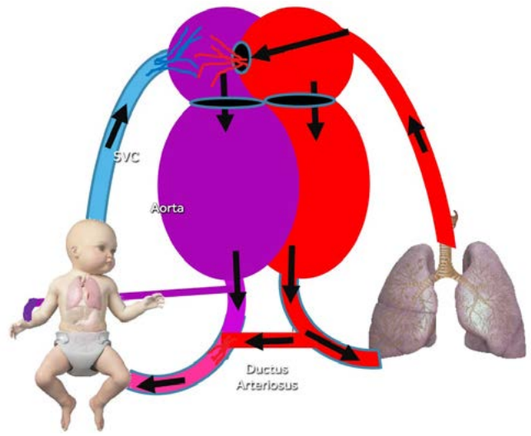
Another use of pulse oximetry, very popular, is the diagnosis of right-to-left shunt throughout the ductus arteriosus. The diagnosis, we know that preductal saturation should be measured in the right hand or ear lobe, most popular in the right hand, as we said in the screening test for heart diseases, postductal in the foot. And generally, the difference should be

higher than 10% for saying that there is pulmonary hypertension. There may be no difference if the main right-to-left shunt occurs throughout the foramen ovale. If it's too high to the foramen ovale, there may be, as we said, no difference. There is a single case transposition of the right arteries, as we will show later, in which the postductal saturation will be higher than the preductal.

In this graph, we can see what happens in persistent pulmonary hypertension of the newborn. Oxygenated blood comes from the lung. The blood which manages to pass through the lungs is oxygenated. And it actually comes to the left atrium. But if there is pulmonary hypertension, part of the cyanotic blood coming from the systemic circulation shunts the lungs and already reduces the saturation at the level of the left atrium. So less oxygenated blood will go to the preductal areas. But what happens? An important amount of the blood will not go through the lungs and will shunt through the ductus arteriosus. Therefore, the postductal areas will be more cyanotic than the preductal areas. I think this is clear.



And just to understand what happens in TGA, there are two different circuits which are connected only through the foramen ovale and the ductus. So, part of the deoxygenated blood goes from the left atrium to the right atrium, improving oxygenation of the cyanotic blood coming from the superior vena cava. And it goes to the preductal areas. And further, oxygenated blood comes through the ductus, causing the postductal areas to be better oxygenated. So, in case we see that the saturation of the legs is higher than the preductal, transposition should be suspected.



Of course, the most common cause could be that the sensor is not well located. But after we rule out that there is a technical problem, transposition should be suspected. Influences of temperature and altitude on saturation. This is a study which was conducted by us in my previous hospital. And we retrospectively examined what happened with the saturation in children which were subjected to therapeutic hypothermia and after rewarming. the saturation was higher during the hypothermia period because of the shift of the oxygen hemoglobin curve. the saturation increased after rewarming, the SpO2, as well as the arterial saturation, but it decreased less than the SpO2.

The mean decrease in SpO2 was 2.6, which was higher than the mean decrease in SaO2. We considered that the cause of a higher difference in SpO2 is that this was checked really reflected the differences in temperature because arterial saturation is conducted in a gas analyzer, which warms the sample before delivering a result and therefore may be causing an artificial decrease in saturation.[11]

A study actually checked the pre and postductal saturation at different altitudes at less than 24 hours and before discharge. The results showed that as altitude increase, saturation decrease. And this is important for the screening.[12]

Another study from China shows that both pre and postductal saturation decreases with altitude. And the conclusion of this study is that in case of congenital heart disease screening, the cutoff value should be adapted to the altitude.[13]

Automatic regulation of FiO2 is a recent popular issue which is being introduced for mechanical ventilators of newborns. And the rationale is that especially very low birth weight infants have frequent episodes of hypoxia because they have an irregular respiratory effort which causes hypoventilation or apnea. And many times, they make active expiration which causes loss of functional residual capacity.

This causes episodes of hypoxia, which, in cases of being prolonged or severe, have the potential of brain or other damages. So, the typical reaction of the staff would be to increase the FiO2 by switching the blender up. And then subsequent hyperoxia could be seen in these patients. And then again, the staff would have to put down the blender in order to avoid hyperoxia. But this up and down would cause intermittent episodes of hyperoxia and hypoxia, which may increase the potential brain and lung damage or retinopathy of premature which we were trying to avoid. And the constant tuning is very difficult and time consuming, especially in centers with limited resources or relatively limited resources in which the nurses have to treat more than one or two newborns which are ventilated.

The idea of a closed-loop control of inspired oxygen concentration came, and devices for ventilating newborn were adapted for this technology. The FiO2 is automatically adjusted to maintain saturation between a targeted range. The target saturation is set on the ventilator or high flow nasal cannula device. And the devices have a built-in pulse oximeter.

Therefore, the saturation beyond going to the monitor, also the sensor has to be connected to the ventilator in order to provide the information on the SpO2 of the infants. And these devices have an automatic gas blender which can increase or reduce the FiO2.

So, the blender constantly adjusted the baseline FiO2 to maintain saturation within the target range based on an algorithm.

There are different algorithms for different devices. A study was conducted using a mechanical ventilator in order to check the effects of this technology in arterial and regional tissue oxygenation. It was randomized crossover trial which compared automatic to manual FiO2 adjustment. The same patients were changed over periods of 24 hours before and after with one of both possibilities, automatic or manual adjustment of FiO2. So, the findings were that the automatic adjustment increased the time within the target SpO2, which was 88% to 96%. This was a primary outcome. The time above the intended arterial oxygen range median FiO2, mean SpO2 over overtime, and local saturation of brain, liver, and kidney did not differ significantly.[14]

But in this table, we can see beyond the primary outcome, other outcomes which included time of hypoxia below 88%, which was also statistically significantly lower in the automated. Opposite to this, time with saturation above 96% did not differ between both systems. I will speak about this later of the reasons.[14]

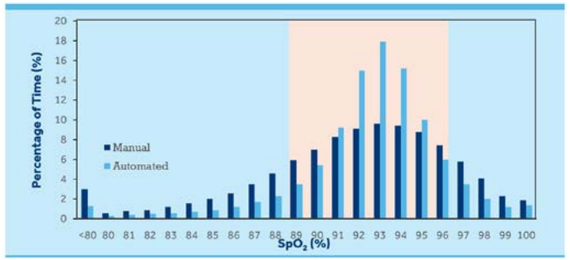
Outcome Parameter	Manual	Automated	P values
Time (%) with SpO_2 88%–96%, mean±SD	68.52 (±7.7)	77.83 (±7.1)	0.0012*
Time (%) with SpO_2<88%, mean±SD	25.61 (±7.6)	18.12 (±6.4)	0.002*
Time (%) with SpO_2>96%, mean±SD	5.88 (±3.6)	4.05 (±3.8)	0.189*
Mean SpO_2 (±SD)	89.76 (±1.3)	90.5 (±1.0)	0.0198*
Events bradycardia >10 s, median (range)	7.2 (0–18)	6.9 (0–22)	0.52*
Manual FiO_2 changes per hour, median (range)	7.5 (2.1–14.3)	0.5 (0–1)	<0.001†
Time (%) SpO_2<80%, median (range)	6.15 (2.4–14.7)	4.32 (0.8–10.7)	0.03†
Events SpO_2<88% >60 s/day, median (range)	**90.5 (31–216)**	**34.6 (6–72)**	<0.001†
Events SpO_2<88% >180 s/day, median (range)	**10.4 (0–37)**	**2.1 (0–10)**	<0.001†
Events SpO_2<80% >60 s/day, median (range)	75 (22–165)	43 (3–60)	<0.001†
Events SpO_2<80% >180 s/day, median (range)	6 (0–25)	1 (0–2)	<0.001†

*Paired t-test.
†Wilcoxon signed-rank test.

The mean saturation was a little bit higher in the automated. Events of bradycardia of more than 10 seconds, were not different. But more important events such as number of manual changes per hour requiring burden to the staff were much higher, 7.5 events per hour of needing to adjust, while almost minimal for the automated. In cases of understaffed, this is very important. Time of saturation below 80% was significantly lower in the automated as was episodes of more than 60 and 160 seconds of hypoxia because the duration of hypoxia period is important and may have a higher influence for the toxicity.[14]

Another study used the newly developed high flow nasal cannula device with the automatic oxygen control. The design was similar to the previous. And they found a significant increase of time spent in the target range 80% of the time for the automated versus 50% for the manual device. And they found fewer and shorter episodes of saturation below 80% for more than 60 seconds and an overall reduction in the proportion of time in hypoxia and hyperoxia, differently to the previous study. And it is believed that the difference also in favor of the automatic of shorter times of hyperoxia are because of the high flow which causes actually to the changes in the algorithm to be reached to the patient much faster.[15]

And if we see these bars are in dark blue, they're manual. And then light blue, they're automatic. And we see that in the center, the proportion, the percentage of time in light blue is much higher. And as we go far from the center, the proportion of dark blue is higher than light blue.[15]



And if we see each single patient in all cases, they spent a higher proportion of time within the target range.

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Assessment of a Neonates' Respirations

Leslie Altimier, RNC, NEA-BC, DNP and Apoorva Jayaram, MS Engineering

Neonatal Healthcare Statistics

Worldwide each year, an estimated 15 million babies are born prematurely (before 37 completed weeks of gestation) making preterm birth complications the leading cause of death among children under five years of age, responsible for approximately one million deaths globally (Liu, et al., 2016). In the United States, preterm complications are the number one cause of death and those who survive often have long-term health problems, such as chronic lung disease or Bronchopulmonary Dysplasia (BPD), asthma, cerebral palsy, intellectual disabilities, mental health issues, and blindness due to Retinopathy of Prematurity (ROP), hearing loss, and more (March of Dimes, et al., 2012).

Born Too Soon: The Global Action Report on Preterm Birth features the first-ever estimates of preterm birth rates by country (March of Dimes, et al., 2012; Liu, et al., 2012). Across 184 countries, the rate of premature births range from 5% to 18% and in almost all countries with reliable data, preterm birth rates are increasing (Liu, et al., 2012). Preterm birth is now the single most important cause of neonatal deaths (babies under 28 days) and the second leading cause of death, after pneumonia in children under 5 (Born to Soon). The preterm birth rate in the United States was ranked 131st in the world at 9.8% with approximately 380,000 babies born prematurely each year, making the U.S. preterm birth rate among the worst of high-resource nations (March of Dimes, et. al., 2012; WHO, 2016).

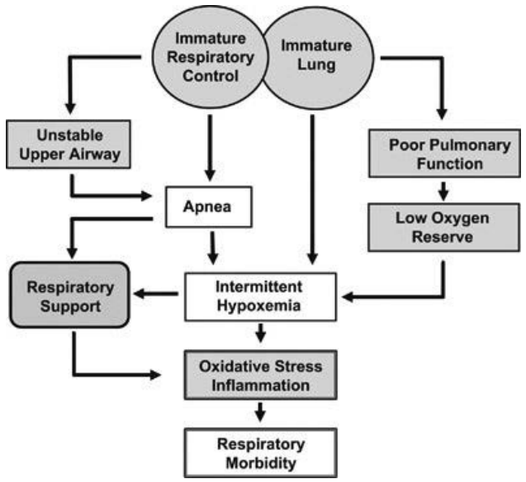
Most preterm births happen spontaneously, but some are due to early induction of labor or caesarean birth, whether for medical or non-medical reasons. Common causes of preterm birth include multiple pregnancies, infections, and chronic conditions such as diabetes, high blood pressure and preeclampsia; however, many times the cause is unknown.

Respiratory Distress Syndrome (RDS) is a common neonatal problem and accounts for most admissions to Neonatal Intensive Care Units (NICUs) (Saboute, et al., 2019). Respiratory distress may be due to either obstetrical, medical, or surgical causes and is often secondary to surfactant insufficiency (Gentle, et al., 2020). A variety of factors are associated with neonatal respiratory distress such as prematurity, low first and fifth minute APGAR scores, meconium aspiration syndrome, cesarean section delivery, maternal gestational diabetes, maternal chorioamnionitis, and premature rupture of membranes (Tagliaferro, et al., 2019). The incidence of RDS is inversely to gestational age (GA) and neonates with RDS are 2 to 4 times more likely to die (Wen, et al., 2019; Seigel & Jane, 2014).

Failure to readily recognize symptoms and treat the underlying cause of RDS in the newborn can lead to respiratory failure, cardiopulmonary arrest, and even death (Reuter, et al., 2014). It is vital that health care professionals caring for newborn infants recognize the signs and symptoms of respiratory distress, differentiate the various causes, and initiate management strategies to prevent significant complications or death (Harshini, et al., 2020; Kumar & Bhat, 1996).

Respiratory assessments are important in all babies, but especially important in premature babies who are prone to respiratory distress and apneic events. Apnea is defined as a respiratory pause > 20 seconds or > 15 seconds if associated with a heart rate < 80/min or oxygen saturation < 85%. A "true apneic" event occurs by visual inspection of the continuous electronic cardiorespiratory waveform on the central monitor. A study by Amin & Burnell, (2013) compared apnea events recorded by bedside cardiorespiratory monitors and nursing documentation with those detected by visual inspection of continuous electronic cardiorespiratory waveform. The number of apnea episodes recorded by nursing documentation and bedside monitors were 207 and 418, respectively. Only 7.7% of apnea events recorded by nursing documentation were confirmed as "true apnea events" compared with 50.4% of apnea recorded by bedside monitors, which was statistically significant. Of true apnea (n = 211) episodes recorded on central monitors, 99% were recorded

Leslie Altimier is an Affiliate Associate Professor at the Northeastern University, Boston, MA, USA, and a Sr. Director of Clinical Innovation & Research at Masimo, Irvine, CA, USA. E-mail: laltimier@gmail.com. Apoorva Jayaram is a Senior Product Manager at Masimo, Irvine, CA, USA.



by bedside monitors but only 7.6% of apnea occurrences were recorded by nursing personnel.

Respiratory rate as a forgotten vital sign

There is evidence that healthcare personnel believe that some vital sign measurements are currently valued little, not regularly or accurately recorded, and frequently not acted on appropriately. If vital signs were more accurate, frequently measured and acted on promptly and appropriately, hospital care would be safer, better, and cheaper (Kellett, and Sebat, 2017). In the neonatal intensive care unit (NICU), heart rate, respiratory rate, and oxygen saturation are vital signs (VS) that are continuously monitored in infants, while blood pressure may be monitored continuously immediately after birth or during critical illness, but is then only spot-checked. Recent studies demonstrate that analysis of continuous vital sign trends can predict sepsis, necrotizing enterocolitis, brain injury, bronchopulmonary dysplasia, cardiorespiratory decompensation, and mortality. When reviewing spot vital sign data or vital sign trends captured on a monitor, even the most experienced nurses were unable to discern subtle differences (Cardona-Morrell, 2016). In contrast, objective analysis of continuous VS data can improve neonatal outcomes by allowing heightened vigilance or preemptive interventions. Therefore, a pressing need exists to improve the reliability of RR monitoring in this patient population (Kumar, et. al., 2020).

Respiratory rate is the sentinel and most important vital sign because normal RR values are frequently breached before other vital signs in nearly all states of clinical decline. Respiratory rate (RR) is an independent predictor of adverse outcomes and an integral component of many risk prediction scores for hospitalized infants; yet RR is frequently referred to as the "forgotten vital sign" (Warburton, et al., 2019).

Need for respiratory monitoring

The immaturity of a premature infant's brain governs the respiratory rhythm, resulting in irregular breathing patterns. Monitoring the breathing patterns of preterm infants allows for better recognition of physiological instability and can provide valuable insights into the cardiorespiratory status of the neonate, as well as their maturation level. (Jorge, et al, 2019)

Changes in respiratory rate and sounds are often the earliest warning of apnea, respiratory insufficiency, and sepsis, among others. In these conditions, abnormalities in respiratory rate are the first signs that warrants further assessment and rapid intervention to prevent further decline and unexpected cardiac arrest. Despite strong evidence that abnormalities in respiratory rate are an early predictor of preventable patient deterioration, it remains the most inaccurately measured and recorded vital sign.

Technologies to help monitor neonatal ventilation

Vital signs are the simplest, least expensive, and probably the most important information gathered on patients in hospital. In adherence to clinical care standards, preterm infants admitted to a NICU undergo continuous monitoring of heart rate (HR) acquired using the electrocardiograph, and peripheral blood oxygen saturation (SpO2) acquired using pulse oximetry. While other vital signs such as heart rate (HR) are measured objectively using automated technology, RR is visually assessed subjectively and manually counted increasing the chance of imprecision and error (Badawy, et al., 2017).

Progress in medical sensors and computational intelligence has facilitated the development of smart bedside monitors that can integrate multiple parameters into a single monitoring system. Respiratory monitoring can occur with a variety of technologies like electrocardiography, infrared spectrometry, piezoelectric transducer, optical sensors, nasal thermocouples, respiratory-effort belt transducer, infrared thermal imaging, and etc. The unique physiology of neonates with their small size and fragile conditions can be challenging when monitoring and measuring vital signs. Continuous monitoring of a neonate's vital signs enables earlier detection of physiological deterioration and opportunities for life-saving interventions (Warburton, et al. 2019). The development of new, innovative, non-invasive, multi-parameter continuous physiological monitors is especially important for neonates. Utilizing a new innovative sensor that monitors respiratory rate continuously and acoustically offers the promise of improving clinical outcomes in this vulnerable population.

The criterion 'gold' standard for measurement of RR is to visually observe or auscultate the chest to count breaths for 1 min, or at a minimum 30 s with multiplication of the number of observed breaths by two (2) in order to obtain breaths per minute. A clinician can gently place a hand on the baby's stomach or chest, counting each rise of the abdomen as a single breath. Alternatively, they can position a hand a few inches away from the baby's nostrils and count every exhalation from the nose as a single breath.

Alternatively, continuous monitoring of respiratory rate (RR) in neonatal units is generally achieved by electrical impedance pneumography (IP). IP is a convenient method in the NICU setting, as neonates are already monitored by electrocardiography; however, inaccurate readings occur due to several factors including poor probe placement, motion artefact, and physiologic events which cause thoracic movements unrelated to breathing (such as coughing or crying). Additionally, there are fundamental challenges in that premature infants have fast breathing rates (upwards of 80 bpm) (Brouillette, et al., 1989). As a result, there is a high prevalence of false alarms, which can create alarm fatigue and stress in nurses, as well as the overstimulation of premature babies' developing brains (Altimier & Philips, 2022).

For neonates that are mechanically ventilated, non-invasive end-tidal carbon dioxide monitoring by capnography is an alternative method of respiratory assessment. Although mechanical ventilation can be lifesaving, the long-term complications may increase in infants who have suffered abnormalities in carbon dioxide (CO_2) levels. Disturbances in cerebral blood flow caused by vacillating differences in CO_2 levels can lead to intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), and subsequent cerebral injury. Capnography assesses the respiratory rate and the exhaled breath-by-breath CO_2 levels in real time and gives a continuous waveform together with the end-tidal CO_2 ($EtCO_2$) measurement (Gravenstein, et al., 2019; Chandrasekharan, et al.). Mainstream or sidestream capnography can be used in neonates; however, sidestream capnography is preferred due to the reduced weight of breathing circuits.

There are several methods of monitoring a patient's respiration, yet many of these can bring discomfort and soreness to the patient. Apnea (abrupt stopping of respiration) and bradycardia (rapid decrease of heart rate) are common and serious problems in premature infants. An innovative technology that exists can provide continuous, non-invasive respiratory rate through a small sensor that has a thin, flexible adhesive allowing for comfortable application on patients with fragile skin. This acoustic based technology provides accurate respiratory rate measurements and acoustical sounds that flow into the EMR. Detecting acoustic signals produced by the turbulent airflow in the upper airway that occurs during inhalation and exhalation provides the accurate respiratory rate. The respiratory signal is separated and processed to display continuous respiration rate and an acoustic respiration waveform; a visualization of the signal caused by the patient's airflow. Additionally, the clinician can monitor for any pauses in breathing throughout the baby's stay. With technology like this, clinicians will be able to listen normal breath sounds and adventitious lung sounds (wheeze, rhonchi, crackle, etc.), which are usually associated with certain pulmonary pathologies.

Future Innovations

The design of alternative non-invasive solutions for the physiological monitoring of these vulnerable patients are greatly needed, especially technology to improve the reliability of RR monitoring. Heart and lung sounds heard using a stethoscope are the result of mechanical interactions during the operation of cardiac and respiratory systems, respectively (Padilla-Ortiza, et al., 2018). The ability to listen to these sounds in combination with monitoring would improve the assessment of a neonate's respiratory system. Normal breath sounds occur when no respiratory problems exist, whereas adventitious lung sounds (wheeze, rhonchi, crackle, etc.) are usually associated with certain pulmonary pathologies.

As new and innovative solutions are developed, one should consider the future use of these in telehealth monitoring. The possibility of seeing and hearing respiratory rate and lung sounds remotely could benefit patients who live in rural towns without access to healthcare or for neonatal transports. A full and thorough assessment of a baby's respiratory system is a critical part of patient care and should never be the forgotten vital sign.

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Applying Improved Growth Metrics for Preterm Infants Supported With a Human Milk Diet

Patti Perks, MS, RDN, CNSC; Stacia Pegram, MA, RDN, LD; Andi Markell, RD, LD, MSL-BC, CSP; Melinda Elliott, MD, FAAP

Tracking and optimizing preterm infants' growth in the neonatal intensive care unit (NICU) is paramount to their care, impacting short-term mortality and morbidity and long-term neurodevelopmental outcomes.[1,2] The gestational period from 20 to 41 weeks is a time of exponential brain growth. This dynamic phase of brain maturation is demonstrated in substantial growth of specific fetal tissues or zones,[3] with a 20-fold increase in brain volume occurring between 20 weeks and term gestation.[4] In order to support this rapid growth, preterm infants require increased and optimized nutrition along with protection from inflammation, with the goal of supporting appropriate growth rates and optimal neurodevelopment.

Barriers to Tracking Growth in the NICU

Preterm infants must grow rapidly during those critical first weeks of life in order to promote healthy neurodevelopment over the long term.[5] However, what constitutes healthy growth in this unique patient population is less clear. Despite the critical importance of accurately tracking growth metrics in preterm infants, current approaches used for assessing growth remain both inadequate and non-standard.[6] Seminal work by Ehrenkranz et al led to a target weight gain velocity approaching 21.2 g/kg/day. The current gold standard growth goal for infants born weighing <1500 g is 15-20 g/kg/day in weight gain and >0.9 cm/week in length and head circumference gain.[7] While these numbers are widely accepted, methods for calculating growth across NICUs and studies remain non-standard. For example, the early 1-point method, average 2-point method, and the exponential 2-point method will each yield substantially different growth velocity calculations for a single infant. There is also lack of standardization with regard to the time period over which growth is measured, with some experts calculating from birth to discharge and others calculating from point of regained birth weight to discharge.[6,8] Given that different calculation methods yield different results, targeting an absolute number as a sign of healthy growth has significant limitations.

To complicate matters further, the Fenton growth chart, which is the standard tool for determining healthy growth velocity in preterm infants, is based on measured birth weights at each gestational age and does not take into account how infants grow ex utero, compared with in utero. The impact of these different environments in term infants is recognized, with term growth charts taking into account normal weight loss that occurs at birth. Preterm infants are subject to the same changes that occur when moving from an aqueous to a non-aqueous environment, most notably diuresis, yet preterm infant growth charts fail to accommodate this physiologic change.[6] New and emerging evidence suggests that preterm infants should not be expected to grow right along the percentile at which they were born. Rather, it is expected for them to lose weight soon after birth, similar to term infants.[9]

Another limitation to the current approach to measuring growth among preterm infants is an often narrow focus on weight alone. To obtain a fuller picture of healthy growth, it is important to also measure length and head circumference as well as calculate z scores, which measure the number of standard deviations above or below a standard reference mean, and percentiles. There is evidence that these metrics are predictive of neurodevelopmental outcomes.[2,6,8,10,11] Equally important is to accurately quantify nutritional intake and provide sufficient nutrition to support desired growth.[12]

Role of Breastfeeding in Growth and Development

Breastfed term infants may gain weight more slowly than formula-fed infants. The Centers for Disease Control and Prevention recommends using the 2006 World Health Organization Child Growth Standards for assessing growth in term infants, as these take into account the impact of breastfeeding as the optimal nutrition.[13-15] This has led to the "breastfeeding paradox" in which preterm infants who were breastfeeding at discharge were at increased risk of losing more than 1 z score for weight during hospitalization but also demonstrated improved neurodevelopment.[16] Subsequently, Bergner et al demonstrated neurodevelopmental cognitive outcomes within normal limits in preterm infants who were exclusively fed human milk, with appropriate catch-up growth and body composition as compared with term infants at age 2 years.[17] Bergner et al and Visuthranukul et al have demonstrated that preterm infants, both appropriate for gestational age and small for gestational age (SGA), fed an exclusive human milk diet (EHMD) may have slower weight gain velocity but develop healthier body composition as compared with preterm infants with central adiposity, short stature, and an associated increased risk of metabolic syndrome.[17,18] Clearly, weight gain velocity alone does not tell the whole story when evaluating preterm infant growth in the NICU.

Moving Toward Better Growth Metrics in Breastfed Preterm Infants

Evidence of slower but more healthy growth patterns observed

Author information are listed at the end of this article.

among preterm infants has led Fenton et al to recommend moving away from terms like "extrauterine growth restriction" and "postnatal growth failure" because these are based on arbitrary cutoffs, ignore normal postnatal weight loss associated with diuresis, do not consider each infant's genetic potential, are not predictive of poor neurodevelopmental outcomes, and do not take into account other growth assessments, such as length and head circumference.[2]

Guidelines on the management of neonatal malnutrition provide guidance as to how to appropriately assess growth and nutritional status in preterm infants. The guidelines emphasize that, in addition to weight gain, important metrics include weight-for-age z score, nutrient intake, days to regain birth weight, linear growth velocity, and length-for-age z score.[10] Another very important growth metric in preterm infants is head circumference.[7]

Cormack et al have taken steps to standardize assessment of growth in the preterm setting, developing the StRONNG checklist, which includes both growth velocity and z scores and suggests an international standard for assessing growth, body composition, and nutritional calculations.[6]

Role of an EHMD

While there is good evidence that preterm infants thrive on breast milk, unfortified breast milk cannot meet their increased nutritional needs.[12] In addition, the variability in the composition of human milk,[19-21] and the fact that fat[22] and other essential nutrients[23] can be lost in the equipment used to store, collect, and feed human milk to preterm infants, are major challenges of feeding breast milk to preterm infants and meeting nutritional goals.

Thus, a nutritional fortifier is necessary to provide adequate nutritional intake among preterm infants fed breast milk, and the only way to maintain the benefits of a human milk diet when using a fortifier is to select one made exclusively from human milk. This is known as an exclusive human milk diet, or EHMD.

An EHMD has been shown to reduce complications and improve both short- and long-term outcomes in preterm infants,[24-32] but a lingering concern has been that growth may be slower in infants fed an EHMD, compared with those who received cow milk-based formula. A better understanding of what comprises healthy growth and development in a preterm infant during the NICU stay offers an opportunity to better evaluate the benefits of an EHMD.

Typically, an EHMD is targeted to the most fragile and complex infants, a population subject to many reasons for suboptimal growth. Sepsis and inflammation can delay growth, particularly brain growth.[33] Intrauterine growth restriction and SGA status or metabolic syndromes can all result in altered growth trajectories after birth. Contributing factors to postnatal growth delays include hyponatremia, metabolic acidosis, steroids, inflammatory processes, and individual nutrients such as zinc.[34] Hyponatremia must be addressed to achieve good growth.[35] Preterm infants receiving dexamethasone therapy for chronic lung disease demonstrated decreased growth not explained by increased energy expenditure or reduced intake.[36] It is therefore important to determine realistic growth standards in these infants that correlate with improved long-term outcomes and to ensure that all factors that impact growth in these complex

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patients, including drugs and concomitant medical conditions, are addressed.[11]

Evidence continues to demonstrate that providing an EHMD can help promote healthy growth and better neurodevelopment in preterm infants.[17,18,37] One important role an EHMD plays in this regard is the ability to safely initiate and advance enteral feeding, thus achieving full enteral feedings more rapidly.[25,26,28,38] The ability to achieve full enteral feeds early in life appears to be related to better neurodevelopmental outcomes in addition to simply shortening central line and parenteral nutrition days. Schneider et al demonstrated that nutritional intake in the first 2 weeks of life is predictive of neurodevelopmental outcomes at 18 months, but variations in intake were almost entirely due to enteral, not parenteral, feeding.[39] Nakanishi et al demonstrated that the shorter time to establishment of full enteral feeding, the lower the risk of suboptimal neurodevelopment.[40] Additionally, if fortification is delayed and/or attainment of adequate enteral feeds is delayed, this can impact growth metrics and may be associated with poorer neurodevelopmental and metabolic outcomes.[39]

Studies demonstrating slower growth velocity in EHMD infants, compared with those who received cow milk-based nutrition, should be evaluated closely, as weight gain and growth calculations may be describing very different ways of assessing growth. For instance, O'Connor et al demonstrated no significant difference in growth between preterm infants fed an EHMD and those who received cow milk-based nutrition, but growth charts of these infants' length and head circumference clearly demonstrate a non-significant trend toward better growth in the EHMD infants by the end of the study period.[29] There is a need to better characterize what constitutes healthy growth in preterm infants, both early in their NICU stay and over the course of their development, correlating growth patterns in the first weeks of life with long-term neurodevelopmental outcomes. With improved metrics and evaluation of the entirety of clinical outcomes, clinicians and researchers will be better equipped to identify the benefits of an EHMD.

Summary

Current practice with regard to tracking growth in preterm infants in the NICU is overdue for an update. A comprehensive growth assessment takes into account weight gain, increases in length and head circumference, z scores, percentile rankings, and nutrient intake. There is a need to standardize methods used to calculate these metrics and, absent such standardization, absolute numbers should not be used as growth targets. Preterm growth charts need to be updated to accommodate normal physiologic changes associated with entering the non-aqueous ex utero environment. While preterm infants must grow quickly in the first weeks of life in order to optimize short- and long-term outcomes, all growth is not equal, and standardization of growth metrics is essential, as is consideration of medical conditions that delay growth. Once these challenges have been addressed, evaluating the benefits of breast milk and an EHMD in preterm infants can be presented more accurately and encompass all aspects of an infant's development. Assessing and reporting healthy growth patterns as well as desired clinical outcomes in preterm infants require better and more consistent characterization through further research.

About the Authors

Patti Perks has specialized in neonatal nutrition support for over 20 years, and is currently a neonatal nutrition support specialist in the NICU at the University of Virginia Children's Hospital in Charlottesville, Virginia. She is involved in numerous quality improvement initiatives, and provides infant nutrition education to residents, nurses, nurse practitioners, and fellows. Her responsibilities include oversight of inpatient and outpatient pediatric nutrition services at UVA Children's Hospital. She is a founding board member and past president of the Virginia Neonatal Nutrition Association, a nonprofit educational organization.

Stacia Pegram has been a clinical dietitian at the Prisma Health Richland NICU in Columbia, South Carolina, for over 20 years. She has a wide range of experience and expertise in leading NICU nutrition initiatives, including the development and management of feeding guidelines, quality improvement programs, and education of NICU staff. She has been involved in the South Carolina Neonatal Nutrition Consortium to develop statewide NICU nutrition initiatives and is an active member of several nutrition-related professional societies.

Andi Markell is director, medical science liaisons and clinical nutrition at Prolacta Bioscience. As a medical science professional with nearly 20 years' experience in NICUs, she believes in linking science and bedside care to provide the best nutrition for premature infants. As a neonatal dietitian, she has worked to understand the benefits of an EHMD in the NICU since 2008. She aims to help hospitals generate the best outcomes for very low birth weight infants.

Dr. Melinda Elliott is a practicing neonatologist and chief medical officer of Prolacta Bioscience, where she serves as the voice of the patient, working to ensure that the needs of premature and critically ill infants are being articulated and that the relevant treatment and product opportunities are identified. As a neonatologist and experienced researcher in neonatal intensive care, she has committed her career to the care of vulnerable, premature infants and has researched the benefits of an EHMD for extremely low birth weight premature infants in the NICU.

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When Feeding Error Prevention Isn't Enough

Jaylee Hilliard, MSN, RN, NEA-BC, CPXP and Grace Dwyer, MS, MA, RD, LDN, IBCLC

Healthcare professionals universally agree that patient safety is a top priority. When it comes to feeding and milk management in the NICU, awareness is beginning to shift regarding just how many errors can occur in this process that risk neonates' safety (including those that go undetected). Yet, surprisingly, it can nonetheless be difficult for clinical leaders to get buy-in from their executive leadership to install solutions that have proven to drastically reduce milk- and formula-related mistakes in the NICU. How does one make the case for the adoption of feeding management technology when error prevention is so difficult to quantify?

The NICU Misfeed Landscape: Feast or Famine

It's understandably a challenge to avoid feeding errors in the NICU, given dynamic and complicated feeding regimens using ingredients that are easily subject to contamination. The most common feeding errors in the NICU can vary from microbiological contamination to inaccurate fortification to misappropriation (providing the wrong mother's milk to a patient).

While feeding errors are concerning for any patient population, they are particularly problematic for premature and high-risk infants, who are less mature and more vulnerable to becoming sick from feeds. Infants who are very low birth weight (<1500 g) or are born before 32 weeks gestation are at the greatest risk of developing sepsis or necrotizing enterocolitis (NEC) from even a relatively small number of microorganisms or microbial toxins in their feeds.[1]

According to Mark Hudak, MD, Chief, Division of Neonatology at the University of Florida College of Medicine at Jacksonville, feeding a baby breast milk from another mother introduces risks of infectious disease transmission and exposure to small quantities of drugs or other substances secreted in that mother's milk. For example, a mother with active cytomegalovirus or untreated HIV may pass these viruses into breast milk and the infant can acquire these infections through this milk. Infection is a risk that can result from just one incorrect milk feeding.

> "Feeding errors commonly generate parental alarm and lead to lack of confidence in the hospital and clinical team"

"Feeding errors commonly generate parental alarm and lead to lack of confidence in the hospital and clinical team," Hudak said. "Feeding an infant with another mother's milk requires testing for infectious agents, an expensive anxiety-generating process."

The True Cost of NICU Feeding Errors

Feeding errors often result in significant financial consequences that are far more expensive than any technology platform designed to mitigate the issues.

"Medical errors in the United States alone cost approximately 20 billion dollars per year," said Anthony Orsini, Neonatologist for MEDNAX and Vice-Chairman of Neonatology, Winnie Palmer Hospital. "In addition, the social and emotional impact on patients and families is immeasurable, especially when it involves NICU families. Parents of premature and at-risk babies have many complications to worry about. Feeding errors should not be one of them."

Risks related to milk mismanagement are plentiful and can range from lower patient satisfaction scores to the potential for litigation and reputational damage. Any of these potential threats can substantially impact a hospital's bottom line.

Research has demonstrated the impacts of scanning systems on error prevention, giving us a sense of how many errors would have otherwise gone undetected. For example, a recent review found that barcode scanning prevented human milk errors 1226 times over seven years and prevented formula errors 480 times over 2.5 years. This equates to an average of 3.4 human milk errors and 3.7 formula errors per week, respectively.[2]

These feeding errors can have medical consequences that, in turn, have high financial and psychological costs. Feeding

Jaylee Hilliard, MSN, RN, NEA-BC, CPXP is Senior Director of Clinical Strategy at AngelEye Health where she is focused on supporting hospital and health system partnerships to deliver specialized patient and family support via state-of-the-art technology. In her role, she drives product innovation and support development, leads the clinical team to effectively support healthcare leaders across the nation in technology optimization and supports hospitals in their pursuit of achieving the quadruple aim. Grace Dwyer, MS, MA, RD, LDN, IBCLC is a Clinical Product Manager at AngelEye Health with a focus in milk and formula management. Prior to joining AngelEye's team, Grace provided medical nutrition therapy and lactation counseling for mothers and infants, including dyads with high-risk and preterm births.

expired milk or formula contaminated with bacteria can result in NEC or sepsis, for which a single case can cost $400,000-$500,000 (for surgical NEC) and up to $129,632 (for sepsis).[3,4] Human milk misadministration can transmit infectious disease, requiring a series of labs for both parent and baby. While the actual risk for transmission of an infectious agent to the infant from a single instance of improperly administered breastmilk is extremely low, the CDC recommends treating the misappropriation as an accidental exposure to a bodily fluid, which could be infectious.[5] That scenario requires managing the situation from both the infection control/prevention and the medical-legal perspectives which can be time and resource-intensive.

Misadministration errors also cost hospitals clinical staff time. Nurses and their supervisors must spend time on incident reporting and navigating this sensitive issue with families. Today's average hourly wage for Registered Nurses is $38.74 per hour but can be much higher given bonuses and travel nursing fees amidst the current staffing challenges.[6] Healthcare providers must also communicate with impacted families, order appropriate labs and follow-up care, and document the event. This diverts much-needed resources away from direct patient care in a setting where resources may already be strained.

Feeding errors have psychological costs, as well. Families with hospitalized children are already under extreme stress and anxiety. Parents expect that staff will provide the highest quality of care to their child, but staffing shortages frequently requiring clinicians to care for more patients increase the risk of error.

Technology to the Rescue for Safer, More Efficient Feeds

Various professional organizations have recognized the importance of safe, accurate human milk handling (both maternal and donor milk) and have published guidelines accordingly; these organizations include the Academy of Nutrition and Dietetics, the American Society for Parenteral and Enteral Nutrition, the National Association of Neonatal Nurses, and the Human Milk Banking Association of North America.[7] Additionally, barcode scanning for human milk is recommended as an essential safety practice by the Academy of Nutrition and Dietetics, the Agency for Health Research and Quality, and the Healthcare Information and Management Systems Society. [8,9,10]

Additionally, some scanning technology can make workflows cumbersome for staff, says Susan Bowles, DNP, APRN-CNS, RNC-NIC, CBC Nurse Consultant, Florida Perinatal Quality Cooperative. "I've encountered times when, on a busy shift, nurses have 'clustered' their feed scans to save time which defeats the entire purpose of the technology in the first place. This can lead to potential errors."

Efficiency is a critical component when evaluating milk management systems. Research shows that feeding management software can meaningfully enhance efficiency, thanks to automating tasks like generating labels, charting feeding data, and eliminating two-nurse verification.[2] Amid staffing shortages, nurses are expected to provide top-notch care despite having less bandwidth and energy than ever before. Streamlining processes is, therefore, more critical now than ever for staff retention and quality of work life. When assessing milk management solutions, consider if the vendor performs a clinical workflow assessment and gap analysis which ensures current workflows are supported further decreasing the desire for staff to find loopholes in the technology.

> "Parents of premature and at-risk babies have many complications to worry about. Feeding errors should not be one of them."

Feeding Safety as an Ongoing Process: The Next Steps

After deciding to move forward with implementing a milk and formula management software, it's important to realize that how the software is implemented matters too, Bowles added.

Every unit is different regarding feeding workflows - physical layout, feeding protocols, acuity level, and unit culture (among others) influence how the system is configured and implemented. Therefore, it is best practice to begin feeding management system implementations with an on-site clinical assessment and gap analysis to thoroughly understand the unit's current practices. Ideally, these can inform decisions on how technology can best support the unit's individual needs while implementing the most efficient workflows determined by clinical best practices.

Feeding safety is an ongoing process after the software is installed. In exploring human milk errors in their NICU, researchers Luton et al. found that a "culture" of an ongoing commitment to quality improvement was paramount for safe feeding processes.[11] Having a system that incorporates data collection and robust reporting capabilities makes the goal of continuous quality improvement achievable. When clinical leaders have easy access to key information, they tend to spend time reviewing on a regular basis to inform quality improvement projects that align with their priorities.

Feeding Errors in the Hospital: If It Were a Snake It Would've Bit You!

In many hospitals, patient safety errors occur directly under the noses of clinical leaders who often rely on staff to self-report their mistakes. Not only is self-reporting an inefficient way to track patient safety errors, but it also leaves room for these mistakes to go unnoticed as many nurses and staff do not even realize they are making a feeding misstep. These unnoticed errors can have detrimental downstream impacts on staff, patients, and their families.

It can be challenging to articulate the risk when there is no reliable process in place to identify all of the near or actual misses in feeding management. NICU leaders may find themselves wondering, how many milk-related errors are acceptable before really addressing these risks is prioritized? If patient safety truly is a priority for healthcare organizations, deciding to invest in technology that can minimize risk shouldn't be so difficult.

Cost-effective technologies are available to hospitals that improve feeding accuracy and reduce feeding errors, saving both time and money. Without technologies like these in place, hospital leadership can't measure the true extent of milk and formula management near misses and errors, presenting a catch-22 dynamic for understanding the true value of the technology.

While Available, Error Prevention Resources Are Currently Under-Utilized

NICU Nurses spend close to 13,000 hours every year, across roughly 1,100 NICUs, managing breast milk for the nearly 500,000 babies born prematurely in the United States that require special and often critical care in the first months of their lives. That is 13,000 hours (the annual equivalent of six full-time nurses) not only feeding, but monitoring, labeling, printing, and logging feeds.[12] There are specific platforms available to hospitals that have been purpose-built to address these resource challenges, offering a simplified way to manage breast milk inventory supply while ensuring that the right feed matches the right patient every time. These systems reduce errors and enhance safety throughout the entire feeding process. Technology that has the potential to prevent a substantial number of errors is not being widely utilized because some executives are just not aware of the scope of the problem or the financial ramifications. It will not be appropriately prioritized until the cost-saving story is broadly shared.

Hospitals today have several feeding management systems available to choose from. Nursing, lactation, and nutrition leaders should strongly consider a system that supports and engages parents as integral members of their child's care team, while also ensuring patient safety and clinical efficiency. Given mothers' vital role in milk production, it is a missed opportunity to invest in software that lacks the ability to support family engagement and lactation during such a critical time. Features such as enhanced transparency into inventory, virtual pumping logs, breastfeeding education, and communication with hospital lactation resources are available and should be leveraged to support and improve the feeding experience for families while ensuring the safe passage of patients for the highest quality of care.

A Special Thank You to Our Contributing Commenters

Anthony Orsini, DO, is the NICU Medical Director at Jupiter Medical Center, Keynote speaker, author of the book "*It's All in the Delivery*", Top 100 podcaster, TEDx speaker, President and Founder of The Orsini Way, Chief of Patient Experience Pediatrix Medical Group of Florida.

Mark Hudak, MD, is the Chief, Division of Neonatology at the University of Florida College of Medicine at Jacksonville and serves as the Associate Dean of Managed Care and Professor of Pediatrics. Dr. Hudak is the immediate Past Chair of the American Academy of Pediatrics, Section on Neonatal Perinatal Medicine.

Sue Bowles, DNP, APRN-CNS, RNC-NIC, CBC is a doctorally prepared Neonatal Clinical Nurse Specialist. Sue has been involved in all areas of Neonatal Nursing for the past 38 years. She currently serves as the Nurse Consultant for the Florida Perinatal Quality Collaborative for the statewide Paired Project.

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Feeding Babies During a Formula Shortage

Sandra Sundquist Beauman, MSN, RNC-NIC

Shortages have become commonplace in daily life and in healthcare. For years now, medication shortages have occurred from time to time leading to clinical practice changes or less than optimal replacements. With the onset of the COVID-19 pandemic, closures in various countries and areas, delayed shipping and other societal changes, shortages have become more frequent. It all started with toilet paper and bottled water hoarding resulting in shortages, progressed to mask shortages and so on. The most recent shortage that has created panic and stress is the formula shortage. Food insecurity is defined by the United States Department of Agriculture (USDA) as a lack of consistent access to enough food for an active healthy life.[1] This may be further defined as a lack of financial resources for sufficient food but with infant formulas as well as other foods from time to time and in certain areas, it can be both a lack of availability and money. This recent spike in shortages in infant formulas can be addressed in several ways that will be discussed in this article.

Formula shortages were occurring before it became widespread in early 2022 with hospitals and families experiencing intermittent shortages, particularly of certain specialty formulas related to supply chain issues.[2] With the shut down of the Abbott Nutritionals plant in February 2022,[3] formula shortage became much more widespread and was felt by families across the nation. Being faced with the inability to purchase formula to which they had become accustomed or any formula in some cases, and a hungry crying baby, families were understandably stressed by the situation. Mothers grasped on to leads via social media on how and what to feed their infant. Information provided was often misinformation. While various measures have been taken to address the formula shortage, as of June 24, 2022, it was reported as still ongoing.[4] A long term solution is needed.

While reliance on specialty formulas may be necessary for such conditions as severe allergies, renal failure, intestinal failure and metabolic disorders, reliance on formula in general in the United States is high compared to other high-income countries. The U.S. is reported as having one of the lowest exclusive breastfeeding rates in the world at 26%.[5] There are many reasons to increase breastfeeding rates in the US besides lack of availability of infant formulas. These include less incidence of illness in the newborn period, particularly diarrhea and respiratory illness, higher cognitive scores, significantly lower risk of obesity and a reduction in the risk of type 2 diabetes.[6]

Infants and families that have been reliant on infant formulas for non-medical reasons should be encouraged and assisted to feed their infant human milk. The Academy of Breastfeeding Medicine (ABM)[7] makes several recommendations during this shortage. For those who are currently expecting, make plans for infant feeding. Prenatal breastfeeding education and connecting with those who are supportive of breastfeeding will prepare the new mother to meet her goals for infant feeding. This is particularly important for first-time mothers or women who have not previously breastfed. In a meta-analysis of factors associated with breastfeeding initiation and continuation, the authors found that maternal breastfeeding education resulted in an overall increase of 41% in breastfeeding initiation and continuation.[8] This means discussion and encouragement to breastfeed should start during prenatal care and include specific breastfeeding education. Qualified lactation services and support should be readily available for pregnant women to prepare them for the first few days to weeks of breastfeeding thus increasing the likelihood for long-term breastfeeding

For mothers who are currently not breastfeeding or not making any milk, the ABM recommends consideration of re-lactating.[7] This is challenging and requires assistance from a knowledgeable lactation provider and may not be for every woman. The longer it has been since weaning, , the more difficult re-lactation may be. Instead, many have turned to pasteurized donor human milk. It is important that this milk come from a certified human milk bank with quality control over the collection, handling and pasteurization of the milk. Many of these banks have attempted to increase donations to fill this need. The Denver Mother's Milk Bank offered free human milk to those in need for 1 month starting at the end of May, 2022.[9] Normally, there is a charge for the milk to cover processing and delivery of the milk. Previously, milk banks may have also required a prescription, although not all. Most have dropped that requirement.

There are many opportunities to buy (and sell) milk via the internet. Geraghty et al[10] identified several sources from which to purchase human milk via the Internet. They ordered this milk in small quantities and evaluated it for condition of the box, packing materials and container as well as milk temperature and condition upon arrival. Some boxes arrived quite damaged raising concerns about the safety of the contents. In addition, temperatures were variable. This same group, in a separate publication, analyzed the milk received and found some of the samples had been contaminated with cow's milk in sufficient amounts to potentially cause issues for fragile infants.[11] They also found high levels of bacterial contamination, particularly pathologic bacteria which likely reflects less than optimal collection, handling and storage of the milk.[12] Based on their work, it is clear that obtaining human milk via the Internet is not ideal and should be avoided. ABM discusses the use of another's milk, not obtained through a milk bank. Wet nurses have been and still are used in many societies and cultures, as well as close family members who are breastfeeding and have extra milk. Families should be cautioned, though that even these close friends and family members should be screened for infectious diseases that could be transmitted through the milk.[7] If milk is collected and transferred, care should be taken to avoid contamination of the milk as well.

It is important to safeguard against mis-information regarding how and what to feed babies during this shortage. There are reports of advice on-line for early breast milk initiation and pumping, prior to delivery so that mother's have sufficient milk to feed their infant once the infant is delivered.[13] As many healthcare providers are aware, pumping the breasts releases oxytocin, a hormone that also induces labor. Therefore, pumping and freezing milk at early gestational ages could result in preterm labor and delivery. This is not advised until at least 37 weeks.[13] One of the wonders of human milk is that as stimulation increases, supply increases. Newborns don't need as much milk, yet sufficient amounts without excess in most mothers is available. As the infant grows and needs more nutrition, milk supply increases when breastfeeding is exclusive. Many mothers are able to pump in addition to breastfeeding and produce "extra" milk for times when they may be away from their infant.

In addition, suggestions exist for how to make formulas last longer. This includes things like mixing powdered formulas with more water and less powder to make it last longer, feeding cow's milk, goat milk, soy or almond milk. Mixing formulas inappropriately can result in electrolyte imbalances as well as poor nutrition. Use of cow's milk for infants under 1 year increases the risk of iron deficiency.[6] Iron is a necessary nutrient for cognitive development in this age group and can have long term consequences. If use of cow's milk is necessary, it should only be between 6 months and 1 year and then only for a short time and with close supervision of the infant's iron status.[6] Supplemental iron may be needed.

Parents should be informed that it is safe to switch from one formula to another in healthy term infants.[6,14] Infants under the age of 6 months should not be given water, tea or juice unless specifically instructed to do so.[7] The introduction of solid foods should only be done after consultation with a healthcare provider. In order to avoid waste, parents should be instructed to only put into the bottle the amount of milk the infant will take whether feeding an infant formula, donor human milk or pumped mother's own milk.

Clearly, there are several messages here for healthcare providers. Parents and families rely on advice received, if not from their healthcare provider, from other mothers, social media and elsewhere. It is important that they receive the best evidence-based advice from healthcare providers quickly and efficiently to avoid infants being fed a diet that can be harmful. Most importantly, evidence-based breastfeeding support should be readily available to mothers who are breastfeeding, wish to breastfeed or re-lactate as well as those who may wish to donate milk. Snyder and Worlton[15] conducted interviews with breastfeeding mothers during the COVID-19 pandemic to determine the effect of social support on breastfeeding. Social support was defined as emotional, instrumental, informational and appraisal. Emotional support was most often provided by family and friends, those closest to the breastfeeding mother. Informational support was often provided via social media or lactation support. While telemedicine lactation support was not reported to be ideal by first time breastfeeding mothers, it was better than nothing and perhaps better than social media, depending on the source. Particularly when specific issues were encountered, a face-to-face, hands-on visit to a lactation consultant was preferred for obvious reasons. This study was performed during this time period due to the recognition that many breastfeeding mothers no longer had in-person support as recommended. While this may be more available now, there are still many mothers who are in rural areas or otherwise unable to access in-person support. One important finding which has previously been demonstrated is that mothers discovered during the pandemic found that additional time to be home with their infant helped make long term breastfeeding successful. With many women only able to take little time away from work for maternity leave, breastfeeding has not yet been established. Many women stop because of difficulties faced when they must return to work. Lessons from this study, primarily the need for more in-person support should be incorporated into practice even though many pandemic related issues no longer exist.

The Baby-Friendly Initiative[16] has been in place for many years now. It is important to evaluate this program continuously to make sure it is not just a designation but truly integrated with maternity care. Exclusive breast milk feeding among term newborns during the initial hospitalization is a Core Quality Measure by which the Joint Commission evaluates hospitals.[17] In order to make this happen, the mother/infant dyad should room together 24/7 with the infant offered exclusively mother's own milk. The most common reason this does not happen is maternal request for the infant to go to the nursery and/or be given a bottle to feed.[18] If the mother has not been educated about what to expect, such as normal infant crying, expected frequency of breastfeeding, initiation of milk supply and others, they may be set up for failure. Evidence shows that introduction of formula feeding in the hospital leads to shortened time of exclusive breastfeeding after discharge.[19]

Photo supplied

Sandra Sundquist Beauman has been a neonatal nurse for her entire career, spanning over 40 years. She is currently the manager of clinical trials operation in neonatology at the University of New Mexico, Health Sciences Center, Department of Pediatrics, and an independent consultant with Medela LLC. She also provides neonatal consultation and continuing education through CNS Consulting.

Due to short maternity hospital stays, breastfeeding is not well established by discharge. A follow up visit, with a lactation specialist is recommended within 3-5 days of discharge as well as another visit at around 2 weeks. Other types of support should be offered in the interim such as peer support or a "warm line" where breastfeeding women can call for advice and support at the time it is needed. Otherwise, waiting until their next appointment may result in supplementation or abandoning breastfeeding altogether.

Another barrier to exclusive breastfeeding until 6 months is mother's returning to work. The US mandates that women are allowed at least 12 weeks of maternity leave.[20] However, it is not required that this leave be paid time. The result is that many women return to work much sooner because they cannot afford to take unpaid time off. Dinour and Szaro[21] completed a systematic review regarding employer-based programs to support breastfeeding mothers. Various measures included a dedicated lactation space, which was the most common, breastfeeding breaks and a comprehensive lactation support program. Each of these individually and in combination resulted in an increase in breastfeeding duration to 6 or 12 months, depending on the study as well as longer time for exclusive breastfeeding. Studies reviewed were from a variety of countries and types of employment including both public and private. Balkham, Cadwell and Fein[22] were able to demonstrate an increase in breastfeeding duration and exclusivity with each workplace support added, in other words a dose-response scenario.

Conclusion

There are many well-researched advantages to breastfeeding and several well-known factors that can influence this both positively and negatively. Infant formula shortages may ~~well~~ continue and/or be intermittent. The only way to ensure that infants have a sufficient food supply is to increase the likelihood that mother's own milk is available. This may be via direct breastfeeding or pumping the milk to be given to the infant. Breastfeeding is not something that women can accomplish without support of many. This includes society in general where breastfeeding becomes the norm rather than an alternative to formula feeding.

A key message offered by the *Lancet* Breastfeeding Series Group (2016), "success in breastfeeding is not the sole responsibility of a woman — the promotion of breastfeeding is a collective societal responsibility."[23] Society's support of breastfeeding may include paid time off for maternity leave sufficient to allow for the establishment of breastfeeding, less (no) advertisement of formula products to new mothers, education about the benefits of breastfeeding well before pregnancy and/or delivery, lactation support readily available in all neighborhoods to all socioeconomic levels, and promotion of mothers breastfeeding their infants in public spaces to name a few.

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

Ahlam M Saber, Magdy A Mohamed, Abdelrahim A Sadek and Ramadan A Mahmoud

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 ± 8.84 mg/dl for the hypoglycemia group and 54.10 ± 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 ± 0.96%) compared to normoglycemic babies (HbA1C 6.11 ± 0.38%), (*P*-value < 0.0001). The mean (SD) of UC C-peptide level in hypoglycemic neonates increased to 1.73 ± 1.07 ng/ml compared to normoglycemic ones with 1.08 ± 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.

Ahlam M Saber, Abdelrahim A Sadek and Ramadan A Mahmoud are with Department of Pediatrics, Faculty of Medicine, Sohag University, 15 University Street, Sohag 82524, Egypt. Magdy A Mohamed is with Department of Obstetrics and Gynecology, Faculty of Medicine, Sohag University, Sohag, Egypt.

Introduction

Despite marked declines in neonatal mortality nowadays,[1] 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.[2] Infants of a diabetic mother (IDM) often have complications closely linked to fetal hyperglycemia and hyperinsulinemia, induced by maternal hyperglycemia.[3]

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.[4]

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.[5] 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.[6,7]

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.[8]

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.

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

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

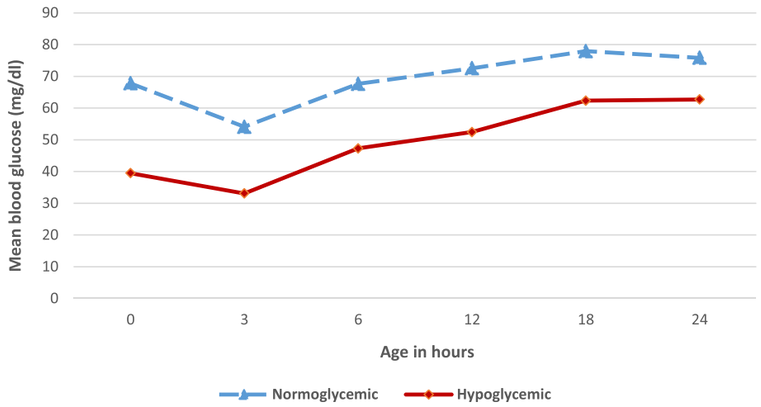

Figure 1. Comparison between normoglycemic and hypoglycemic IDM according to blood glucose during the first 24 h of life

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 ± 0.81) kg when compared to IDM with normoglycemia (3.78 ± 0.49) kg, although this difference was not statistically significant (P-value = 0.07). As regard the echocardiographic finding, ventricular septal hypertrophy (≥ 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 ± 8.84 mg/dl for the hypoglycemia group and 54.10 ± 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 ± 0.96%) compared to normoglycemic babies of mothers with good diabetes control (HbA1C 6.11 ± 0.38%), (P-value < 0.0001).

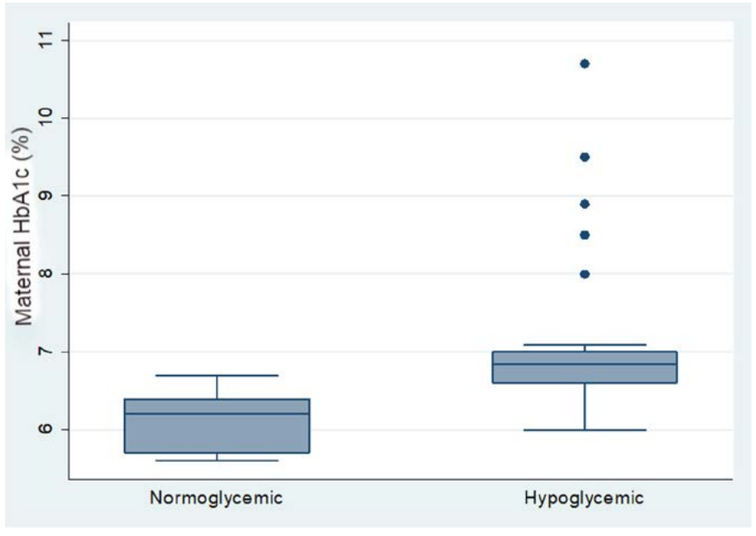

Figure 2. Comparison between normoglycemic and hypoglycemic infant according to maternal HbA1c

C-peptide measurements

Moreover, as shown in Fig. 3, the mean (SD) of UC C-peptide in the case group was 1.73 ± 1.07 ng/ml, ranging from 0.13 to 3.3 ng/ml, while in the control group, it was 1.08 ± 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

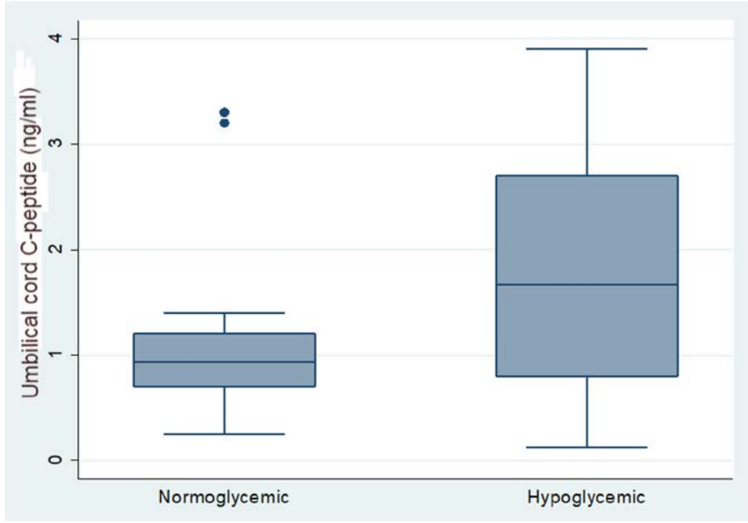

Figure. 3 Comparison between normoglycemic and hypoglycemic IDM according serum level of umbilical cord C-peptide

history of macrosomia in a previous pregnancy, and an increased pre-gravid body mass index.[2] In our study, 35 (42.17%) mothers had GDM, the mean ± SD of maternal age was 36.03 ± 6.93 years, and the mean ± SD of maternal weight was 77.76 ± 8.60 kg.

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.,[9] in which the occurrence of hypoglycemia was 73.3% within the first 6 h of life, while in Agrawal et al.,[10] 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.,[9] about 93.3% of the hypoglycemic babies were asymptomatic, while in Agrawal et al.[10] and Van Howe et al.,[11] 100% of the hypoglycemic babies were asymptotic.

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.[12] Previously, asymptomatic hypoglycemia has been considered to be of no clinical significance.[13] However, numerous studies have demonstrated that even asymptomatic hypoglycemia can have a poor neurodevelopmental outcome immediately after birth[14] and even later on up to school age.[15] 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.[9] In contrast, Agarwal et al.[10] 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.,[16] 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.[17] and Cooper et al.[18] 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.[19] and Fallucca et al.,[20] 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.[10,16,21] Even for some other IDM complications, we found no correlation between the presence of ventricular septal hypertrophy in IDM either with hypoglycemia or normglycemia cases. Other research by Vela-Huerta et al.,[22] 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 predicator 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.[9,17,18,20] Furthermore, the increased UC C-peptide level may be associated with infant macrosomia[17,23] and neonatal septal hypertrophic cardiomyopathy.[18] Therefore hyperinsulemia is the cornstone in the development of many complication in IDM.[24] 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 glycose; 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

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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