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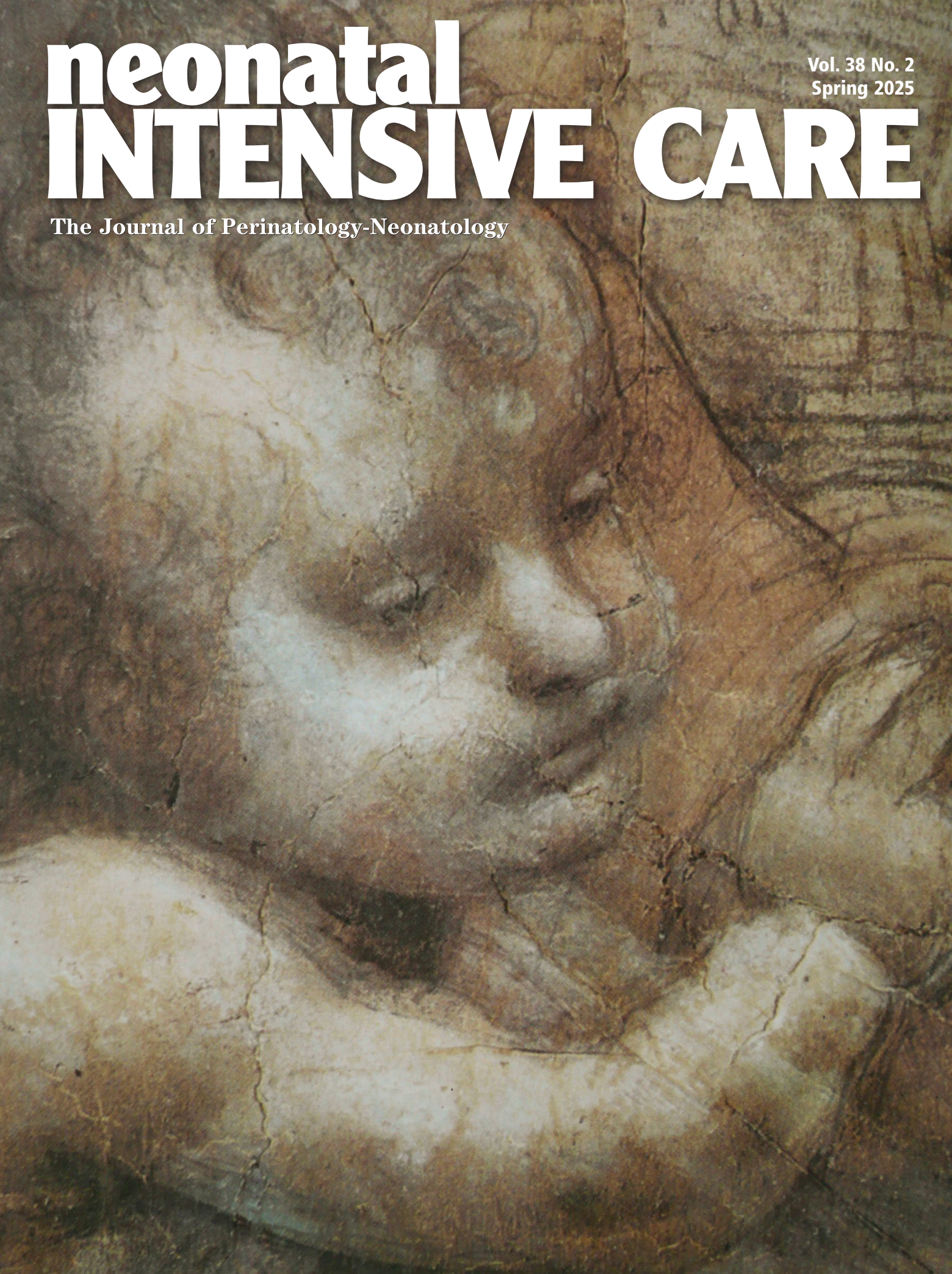

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Nirsevimab Cuts Hospitalisation Risk in Infant Bronchiolitis

Immunisation with nirsevimab reduced bronchiolitis-related hospitalisations among infants younger than 3 months who visited the emergency department (ED), according to a new study. Nirsevimab also reduced respiratory syncytial virus (RSV) positivity and paediatric intensive care unit (PICU) admissions.Researchers conducted a retrospective study across six paediatric EDs in France, including 739 infants younger than 3 months with a clinical diagnosis of bronchiolitis during the 2023-2024 RSV epidemic season. The primary outcome was hospitalisation after an ED visit, and the secondary outcomes included PICU admissions and RSV positivity. Subgroup analyses considered prematurity, age groups, and social deprivation, as assessed by the French Deprivation Index. The analysis was adjusted for age, sex, centre, visit week, comorbidities, bronchiolitis history, gestational age, and deprivation score. Nirsevimab showed 53.5% adjusted effectiveness in reducing bronchiolitis-related hospitalisations among infants after ED visits (95% CI, 34.1-67.3; P < .001). Hospitalisation rates were 51% in immunised infants and 69% in non-immunised infants. Nirsevimab showed 51.1% (95% CI, 10.7-74.3) and 79.6% (95% CI, 68.0-87.1) effectiveness in reducing PICU admissions and RSV positivity, respectively. Immunisation showed a consistent protective effect in preterm infants, neonates, and deprived groups, though statistical significance was not reached in smaller subgroups. "These findings support the widespread use of nirsevimab to prevent severe respiratory infections caused by RSV in young infants, highlighting its potential to substantially reduce the healthcare burden associated with bronchiolitis," the authors wrote. The study was led by Alexis Marouk, SAMU 93 - SMUR - Emergency Department, Avicenne Hospital, Public Assistance Hospitals Paris, Bobigny, France. It was published online on March 5, 2025, in the European Journal of Pediatrics.

Tocolytics Do Not Improve Neonatal Outcomes in Preterm Birth

The contraction inhibitor atosiban (Tractocile) was no better than placebo for neonatal outcomes in the context of threatened preterm birth, the investigators in the multicenter, randomized, placebo-controlled assessment of perinatal outcome after specific tocolysis in early labor (APOSTEL) 8 superiority trial reported in The Lancet. "The most important result of our study, that tocolytic drugs do not improve neonatal outcome when administered above 30 weeks of gestation, was unexpected," the study coauthor Larissa I. van der Windt, MD, an obstetrician and PhD candidate at Amsterdam University Medical Center in Amsterdam, the Netherlands, said. "The primary goal of tocolysis should not be prolongation of pregnancy but improvement of neonatal outcomes." Between December 2017 and July 2023, a total of 755 adult women at 26 Dutch, English, and Irish hospitals were randomized; 752 were included in the intention-to-treat analysis. The primary endpoint was a composite of adverse neonatal outcomes. These included perinatal mortality up to 28 days postpartum, which included bronchopulmonary dysplasia, periventricular leukomalacia > grade 1, intraventricular hemorrhage > grade 2, necrotizing enterocolitis > Bell's stage 1, retinopathy of prematurity > grade 2 or needing laser therapy, and culture-proven sepsis. The primary outcome occurred in 37/449 (8.2%) infants in the atosiban group and 40/435 (9.2%) in the placebo group (relative risk [RR] 0.90; 95% CI, 0.58-1.40). Three (0.7%) and four (0.9%) infants died in the two groups, respectively (RR, 0.73; 95% CI, 0.16- 3.23). All deaths were deemed unlikely to be related to the study drug, and maternal adverse events did not differ between groups. In the atosiban group, significantly more pregnancies were prolonged beyond 48 hours than in the placebo group (292/375, 78% vs 261/377, 69%; RR, 1.13; 95% CI, 1.03-1.23). There were 15 (4%) planned cesarean sections in the atosiban group vs 29 (8%) in the placebo

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Cover: The Virgin and Child with St Anne and St John the Baptist. Leonardo da Vinci. The image is public domain.

group (RR, 0.52, 95% CI, 0.28-0.95). The overall cesarean section rate, however, was similar in both groups (RR, 0.90; 95% CI, 0.69-1.16). Other secondary neonatal and maternal outcomes did not significantly differ between groups. There were 17 serious adverse events in the atosiban group and 12 in the placebo group, again, not considered treatment related. Although atosiban itself is not approved in the United States, tocolytic drugs have long been part of standard care, primarily based on studies investigating surrogate outcomes such as increasing gestational age and are often used off-label to prevent premature labor. In the APOSTEL 3 trial, the tocolytics nifedipine and atosiban were equally effective in prolonging pregnancy, but nifedipine showed a nonsignificant twofold increase in neonatal mortality. "When we looked into the evidence for whether these drugs are actually associated with better neonatal outcomes, we found no study demonstrated a positive effect of tocolytic therapy," van der Windt said. "We felt it was time to investigate these drugs with the proper primary outcome because tocolytic drugs should be given with the purpose of improving neonatal outcomes." Van der Windt questioned the advisability of inhibiting contractions in the setting of preterm labor since most women affected go into preterm labor for reasons such as infection or placental problems. "In this setting, it might not be the best option to try to inhibit contractions." In her opinion, further research should primarily focus on preventive therapies/interventions for preterm birth.

Company Expands Global Distribution

Beyond Air, Inc., a commercial-stage medical device and biopharmaceutical company focused on harnessing the power of nitric oxide (NO) to improve the lives of patients, announced the expansion of its global distribution channels for LungFit PH with several new distribution agreements that will cover four countries, including France, Romania, Turkey and Morocco. "Global interest for our LungFit PH system, which only just received CE Mark about 15 weeks ago is very strong. With the addition of these latest agreements, our international commercial footprint currently includes 18 countries, and we are rapidly moving towards signing additional agreements that will further expand our distribution network," said Steve Lisi, Chairman and Chief Executive Officer of Beyond Air. "Considering the commercial experience we have gained over the past couple of years, and positive feedback from a rapidly growing list of leading US hospitals actively using the LungFit PH system, we anticipate a more rapid commercial ramp-up in the international market than seen in the US. We also will have the advantage of distribution partners that have established medical device infrastructure to help generate positive early momentum." Beyond Air's LungFit PH generates nitric oxide from room air, eliminating the need for traditional high-pressure cylinders. This tankless technology streamlines operations, enhances efficiency, and supports sustainability efforts within hospital settings. Potential customers can visit the LungFit PH website, www.lungfitph.com for additional information, including the product label, and to sign up for company updates.

Company Reaches Milestone

Passy Muir celebrates 40 years of providing quality tracheostomy products made in the USA. With a commitment to enhancing quality of life through quality products, and a continuing focus on providing excellence in education, Passy Muir is proud to announce the release of two new products this year: The new Passy Muir Tracheostomy Viral and Bacterial Airway Protection Filter (PM-APF15) attaches easily to the 15mm hub of a tracheostomy tube and safely and effectively filters out viral, bacterial, and other particulate matter. The new lightweight, non-sterile filter is designed for single-patient use for non-mechanically ventilated pediatric and adult tracheostomy patients, and provides bacterial and viral filtration efficiency of 99.9%, while effectively filtering out 99% of all airborne particulates. For use in clinical settings, including hospitals, sub-acute, rehabilitation, outpatient, skilled nursing, and long-term care, as well as in the home setting. For adults with Tidal Volumes at 300 ml and pediatrics with Tidal Volumes at 80 ml. Not for use on neonate or infant patients. The PM-APF15 filter comes with detailed instructions for use, and is manufactured in the United States. Not to be confused with a speaking valve, the PM-HME Heat Moisture Exchanger is a non- sterile, lightweight, single patient use, device designed to be positioned on a tracheostomy tube to warm and humidify air breathed by a patient. The PM-HME is intended for use in clinical settings including hospitals, sub-acute, rehabilitation, outpatient, pre-hospital, skilled nursing, long-term care, and the home setting. Made in USA and Latex free. For more information, or to order, visit www.passymuir.com, or call 1-800-634-5397.

FDA Approval of First Human Milk-Based Nutritional Fortifier Indicated for Term Infants

Prolacta Bioscience, the world's leading hospital provider of 100% human milk-based nutritional products, announced the US Food and Drug Administration (FDA) has approved Surgifort human milk fortifier (human, pasteurized) for term infants (≥37 weeks) following corrective surgery for the gastrointestinal disorder gastroschisis. Surgifort fortifier is the latest addition to Prolacta's line of human milk-based nutritional products, and it is

the first fortifier indicated for use in term babies. Gastroschisis is a birth defect where the intestines, and sometimes other organs, protrude through the abdominal wall. Similar to premature infants, term infants recovering from corrective gastroschisis surgery require high macronutrient intake for optimal growth.1 Surgifort fortifier is specifically formulated to deliver optimal protein and calories to promote growth. When Surgifort fortifier is mixed with term human milk, and given at an appropriate volume, clinicians can achieve nutrition that is within the recommendations established by the National Academy of Medicine. Annually, fewer than 2,400 babies are born with gastroschisis in the US. Despite this exceptionally small patient population, Prolacta's dedication to the lifesaving benefits of human milk nutrition inspired the development of Surgifort fortifier to address the unmet nutritional needs of these critically ill infants. "With Surgifort fortifier, we're entering a new chapter in specialized human milk-based nutrition, extending its clinically proven benefits to babies who are not born prematurely," said Scott Elster, CEO of Prolacta. "This advances our commitment to develop human milk-based nutritional solutions for infant populations with complex medical needs." Surgifort fortifier is a concentrated, pasteurized, liquid human milk-based product that contains calories, protein, fat, and carbohydrate derived from donated human milk, with added minerals. As part of an Exclusive Human Milk Diet (EHMD), Surgifort fortifier has been found to reduce the time to full feeds as well as improve weight gain velocity in babies recovering from gastroschisis repair (weight gain from the day Surgifort fortifier started until the day it was discontinued = 33.3 g/day). "Clinicians caring for infants requiring gastroschisis repair now have a human milk-based nutritional option to support healthy growth and recovery," said Melinda Elliott, MD, FAAP, practicing neonatologist and chief medical officer at Prolacta. "Surgifort fortifier extends the benefits of Prolacta's Exclusive Human Milk Diet beyond premature infants to this fragile surgical population."

Help With Skin-to-skin Contact Arrives

Parenting in the wellness era often means navigating a parade of gadgets more focused on "bouncing back" than the health of new families. So, many parents are surprised to discover this simple solution for maternal pain and infant development — which is incredibly accessible, affordable and science-backed. Skin-to-skin contact, especially in the first hour after birth, is clinically proven to reduce postpartum bleeding, reduce infant crying and encourage early breastfeeding. Research also indicates the importance of skin-to-skin contact throughout the fourth trimester for both birthing parents' recovery journey and to support the new baby. Those early moments where a baby lies directly on their mother's bare chest is aptly called "The Golden Hour," but to prevent falls in the delivery room, clinicians hold babies to their mother's chest for only 15 minutes at a time, cutting the magic short. Joeyband, an innovative technology invented by a Canadian who experienced the impact of an unsafe delivery, offers a simple fix by providing easy skin-to-skin contact in the delivery room, at home and especially in the NICU. Joeyband is the premiere skin-to-skin device used by hospitals around the world, and backed by data proving its effectiveness in the golden hour and in boosting breastfeeding rates. The Joeyband increased exclusive breastfeeding rates by 8.2 per cent when implemented in a Connecticut Hospital for five months. The Joeyband can also lead to 50.4 average minutes of uninterrupted skin-to-skin contact in the operating room, according to research

from a California Hospital. Another study, which was presented at the largest neonatal conference in the US, showed a reduction in pain medication allocated to mom post c-section, in addition to a reduction of NICU admissions. These results quickly gave way to exciting expert-reviews. "It should be a standard of care in the operating room," says Janet Stevens, MSN, RNC-OB, CNE, CNL, high risk obstetrics." Joeybands are the miracle that helps skin-to-skin happen for our maternal/parental newborn." Gentle C-sections are gaining popularity with mothers who want to bring personal birth-plan elements into the operating room. Usually, mothers undergoing C-sections don't have a chance to experience immediate skin-to-skin contact. But when the Joeyband was tested at Long Island's Good Samaritan University Hospital, this golden hour was achieved — with 100 per cent of participants reporting decreased maternal anxiety. "Baby's first embrace should be a sacred and safe one," says Janet Stevens, MSN, RNC-OB, CNE, CNL, high risk obstetrics. "With Joeyband, we provide newborns a circle of support, connecting them to their caregiver for the incredible benefits of skin-to-skin contact—regulating body temperature, heart rate, breathing, promoting bonding, and releasing calming hormones," she adds. As an added bonus, the Joeyband provides mothers with comfortable belly compression, soothing the pain that comes with C-section incisions. Preventing infant falls was another concern for Joeyband inventor Hayley Mullins after her two-week-old baby fell to the ground while they practiced skin-to-skin contact. "I didn't want other parents to go through what I did," said Mullins. "The more I learned about the importance of skin-to-skin contact with newborns and babies, the more surprised I was at the lack of options available. We wanted to create a technology that wasn't your typical carrier or sling, but a circle of support designed specifically for skin-to-skin, with an emphasis on ease-of-use and good, ergonomic positioning' she added. Fast forward 13 years later and Joeyband has an extensive (globally) patented portfolio to back up this design. A study from a Colorado hospital found that, with Joeyband, 90 per cent of the moms who participated in their study felt their baby was better protected from a fall. Joeyband was thoughtfully made to empower all caregivers, including members of the adaptive parenting community. The genderless, size-inclusive design offers a wearable solution for every identity, skin tone and body. "We've worked tirelessly with the healthcare community in all newborn care settings over the last 10 years to refine the device. We've looked at everything from colour, fabric, use of velcro (vs zippers, hooks or buttons) down to sizing with a very intentional lens," says Sarah-Almaza Cox, Joeyband co-founder. "To have a hospital device that's available for patients to directly purchase was part of our vision of empowering patients." An example of the device refinement; Joeyband offers sizes 'A', 'B' and 'C' directly to patients, while providing a 'one-size fits most' exclusively for hospitals, in an effort to streamline workflow and accessibility. "My husband loved the Joeyband even more than I did," said one customer. "I think it helps him feel the special bond that a lot of mothers feel through the nursing relationship."

Probiotics Safe in the NICU, but Rare Risks Exist

In a 10-year analysis of multi-strain probiotic formulation (MPF) use in preterm infants, bacteraemia with probiotic organisms occurred in only 0.6% of cases (12 out of 2109 exposed infants), with no deaths directly attributed to the infection. In this single-centre retrospective study conducted in Montreal, Canada, MPF was administered to infants at < 33 weeks' gestational age or with a birth weight < 1500 g, starting at 0.5 g daily with the first enteral feed until 34 weeks' postmenstrual age. Researchers examined 2109 infants who received probiotics containing five bacterial strains: Bifidobacterium longum subspecies longum, B longum subspecies infantis, B breve, B bifidum, and Lactobacillus rhamnosus. Data from the microbiology laboratory database from 2001 to 2022 were used to identify patients with positive blood cultures for bacterial species present in the MPF. MPFs were used since more than 10 years, with bacteraemia occurring in 12 (0.6%) cases; nine of these were due to Bifidobacterium species and three were due to Lactobacillus rhamnosus. No cases were reported before MPF use. Among the affected infants, eight had gastrointestinal complications concurrent with bacteraemia and five required urgent abdominal intervention. Concomitant infections were observed in five cases, including bacteraemia with other pathogens, suspected urinary tract infections, and fungaemia. Two out of eight critically ill infants died after intensive care withdrawal, but their deaths were not attributed to bacteraemia. "In our cohort, bacteraemia with organisms contained in MPF was uncommon, and there were no cases of mortality directly attributed to bacteraemia in preterm infants exposed to MPF. Given the variety of probiotics formulations used in practice, further studies are needed to monitor actively their safety," the authors wrote.

Blood Pressure Variability Linked to Adverse Perinatal Outcomes

Visit-to-visit blood pressure (BP) variability was associated with adverse perinatal outcomes, including foetal growth restriction (FGR) and preterm birth (PTB) in high-risk pregnancies. The study retrospectively analysed data from 996 pregnant women (mean age, 33.8 ± 5.4 years) with hypertension or its risk factors between 2017 and 2021. It included women with at least two antenatal BP measurements using validated digital BP monitors. BP variability was calculated using visit-to-visit mean difference and SD, and its relationship with perinatal outcomes was assessed through logistic regression. The link between visit-to-visit BP variability and adverse perinatal outcomes, including FGR and PTB, was assessed, and the impact of different antihypertensive medications on BP variability was examined. FGR occurred in 13% of pregnancies, PTB in 23%, and PTB before 34 weeks in 8%. Increased visit-to-visit BP variability was linked to elevated risks for FGR (adjusted odds ratio [OR], 1.16; P = .02) and PTB (adjusted OR, 1.16; P = .004). Nifedipine was associated with greater BP variability than labetalol (adjusted difference, 1.93 mm Hg; P = .04). Women on multiple antihypertensives had an increased risk for FGR (OR, 7.08; P = .002) and PTB (OR, 50.37; P < .001). "Variation in BP variability between women taking different antihypertensives may reflect efficacy, duration, or factors influencing antihypertensive choice. Findings from this study do not yet support the clinical utility of BP variability over absolute BP values in obstetric decision-making," the authors wrote.

Company Announces US FDA Filing

Linde Gas & Equipment Inc. announced the submission of a 510(k) premarket notification application with the US Food and Drug Administration (FDA) for NOXBOX I PLUS, a nitric oxide delivery and monitoring system for NOXIVENT (nitric oxide) gas, for inhalation. "This FDA submission builds on the success of our innovative NOxBOX i delivery system," said Jason Aexel, Director of Clinical Healthcare, Linde Gas & Equipment providing healthcare professionals with an enhanced system that offers an economical and reliable way to deliver inhaled nitric

Continued on page 20…

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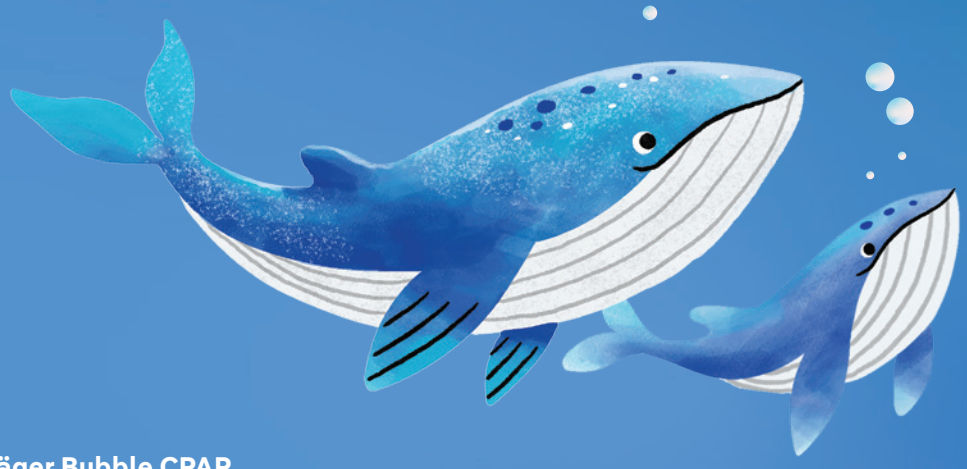

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Extracorporeal Membrane Oxygenation for Chinese Neonates With Severe Respiratory and Cardiac Failure

Xiao-Juan Zhang[1], Ying-Yue Liu[2], Hui Wang[2] and Xiao-Yang Hong[2,3*]

Introduction

Extracorporeal membrane oxygenation (ECMO) is a life-saving procedure for critically ill neonates with severe cardiac and/or respiratory failure and refractory to maximal conventional management. The primary function of ECMO is to act as a surrogate for the cardiopulmonary system of a patient, facilitating the circulation of oxygenated blood throughout the body. Now ECMO remains an important support treatment tool for neonates with reversible congenital cardiopulmonary diseases.[1,2] The use of ECMO to support neonates with cardiorespiratory failure in China has a relatively recent change in care strategy. The overall survival rate in cardiac ECMO is lower, with congenital heart defect representing the main indication. This review provides an overview of the available evidence in the field of neonatal ECMO. ECMO is a life support with a potential impact on long-term patients' outcomes. In the past years, clinical technology, and expertise have push neonatal ECMO towards more premature, but also complex, all doctors want to reduce the burden of ECMO-related complications and improve the outcomes.[3] The ECMO centers doctors should keep on learning, to know as much as possible of the experience. Therefore, we reviewed our institutional experience with Neonatal ECMO support, showed our experiences and our problems, shared our work to explore potential areas for improvement.

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Method and material

Study participants

From 2012 to 2016, 28 neonates diagnosed with severe respiratory and cardiac failure at the BaYi Children's Hospital of PLA Army General Hospital, were provided with ECMO support. Among them, there were 6 females and 22 males with a median age was 5 days (ranging from 1 to 28 days) and a median weight was 3.3 kg (ranging from 2.4 to 4.2 kg). All neonates experienced severe respiratory or cardiac failure post CHD operation, whose clinical symptoms were unresponsive to conventional treatments and had no contraindications for ECMO. Among them, 14 neonates required ECMO support for cardiac conditions, while another 14 required it for respiratory issues. The decision for ECMO support was made after obtaining consent from the families of the neonates.

Indications for ECMO support in this study were as follows:

- Indications for respiratory failure: Oxygenation index > 40 for > 4 h; Oxygenation index > 20 without improvement after prolonged duration (> 24 h), severe hypoxic respiratory failure with abrupt decompensation (PaO2 < 40) resistant to intervention, and progressive respiratory failure and/or pulmonary hypertension with signs of right ventricular dysfunction or sustained high inotropic demand.
- Indications for heart failure: Inability to be weaned from extracorporeal circulation following surgery for congenital heart disease, severe low cardiac output syndrome persisting after surgery for congenital heart disease, and unsuccessful cardiopulmonary resuscitation (CPR) after a cardiac arrest.

Contraindications

Gestational age < 34 weeks, weight < 2 kg, irreparable cardio-pulmonary injury, irreversible nerve injury, multiple organ failure, fatal chromosomal anomalies, and refusal of ECMO support by the families.

Methods

The ECMO setup utilized a Medtronic ECMO bio-console 560 and a water tank, along with a Medtronic Minimax Plus Oxygenator (CB2503R1). The cannulation sites for respiratory support were right jugular vein for venous outflow and the jugular arterial for arterial inflow. For cardiac support, the right atrium served as the venous outflow, and the aorta was used for arterial inflow. Cardiac support was initiated through the chest, following a V-A model configuration. The flow rate range was 100-150 ml/kg/min. Anticoagulation was maintained through a heparin infusion at a rate of 5-10 u/kg.h, aiming to keep activated clotting

Table 1 The neonates requiring ECMO support and survival rate

		Died	Survived	Survival rate
Cardiac		5	9	64%
Respiratory	RDS/SEPSIS	4	2	42%
	MAS	1	3	
	PH	2	0	
	PPHN	1	0	
	CDH	0	1	
Sex (f/m)		3/10	1/14	
Weight (kg)		3.40 ± 0.75	3.54 ± 0.84	

ECMO: Extracorporeal Membrane Oxygenation; CDH: Diaphragmatic hernia; MAS: Meconium aspiration syndrome; PPHN: Neonatal persistent pulmonary hypertension; RDS: Respiratory distress syndrome; PH: Pulmonary hypoplasia

Table 2 Lactate levels (mmol/L) during the initial 24 h of ECMO support

	0 h	6 h	12 h	24 h
Survival group	12.83 ± 2.77	8.31 ± 3.73[1]	6.06 ± 3.83[1,2]	3.01 ± 0.97[1, 3, 4]
Death group	10.33 ± 4.80	9.97 ± 4.83[5]	10.47 ± 5.32[5,6]	10 ± 1.97[5,6,7]

Note Survival group: 1 was 24 h compared with 0 h, $p < 0.05$

2 was 12 h compared with 6 h, $p > 0.05$

3 was 24 h compared with 6 h, $p < 0.05$

4 was 24 h compared with 12 h, $p > 0.05$

Death group : 5 was compared with 0 h, $p > 0.05$

6 was compared with 6 h, $p > 0.05$

7 was compared with 12 h, $p > 0.05$

times within the range of 150-200 s. Blood routine and blood gas samples were monitored, ensuring PLT levels were above 75×10^9/L, HCT ranged between 30 and 40%, and SvO2 levels remained above 50%. During ECMO support, active vascular drug dosage was decreased, with the end-expiratory volume between 5 and 8 ml/kg, high peep pressure between 5 and 8 mmHg, and end-expiratory pressure between 18 and 25 mmHg, in an effort to maintain lung inflation. Hemodynamic stability, blood gas samples, chest X-rays, urine output, and mixed venous oxygen saturation were continuously monitored to assess cardiopulmonary function. If these indicators improved, the ECMO flow rate was gradually reduced. Once the flow rate fell below 10–30 ml/kg/h and both circulation and oxygenation remained stable, the ECMO support was discontinued. The lactide levels in different group were compared by ANOVA using the SPSS version 16 software.

Results

In this study, 28 infants underwent ECMO support, comprising 6 females and 22 males, with ages ranging from 1 day to 28 days, The duration of support varied, ranging from 11 h to a maximum of 173 h. .Out of the 14 cases supported for cardiac-related issues, 9 neonates survived, resulting in a 65% survival rate. For the 14 cases supported for respiratory conditions, 6 neonates survived, leading to a survival rate of 42%. Among the cases, 3 neonates had meconium aspiration syndrome, 2 had respiratory distress syndrome (RDS) due to sepsis, and 1 had diaphragmatic hernia (CDH), as outlined in Table 1. In the 15 successful weaning neonates, four neonates died at the end of the study. One was given up for the cardiac function failure; two were given up for the respiratory failure; one was given up for Bipedal necrosis; the other 11 neonates were successful discharge.

The neonates whose lactate levels declined significantly in the first 24 h had a better prognosis, while those whose lactate levels decreased slowly or did not change had a worse prognosis (see Table 2).

Among the ECMO cases, 5 experienced complications: 2 cases developed diffuse intravascular coagulation, 1 suffered a pipeline accident, and 2 faced venous cannula obstruction, leading to lower limb ischemia necrosis in those instances. Notably, no instances of bleeding or other complications were observed, resulting in a complication rate of 17%.

Discussion

ECMO plays a pivotal role in rapidly and effectively improving severe cardiopulmonary function loss, providing a critical window for recovery. Its widespread application in severe respiratory and heart failure treatment is well-established, encompassing neonates, children, and adults. Specifically in neonatal settings, ECMO serves as a valuable tool for heart support, ventilator assistance, and in vitro cardiopulmonary resuscitation (CPR). The neonatal ECMO requiring specific expertise and technical skill, especially for the special pathophysiological characteristics of neonates. it becomes nearly impossible to separate the role of pediatric surgeons from the continuous involvement with and management of neonatal ECMO patients. This technology, well-established overseas, has recently gained traction in China's clinical landscape. Data from the External Life Support Organization (ELSO, 2016)[4] indicates that 36,946 neonates have undergone ECMO support, comprising 29,153 cases for cardiac support with a 42% survival rate, 6,475 cases for respiratory support with a 72% survival rate, and 1,336 cases for external cardiopulmonary resuscitation (ECPR) with a 41% survival rate,[1,3-10] ESLO(In January 2016) data revealed that there were only 9 neonates who received ECMO, 3 for respiratory support with a 0% survival rate and 6 for cardiac assistance with a 50% survival rate; hence, ECMO for neonates in China lags Western countries. Since 2012, our hospital has developed ECMO for neonates; we have performed ECMO on 28 infants, 14 for cardiac support with a 64% survival rate and 14 for respiratory conditions with a 42% survival rate. So many years passed, the data of 2023 from ESLO shows 167 neonates who received ECMO, 70 for respiratory support with a 68.6% survival rate, 78 for cardiac assistance with a 42.3% survival rate and 19 for ECPR assistance with a 11.4% survival rate. In our center, the survival rate for cardiac support (41%) was marginally higher than that for respiratory support, not consistent with ESLO data., maybe due to the limited number of cases in our center, the comparability is weak, and it is essential to collect more cases for a comprehensive analysis.

The survival rate for respiratory assistance was significantly lower than what is published internationally; potential factors include the following:

1) In our study, the initiation of ECMO procedures was delayed, resulting in fewer than 15 cases annually. This indicates a need to enhance our management and operational proficiency. Freeman et al. demonstrated a correlation between patient survival rate and the volume of cases managed by a center.[11] Notably, centers handling approximately 22 cases annually exhibited a significant decrease in mortality rates.
2) The initiation of ECMO support for neonates in our center was considerably delayed, predominantly due to the limited knowledge and experience with ECMO among neonatal physicians. While surfactant therapy, high-frequency ventilation, and inhaled nitric oxide are commonly employed in clinical settings, by the time

neonates were considered for ECMO intervention, their physiological status had often deteriorated significantly. The majority of these neonates presented with profound internal environmental imbalances, marked hypoxemia (arterial oxygen tension less than 20 mmHg), and cardiac insufficiency. Out of the total cohort, 20 out of 28 neonates exhibited lactate levels exceeding 15 mmol/L prior to ECMO intervention. Consequently, a significant proportion of these neonates experienced severe fluid leakage following ECMO initiation, leading to circulatory instability. This rendered resuscitative measures ineffective, resulting in an inability to rescue these neonates. Within the first 24 h of ECMO intervention, neonates whose lactate levels normalized exhibited a favorable prognosis. Conversely, those who maintained elevated lactate levels or experienced a further rise demonstrated a poor prognosis.

3) In our center, the veno-arterial (V-A) ECMO model was exclusively employed for neonatal patients. While it is widely recognized that the venous-venous (V-V) model is optimal for patients with primary respiratory ailments, the absence of a V-V circuit in our institution necessitated our reliance on the V-A configuration for neonatal interventions.[12] The intricacies associated with the administration of the V-A model, coupled with its potential impacts on circulatory dynamics, may be contributory factors to the observed diminished survival rates.

During the ECMO support phase, lung management plays a pivotal role in patient prognosis, with particular emphasis on modifications in patient positioning, such as adopting the prone position. Kredel conducted a retrospective case analysis in 2014 and scrutinized 9 patients diagnosed with ARDS who were positioned prone during their ECMO support.[13] Based on the comparison of the oxygenation index and lung compliance, there were notable improvements post-proning. Specifically, the oxygenation index improved from a median value of 47 (ranging from 41 to 47) before proning, to 12 (ranging from 11 to 14) after. Similarly, lung compliance revealed enhancement from 20 (ranging from 17 to 28) before proning, to 42 (ranging from 27 to 43) after the intervention, now there also some opinion shows the prone positioning did not facilitate earlier weaning from ECMO.[14] In our center, beginning from June 2016, two patients were placed in the prone position during ECMO support, the lung of two babies occurred hypostatic pneumonia, so we tried the prone intervention. Remarkably, these patients did not encounter complications such as facial edema, pipeline issues, or pump failure. This indicates that positioning patients supported by ECMO in the prone orientation is both safe and practicable. However, we did not find the benefit from the prone position, so we acknowledge the necessity for additional data collection to definitively assess the effects of this positioning on parameters such as the oxygenation index and lung compliance.

Neonates requiring ECMO mechanical intervention present with a diverse array of clinical conditions including congenital diaphragmatic hernia (CDH), meconium aspiration syndrome (MAS), neonatal persistent pulmonary hypertension (PPHN), respiratory distress syndrome (RDS), sepsis, neonatal pneumonia, and air leakage, among others.[15,16] A review of existing literature indicates that MAS has the highest association with ECMO use, followed by CDH, followed by PPHN, sepsis, RDS, pneumonia, and air leakage. Survival rates were most favorable for MAS, estimated around 94%, followed by RDS (84%), PPHN (77%), and sepsis (73%), with CDH registering the lowest at approximately 51%. The reduced survival rate in CDH may be attributed to concurrent pulmonary hypoplasia (PP). In our center, 14 neonates had ECMO support primarily for respiratory issues, 6 had SEPSIS/RDS, 4 had MAS, 2 displayed PP, and 1 was diagnosed with CDH. The distribution of conditions diverges from commonly cited literature, potentially due to unique admission patterns and national circumstances. Our center has proficiency in neonatal transport, but the presented state of the neonate with CDH was critically compromised, and the capabilities of primary healthcare facilities are restricted. Consequently, many neonates were deprived of opportunities for escalated care in tertiary healthcare centers. While the patient volume is insufficient to facilitate a comparison with the ELSO data, it is evident from our observations that neonates with sepsis/MAS generally have a favorable prognosis.

Since the 1970s, technology, management, and clinical applications of neonatal ECMO have improved. Pulmonary diseases still represent the principal neonatal diagnosis, with an overall 74% survival rate, and up to one-third of cases are due to congenital diaphragmatic hernia. The overall survival rate in cardiac ECMO is lower, with congenital heart defect representing the main indication.[3] However, in our center the survival was lower with the pulmonary diseases, the reason may be the seriously ill, or maybe the example was small. Yu et al.[17] reported 23 neonates who received ECMO support for cardiac failure in their center from January 2017 to June 2019, The successful weaning rate was 78.26% and discharge rate was 52.17% in their center, the survival rate was similar with ours, So ECMO is a safe and efficacious therapeutic modality, emblematic of the critical emergency technological capabilities of a hospital, region, or even a country. It was Bartlett, who, in 1976, pioneered the successful application of ECMO for neonates with ARDS.[18] Subsequent to this achievement, the clinical utilization of ECMO expanded, leading to significant improvements in survival rates for patients who are critically ill. In China, while ECMO has been extensively adopted for adult patients, its implementation in pediatric settings has been comparatively gradual.[19,20]

Conclusion

As ECMO becomes increasingly integrated into neonatal critical care, the technology will undergo continuous refinement, paving the way for a new era in neonatal critical care in China.

Abbreviations

ECMO	Extracorporeal Membrane Oxygenation
CPB	Extracorporeal circulation
CPR	Cardiopulmonary resuscitation
CDH	Diaphragmatic hernia
MAS	Meconium aspiration syndrome
PPHN	Neonatal persistent pulmonary hypertension
RDS	Respiratory distress syndrome
PH	Pulmonary hypoplasia

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Author contributions

Conception and design of the research: Xiao-juan Zhang Xiao-yang Hong. Acquisition of data: Hui Wang, Ying-yue Liu. Analysis and interpretation of the data: Hui Wang, Ying-yue Liu. Statistical analysis: Xiao-juan Zhang. Obtaining financing: Xiao-yang Hong.

Writing of the manuscript: Xiao-juan Zhang. Critical revision of the manuscript for intellectual content: Ying-yue Liu. All authors read and approved the final draft.

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Data availability

The datasets used and analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of BaYi Children's Hospital of PLA Army General Hospital.

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Closing the Disparity Divide: The Role of Mobile Health (mHealth) in Equitable NICU Support for Families

Nicole Nyberg, MSN, APRN, NNP-BC

Introduction

Premature birth remains a significant public health concern both globally and in the United States. As the leading cause of infant mortality and long-term morbidity, prematurity poses medical, emotional, and financial challenges for families and healthcare systems alike. Preterm infants face a heightened risk of complications and chronic health conditions that can persist into adulthood. Beyond these medical complexities, families navigating a Neonatal Intensive Care Unit (NICU) stay often experience profound emotional and psychosocial distress. Feelings of fear, anxiety, and uncertainty are common, exacerbated by prolonged hospitalizations and the challenges of caring for a medically fragile infant.

While prematurity affects families across all backgrounds, significant racial and ethnic disparities persist. Black families, in particular, face disproportionately higher rates of preterm birth compared to White and Hispanic families. These inequities not only contribute to unequal health outcomes, but also amplify the emotional burden on affected families, further deepening existing disparities in neonatal care and parental well-being.

This article will examine the inequities within the healthcare system, particularly in NICUs across the country, by exploring key facts, statistics, and previous research. It will also review a 2025 peer-reviewed study published in *The Journal of Pediatrics*, titled "An mHealth Intervention to Support Psychosocial Well-Being of Racially and Ethnically Diverse Families in the NICU." The study, led by Dr. Craig Garfield, Professor of Pediatrics at Northwestern University and Clinical Advisor at AngelEye Health, examined the impact of a mobile health (mHealth) intervention on parental well-being across three urban NICUs. The results from the study demonstrated that this innovative intervention effectively reduced parental stress, particularly among parents with infants <32 weeks, while increasing social support, specifically among Black NICU families. The intervention has the potential to enhance outcomes for preterm infants by improving parental well-being and ensuring families feel more informed, engaged, and supported throughout their NICU journey.

> "We know there are huge disparities in care in this country, and the perinatal period may be one of the most glaring examples. As a pediatrician, I recognize it all starts at the beginning...so finding ways to support parents as they transition into parenthood—especially with a fragile new baby—is the most efficient place to focus our resources across the lifespan."
>
> – Dr. Craig Garfield

Given the emotional toll and complexities of NICU care, additional support is essential to ensure families feel informed, confident, and engaged in their infant's care. mHealth interventions offer a promising solution as a validated, effective, and scalable way to support parents in the NICU. NICU2Home, the mHealth intervention reviewed in this study, was designed to bridge gaps in parental support by providing accessible education, real-time updates, and emotional reassurance. Empowering parents with knowledge and confidence fosters engagement in their infant's care and ensures a smoother transition from the NICU to home.

Prematurity Rates and Racial Disparities

Although preterm birth rates fluctuate slightly each year, they continue to pose a significant public health challenge. In 2022, 10.4% of all US births were preterm.[1] However, significant racial disparities persist, with the preterm birth rate among Black women at 14.6%, compared to 9.4% for White women and 10.1% for Hispanic women.[1] These disparities highlight the urgent need for targeted interventions to address the root causes and improve outcomes for at-risk populations.

The underlying causes of these disparities are multifaceted and deeply systemic. Contributing factors include socioeconomic barriers, limited access to preconception care, short interpregnancy intervals, and persistent healthcare inequities.[2] Additionally, the cumulative effects of chronic stress, racism, and discrimination further elevate the risk of preterm birth.[3,4] These

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interconnected challenges impact birth outcomes and contribute to long-term disparities in maternal and infant health, reinforcing the critical need for equitable, evidence-based healthcare solutions that address both medical and social determinants of health.

Long-Term Impacts of Prematurity: Health, Development, and Disparities

Infants born preterm are at increased risk for both short- and long-term medical and developmental complications, including respiratory distress, neurodevelopmental delays, and heightened susceptibility to infections. While the NICU is critical for survival, it also exposes preterm infants to repetitive stressors such as painful procedures, therapeutic interventions, and overwhelming sensory experiences.[5,6] Research has linked these early stressors to adverse neurodevelopmental and behavioral outcomes, impacting language, motor function, and cognitive abilities into childhood.[5,6,7,8,9] Additionally, preterm birth has been associated with a higher risk of autism spectrum disorder (ASD) and emotional or behavioral challenges, many of which may not become evident until school age.[9,10]

Preterm birth remains the leading cause of infant mortality and morbidity.[9] Historically, Black preterm infants had lower neonatal mortality rates compared to White preterm infants.[11,12,13] However, more recent data indicate that this survival advantage diminished in the 1990s, with racial disparities in mortality beyond 33 weeks' gestation continuing to widen.[11,14] Additionally, Black preterm infants face higher rates of severe neonatal complications compared to White infants, including sepsis (13.6% vs. 9.1%), peri- or intraventricular hemorrhage (3.3% vs. 2.6%), intracranial hemorrhage (1.8% vs. 0.6%), and retinopathy of prematurity (2.6% vs. 1.0%). These disparities highlight the urgent need for equitable healthcare interventions to improve outcomes for at-risk populations.

These findings emphasize the urgent need to address the structural inequities contributing to these disparities. Efforts to understand, mitigate, and eliminate these healthcare gaps must remain a priority to improve outcomes for all preterm infants, particularly those from historically marginalized communities.

The Silent Struggle of Parents and the Urgent Need for Better Mental Health Support

While the NICU is critical for the survival of preterm infants, it can be a highly stressful and emotionally overwhelming experience for parents. Studies indicate that 40-50% of NICU mothers experience postpartum depression (PPD), compared to approximately 10-15% of mothers with full-term, healthy infants worldwide.[15,16,17] Risk factors for prolonged depressive symptoms include earlier gestational age of the infant, low birth weight, lack of social support, and ongoing infant illness or disability.[15,17] Fathers are also at risk, with research showing higher rates of depression and PTSD among NICU fathers.[15,18,19,20]

Parental fear, lack of knowledge, altered roles, and diminished confidence can heighten distress both during hospitalization and after an infant's discharge from the NICU. This heightened stress not only affects parental mental health but it can also impede infant development. Studies show that parents experience the most significant stressors from the NICU experience due to the parent-infant separation, the inability to care for their infant, and the disrupted parent-infant bonding.[21,22] Parents struggle with being physically separated from their infants and their limited parental role as healthcare workers care for their infants. These emotional strains can persist post-discharge, affecting parental well-being and the parent-child relationship if not addressed.

Risk factors thought to worsen parental stress and mental health include the transitions or periods with gaps in mental health support due to the lack of reassurance from medical professionals, managing multiple demands, and social disparities or parents of lower socioeconomic status with limited resources.[23]

However, studies have shown that early and active parental involvement can help mitigate some of these risks, emphasizing the critical need to empower parents through education, support, and equitable healthcare resources. Given the profound emotional toll of a NICU admission, finding ways to support and empower parents is essential. The research underscores that when families are actively engaged and supported, their confidence grows, and they become more effective advocates for their infants.

Impact of Parental Engagement, Support, and Confidence on Neonatal Outcomes

The parent-infant relationship and attachment are vital in neonatal development and long-term outcomes. Research has shown that supporting parental involvement, fostering attachment, and empowering families can help mitigate the stressors associated with a NICU admission while reducing the risk of long-term emotional and developmental challenges.

To ensure families feel comfortable and confident in participating in their infant's care, it is necessary to promote their empowerment by establishing a therapeutic relationship with the healthcare team. With a trusted relationship in place, nurses can transition from being the primary caregivers to taking on the role of a coach, facilitator, and educator.[24] A strong therapeutic relationship is built on a foundation of support and compassion, empowering parents to confidently take on their role as primary caregivers and easing the transition home after discharge. Research demonstrates that when healthcare professionals encourage parental involvement, it strengthens parent-infant attachment, which is essential for the infant's physical, mental, emotional, and social development.[25] Open communication and transparency are key elements in fostering this trusted relationship, ensuring that parents feel informed, supported, and empowered in their role.[24,26]

By actively involving parents and providing them with psychological and educational support throughout the NICU journey, healthcare teams can help families develop the emotional resilience, cognitive understanding, and confidence needed to care for their infants.[5] Family-centered strategies that help parents navigate the challenges of the NICU while promoting trust have been linked to improvements in infant feeding, growth, parental well-being, and self-efficacy.[5] These factors, in turn, are essential mediators of long-term neurodevelopmental and behavioral outcomes.[5]

A study by Pierce (2023) identified two key protective factors that can help shield NICU parents from worsening mental health:

1. **Social support** – Support from family, friends, and the community was cited as the most important factor in reducing stress and improving coping ability.

2. **Support from the healthcare system** – Parents who felt supported and connected to their medical team reported greater optimism and engagement in their infant's care.

Additionally, robust support systems and accessible educational resources have been shown to improve parental self-efficacy and lead to better neonatal outcomes. Effective care coordination plays a pivotal role in enhancing the family experience and supporting the infant's developmental trajectory beyond the NICU.

Barriers in NICU Care for Black Families

Research has identified significant disparities in the quality of care and support Black families receive in the NICU. Many Black parents report concerns regarding inadequate nursing support, a lack of compassionate and respectful communication, and less attentiveness to their infants' needs.[4,27] These challenges are not solely individual experiences, but are deeply rooted in systemic and structural inequities. Factors such as implicit biases, cultural insensitivity, and socioeconomic barriers further contribute to these disparities.

A recent study by Ondusko et al. (2025) revealed that Black families frequently experience differential treatment in the NICU, reinforcing mistrust in the medical system and perpetuating structural racism. Parents expressed the need for greater transparency, advocacy, mental health support, and equitable access to resources to improve their NICU experience and ensure their voices are heard.[28] These findings align with previous research, which has shown that minority families often face barriers to communication, limited involvement in care decisions, and a lack of respect from providers. While explicit discrimination is rare, disrespectful treatment and ineffective communication remain significant barriers to family engagement (Glazer, 2020).

Beyond provider-family interactions, systemic inequities extend to the quality of NICU care. Black and Hispanic infants are more likely to receive care in lower-quality NICUs, where resource limitations and structural challenges can affect outcomes (Ravi, 2021; Howell, 2016). Research has shown that very low birth weight (VLBW) infants born in NICUs with a higher proportion of minority patients are more likely to experience nurse understaffing, suboptimal practice environments, and reduced access to evidence-based neonatal care (Ravi, 2021; Lake, 2015; Lake, 2018; Sigurdson, 2019). These disparities underscore the need for systemic reforms that prioritize equity in neonatal care delivery.

Addressing Disparities Through Support and Communication

Closing these gaps requires a multifaceted approach that prioritizes equitable access to high-quality care, enhanced parental education, and robust support systems throughout the NICU journey and beyond. To effectively address disparities, it is critical to evaluate both clinical care processes and relational aspects of care, such as nonjudgmental communication and meaningful parental engagement (Ravi), as well as consider new and innovative approaches.

All families—especially those navigating the added burden of racial inequities—need comprehensive support that includes clear communication, transparent and relevant information, and a nurturing environment that empowers them to participate in their infant's care and advocacy. Identifying the most effective, accessible, and timely ways to provide this support in a culturally sensitive manner is essential to ensuring equitable neonatal care.

The disparities in neonatal care faced by Black families are not just a matter of statistics—they represent real, lived challenges that profoundly impact the well-being of both infants and parents. Addressing these inequities requires intentional, systemic strategies that prioritize trust, culturally responsive communication, and equitable access to high-quality care and family support services. Closing these gaps requires innovative solutions that enhance communication, support parental confidence, and provide equitable access to resources. One such solution is NICU2Home, a mobile health platform designed to empower NICU families with the information and support they need.

Technology as a Tool for Parent Support

Mobile health (mHealth) interventions have emerged as promising tools to support parental engagement and bridge some gaps in communication, information sharing, and support for NICU parents. Providing parents with relevant information and education through technology about their infant's clinical condition and progress in the NICU empowers them to take an active role in their infant's care and actively participate in rounds as advocates for their infant. As a result, families are well-prepared to confidently care for their infant both in the NICU and, most importantly, at home after discharge.

NICU2Home is an example of an intervention that exemplifies a multi-faceted approach to supporting families in the NICU and beyond. Developed through collaboration among clinicians, families, and culturally diverse stakeholders, the solution provides accessible, scalable support tailored to meet the unique needs of diverse populations. With a focus on parental support, the features of this intervention are designed to empower and inform parents, fostering their engagement and building their confidence during their infant's NICU stay and transition home.

NICU2Home provides families with accessible, evidence-based education tailored to their infant's clinical journey, ensuring they feel informed and empowered throughout their NICU experience. The platform delivers daily updates on their infant's progress through electronic medical record integration, transparently displays who is caring for their infant, and fosters communication between families and the care team through the messaging feature. It also provides a clear, structured NICU roadmap that helps parents understand their infant's physiological milestones relative to discharge, along with a parent task list to keep them actively engaged and well-prepared for the transition home.

By addressing the social determinants of health (SDOH) and meeting families where they are—emotionally and logistically—the platform offers critical support inclusively and equitably. Additionally, with translation available in over 70 languages, NICU2Home ensures that all families, regardless of linguistic or cultural background, can fully engage in their infant's care.

Study Conducted Across Three Urban NICUs Underscores Need for mHealth Solution to Address Disparities

A newly released study by Garfield et al. (2025) conducted across three different urban NICUs with a diverse sample of patients evaluated the effectiveness of NICU2Home among parents of preterm infants. The study revealed that parents using the solution experienced a significant reduction in stress and anxiety, especially those with infants born before 32 weeks gestation (Garfield, 2025). Notably, Black parents reported increased social support when engaging with NICU2Home, highlighting its potential to address disparities in parental support (Garfield, 2025). These outcomes underscore the solution's role in enhancing parental well-being and promoting equitable care experiences.

NICU2Home has demonstrated its potential to address gaps in equitable care by enhancing parental engagement, communication, and trust—key factors in mitigating disparities in NICU experiences. This recently published study, the third primary evaluation of NICU2Home, is the first to examine its impact on health equity in the NICU, following prior research on its role in improving parenting self-efficacy, discharge preparedness, and length of stay (Garfield et al., 2016; Garfield et al., 2022).

A key finding was that Black families using NICU2Home reported higher levels of social support compared to those in the control group. The authors attribute this to the app's ability to provide timely, digestible education, daily clinical updates, and real-time transparency about who their infant's care team includes, fostering trust and inclusion (Garfield, 2025). To gain further insight into the latest study's key takeaways and broader implications, the lead author, Dr. Garfield, was consulted, and he noted:

> ***"Technology, done correctly, may offer unique opportunities to support families in the perinatal period, especially those families frequently marginalized."***

Beyond its role in addressing disparities, NICU2Home helps alleviate NICU-related trauma and distress by creating a trusted companion for parents. The app was intentionally designed to balance the right amount of information—neither overwhelming nor insufficient—so that parents feel engaged, empowered, and included in their infant's care. Dr. Garfield emphasized:

> ***"...with NICU2Home, the information is reliable, vetted, and digestible with a user-friendly reading level. When the 'right amount of information' is provided, it minimizes already stressed parents from becoming too overwhelmed."***

The study's findings highlight the critical role of trust, transparency, and inclusivity in neonatal care, reinforcing what research and this study has demonstrated—families need more support throughout their NICU journey, but the type of support required varies. As Dr. Garfield stated:

> ***"With my 25 years of experience working with NICU families, nearly all families could use more support during their NICU stay... and stress impacts parents differently, so some families do not trust or feel cared for in the healthcare system."***

NICU2Home helps build confidence and trust among families, particularly those who may feel disconnected or underserved in traditional healthcare settings, by providing consistent communication, clear information, and a structured approach to engaging in their infant's care.

Building Confidence, Fostering Trust, and Improving Outcomes

The NICU experience is often marked by high stress, trauma, and uncertainty, leaving parents feeling overwhelmed and disconnected from their infant's care. NICU2Home helps bridge this gap by providing structure, clarity, and inclusivity, supporting parents and care teams. Through timely education, transparent updates, and a clear roadmap of clinical milestones, it guides parents from uncertainty to confidence, allowing them to engage with information at their own pace and actively participate in their infant's care.

For families who already feel marginalized in the healthcare system, NICU2Home fosters trust and inclusion by ensuring they are valued members of the care team. Real-time updates on their infant's condition and insight into their care team help break down barriers, strengthening communication and connection. By serving as a trusted companion throughout the NICU journey, NICU2Home empowers parents to feel seen, heard, and confident in caring for their infant and trusting their medical team.

While NICU2Home has demonstrated its ability to enhance parental confidence and improve outcomes, ensuring widespread access to these solutions requires a more significant commitment from healthcare institutions, policymakers, and payors. Sustainable change cannot rely on digital solutions alone—it must be part of a broader strategy that prioritizes early intervention, equitable policies, and systemic investments in family-centered care.

Creating Meaningful Change: Partnerships and Systemic Investment

Reducing disparities in neonatal care begins with fostering strong, transparent partnerships between healthcare teams and families in the NICU. These collaborations empower parents, ensuring they feel informed and actively engaged in their infant's care. However, real and lasting change extends beyond hospital walls—it requires a broader commitment from policymakers, payors, and community organizations to implement sustainable, equitable solutions.

To effectively address the challenges preterm infants and their families face, healthcare institutions, policymakers, and payors must invest in proven, scalable interventions like NICU2Home that bridge critical gaps in communication, education, and emotional support. These initiatives reduce parental stress, improve infant outcomes, and foster a more connected and equitable care experience. As Dr. Garfield emphasized:

> ***"An investment in the early days will pay off mightily down the line in terms of infant outcomes, maternal and paternal outcomes, and ultimate healthcare expenditures."***

Supporting NICU parents is not just a moral obligation but crucial to improving long-term health outcomes for infants and families. Research consistently demonstrates that when parents are informed, engaged, and supported, their children benefit medically and developmentally. However, the responsibility of ensuring equitable care cannot rest solely on individual healthcare providers or parents—it demands systemic change.

By prioritizing early interventions, adopting equitable policies, and funding family-centered digital solutions, healthcare stakeholders can create a future where every NICU family—regardless of socioeconomic background—can access the resources and support they need. The question is no longer whether we should invest in supporting NICU families but how quickly we can mobilize to ensure no family is left behind. The time for action is now.

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oxide therapy." Linde has made targeted enhancements to the delivery system's functionality including a streamlined setup process, ergonomic refinements, precise controls, and further compatibility with various ventilators allowing for an enhanced user experience "We look forward to NOXBOX I PLUS' 510(k) clearance, and we remain steadfast in our commitment to nitric oxide therapy and continuous improvement in our technology," said Jason Aexel, Director of Clinical Healthcare, Linde Gas & Equipment Inc. Linde's NOXIVENT (nitric oxide) gas, for inhalation is indicated to improve oxygenation and reduce the need for extracorporeal membrane oxygenation in term and near-term neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension in conjunction with ventilatory support and other appropriate agents. The NOxBOX i delivery system has been in commercial use in 40+ countries since 2013 and in the US since October 2018. Currently, in the US, the NOxBOX i delivery system is being used in hundreds of locations. Contraindication: NOXIVENT is contraindicated in neonates dependent on right-to-left shunting of blood. Rebound: Abrupt discontinuation of NOXIVENT may lead to worsening oxygenation and increasing pulmonary artery pressure The NOxBOX i delivery system and NOXIVENT (nitric oxide) gas, for inhalation must only be used in accordance with the indications, contraindications, warnings, precautions, and other information and conditions of use described in the nitric oxide drug prescribing information and labeling (currently neonates). Refer to this material before use. Important safety information and full prescribing information can be found at www.noxiventus.com.

Groundbreaking Achievements Celebrated

Etiometry, the leader in clinical decision support software for high-acuity units, celebrates a year of groundbreaking achievements in 2024 and shares its ambitious vision to transform critical care in the year ahead. In 2024, the company achieved significant milestones across scalability, innovation and clinical impact, thereby solidifying its role as an effective tool to drive better patient outcomes and improved economics within the most complex and expensive hospital units. "2024 was a transformative year for Etiometry, driven by significant growth and adoption of our platform across ICUs, innovation and measurable clinical impact," said Shane Cooke, CEO of Etiometry. "The data our platform uses and provides enables hospital leaders to easily recognize the tangible ways Etiometry supports better outcomes and streamlined workflows—ultimately saving and improving lives." Clinical data continued to highlight the platform's impact, including a 36% reduction in ICU length of stay and a 41% decrease in readmissions in the ICU. Further evidence of the powerful impact of the Etiometry Platform was found at a new site that went live in November 2023 and in the ensuing year saw a 19.5% reduction in ICU length of stay as compared to prior to the deployment, along with an approximate 25% reduction in patient time on ventilation. Last year there were more than 2.5 million clinician interactions with Etiometry and logins into the platform reached 200,000—a 50% increase from 2023, reflecting its growing adoption by care teams seeking reliable tools to improve patient outcomes, support newer clinicians with data-driven communications and enhance workflows to help standardize care. Etiometry signed multiple enterprise agreements in 2024, extending its platform's presence into more adult and pediatric ICUs, including prominent healthcare systems in the Midwest and Mountain
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Nourishing Beyond Growth: Why Human Milk Remains the Optimal Choice for VLBW Infants

Dr Melinda Elliott, Andi Markell, Dr Sandra Sullivan, and Dr Erin Hamilton Spence

Abstract

Growth is a key target for very low birth weight (VLBW) infants being managed in hospital neonatal intensive care units (NICUs). Nevertheless, the definition of what constitutes appropriate or healthy growth in this unique and fragile population is evolving, and there is a lack of standardization across NICUs regarding how their growth should be measured. This situation creates unnecessary confusion and disagreement regarding growth metrics in VLBW infants on an exclusive human milk diet (EHMD). While it is true that these infants may not gain weight as quickly on an EHMD as they would on a diet containing cow milk-based nutrition, a comprehensive evaluation of relevant growth metrics indicates they have healthier patterns of growth on an EHMD, and an EHMD is associated with better morbidity, mortality, and long-term outcomes than a diet containing cow milk protein.

This review aims to identify key metrics that constitute healthy growth in the VLBW infant population and to elucidate how, when these metrics are used, it becomes clear that VLBW infants fed using an EHMD have the healthiest patterns of growth. It also includes an overview of the unique properties of human milk, providing a rationale for how an EHMD produces the most desirable growth metrics and outcomes, as well as a summary of the evidence to date on the myriad clinical benefits of an EHMD in VLBW infants.

Introduction

Every premature infant has their own set of unique challenges. For very low birth weight (VLBW) infants, achieving healthy growth is a key goal in neonatal intensive care units (NICUs). But what constitutes healthy growth in these infants? Postnatal growth is often expected to mirror in-utero growth rates, which is likely unrealistic due to the challenges these infants face. A more meaningful approach considers both the quality and pace of growth based on each infant's individual needs.

A better understanding of the unique physiology of VLBW infants helps define what constitutes healthy growth. This perspective clarifies the "breastfeeding paradox," where infants fed exclusively human milk gain weight more slowly yet experience better outcomes than those fed cow milk-based formula.[1] While weight gain may be slower with human milk, evidence suggests it supports a healthier growth pattern compared with formula-fed infants. *What* VLBW infants receive for nutrition may be as important, if not more so, than how quickly they gain weight.

Human Milk v Cow Milk

To fully grasp the crucial role of human milk in VLBW infants, it is essential to understand its unique properties, originally identified in term infants. Human milk helps protect against multiple infections[2] (particularly those affecting the gastrointestinal and respiratory tracts),[3,4] atopic disease,[5] and sudden infant death syndrome (SIDS),[6] as well as the development of some hematologic cancers[2,7] and autoimmune disorders of the gut, such as Crohn's disease and ulcerative colitis.[8] Finally, feeding with human milk has been associated with lower rates of type 1 diabetes.[2] For these reasons, both the American Academy of Pediatrics (AAP) and the World Health Organization (WHO) recommend that term infants be exclusively fed with human milk for at least the first 6 months of life.[2,9] A 2010 analysis found that if 90% of US families followed this recommendation, it could save approximately $13 billion in medical costs by reducing the risks of SIDS, ear infections, atopic dermatitis, respiratory and gastrointestinal infections, obesity, leukemia, and type 1 diabetes.[10] A more recent analysis expanded this estimate to $100 billion by accounting for lifetime costs related to premature death and the loss of intelligence quotient points, reflecting the broader impact of lost human capital for both parents and infants.[11]

The health benefits of human milk are believed to arise from a diverse matrix of bioactive factors, including lactoferrin,[12] α-lactalbumin,[13] transforming growth factor β,[14] lysozyme, and pathogen-specific immunoglobulins,[15,16] among others yet to be discovered. These bioactive components play a crucial role in the maturation of the gut and immune system[17–21] and contribute to the development of a healthy microbiome.[22] In addition, the fatty acids present in human milk are uniquely suited to support human infant growth and development.[15,23–27] These fatty acids have been shown to regulate intestinal development and protect against injury—one of the proposed mechanisms by which human milk protects against necrotizing enterocolitis (NEC) and other intestinal infections.[28]

Human milk oligosaccharides (HMOs) play a key role in infant health by acting as prebiotics that support the growth of beneficial bacteria and prevent infection through their anti-adhesive properties.[29] In addition to shaping the gut microbiome, HMOs modulate the immune response by reducing pro-inflammatory cytokines and promoting anti-inflammatory ones.[29–31] They also support the maturation of intestinal epithelial cells, a mechanism that may further protect against intestinal infections.[32] Moreover, HMOs serve as an

important source of sialic acid, a nutrient critical for brain development.[29–31]

Given that VLBW preterm infants are born with critically immature immune, neurological, and gastrointestinal systems, the unique composition of human milk plays an especially vital role in their healthy development. Many NICUs in the US and around the world have the option to use nutritional protocols for preterm infants that include either human milk-based or cow milk-based products. While both have their place in clinical care, the advantages of human milk-based nutrition are particularly significant for this vulnerable subpopulation of premature infants and should not be overlooked. These bioactive factors not only support short-term survival but also contribute to long-term developmental outcomes, which inform evidence-based recommendations for infant feeding protocols.

The Evolution of Growth as a Target in Premature Infants

Over the past decade, NICUs have significantly improved their ability to support the survival of extremely premature infants.[33] As survival rates increased, the focus shifted to promoting healthy growth in an effort to enhance quality of life in survivors. This shift was catalyzed by a landmark study by Ehrenkranz et al in 2006, which demonstrated that growth during the NICU stay influences neurodevelopment and growth outcomes long after discharge.[34] Subsequent research confirmed that NICU growth is a valuable surrogate marker for both short- and long-term outcomes in VLBW infants.[35,36]

But what defines healthy growth in this patient population? Initially, the focus on weight gain alone led to concerning growth patterns, with infants often shorter than average and exhibiting higher adiposity—traits associated with adverse long-term metabolic consequences. For example, infants born small for gestational age (SGA) who experienced rapid catch-up growth and developed a high body mass index (BMI) showed reduced insulin sensitivity compared with both appropriate-for-gestational-age children and SGA children who did not experience such rapid catch-up growth.[37] In addition, accelerated weight gain among premature infants has been linked to an increased risk of childhood obesity.[38]

The Role of Macronutrients and Growth Metrics in Preterm Infant Care

Recognizing the limitations of focusing solely on weight gain, researchers shifted their attention from overall caloric intake to the balance of macronutrient intake in the NICU. While protein is essential for growth, the immature kidneys of VLBW infants cannot tolerate excessive amounts, as it can lead to metabolic acidosis.[39] Similarly, a diet too high in fat will lead to steatorrhea. These findings underscore the importance of carefully balancing macronutrient intake to ensure optimal, healthy growth in this fragile population.

The source of macronutrients is likely to be as important as their composition, as it has demonstrable effects on growth. Term infants fed exclusively human milk tend to gain weight more slowly than formula-fed infants, despite the multiple health benefits of a human milk diet listed above. This discrepancy underscores why the US Centers for Disease Control and Prevention and the AAP recommend using the 2006 WHO Child Growth Standards to monitor growth in children under age 2 years.[40,41]

A similar trend is observed in the preterm population with the use of an exclusive human milk diet (EHMD). Concerns about slower weight gain are compounded by the lack of standardization across NICUs regarding how best to measure healthy growth in very premature infants. The gold standard growth target 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).[42] However, NICUs use different methods to measure weight gain velocity, such as: the early 1-point method, the average 2-point method, or the exponential 2-point method.[43] These methods may also vary in terms of measurement periods—some assess from birth to discharge while others measure from the time birth weight is regained to discharge. These differences can yield varying weight gain velocities and must be considered when evaluating an individual infant's growth or when comparing growth across different feeding protocols.[44]

Some efforts have been made to establish a standardized approach to assessing body composition among preterm infants using air displacement plethysmography,[44,45] but no method to date has been widely adopted.

The evolving understanding of preterm infant growth has highlighted the need to reconsider traditional growth targets and adopt more individualized approaches. A complicating factor is that growth targets for preterm infants are typically based on in-utero growth patterns.[46] However, this approach overlooks the significant physiological changes that preterm infants undergo as they move from an aqueous to a non-aqueous environment.[47,48] Emerging evidence suggests that preterm infants should not be expected to grow at the rate they would have in-utero or maintain the percentile at which they were born. Instead, it is normal for preterm infants to lose weight after birth, similar to term infants, and some experts argue that their growth trajectory should be adjusted accordingly.[47,48] Ultimately, refining growth expectations for preterm infants requires a shift from rigid comparisons to in-utero growth toward a more nuanced understanding of healthy postnatal growth patterns that reflect their unique physiology and developmental needs.

"The Breastfeeding Paradox": Balancing Growth and Outcomes in VLBW Infants

The "breastfeeding paradox" discussed above[1] is recognized as normal and physiologic in term infants. Nevertheless, it raises concern among the VLBW population, where every gram is closely monitored. The sight of these fragile infants falling short of anticipated weight gains can understandably cause alarm.

While cow milk-based products may promote faster weight gain, they come with potential risks that must be weighed carefully. An EHMD has been consistently associated with a reduced risk of mortality and morbidity,[49–54] as well as improved long-term neurodevelopmental outcomes.[55,56] In contrast, rapid catch-up growth with cow milk-based products may have negative long-term metabolic consequences.[37,38]

The benefits of an EHMD are likely conferred by the unique composition of human milk. Among VLBW infants, an EHMD has been shown to preserve higher levels of the fatty acids docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and arachidonic acid (AA) concentrations without supplementation.[57,58] Additionally, VLBW infants fed with an EHMD demonstrated higher serum concentrations of vitamin D

than those fed with cow milk-based nutrition, despite receiving lower levels of vitamin D supplementation.[59] Similarly, lactoferrin present in human milk is thought to enhance iron absorption.[12,60] These findings suggest an EHMD may promote superior micronutrient absorption.

The Role of Human Milk-Based Fortifier in VLBW Growth

Nutritional fortification is a cornerstone of care in NICUs for VLBW infants fed a human milk-based diet, as human milk alone does not provide the concentrated nutrition necessary to support healthy growth. With the widespread adoption of donor milk supplementation in US NICUs, access to an EHMD has become increasingly attainable. This progress enables clinicians to shift their focus from availability concerns to optimizing fortification protocols that address the specific nutritional needs of VLBW infants. By combining mother's own milk (MOM) or donor human milk (DHM) with fortifiers made exclusively from human milk, an EHMD provides the optimal nutritional foundation for growth and development.

Research continues to grow around the benefits of an EHMD for VLBW infants. For instance, there is evidence that the forms of choline in human milk and human milk-based fortifiers may help prevent NEC, as VLBW infants have limited capacity to convert choline into phosphatidylcholine, a key protective and developmental compound.[61]

Moreover, protein derived from human milk is better tolerated by VLBW infants than protein derived from cow milk, allowing for safer early fortification.[62] This enables VLBW infants to receive essential calories and protein sooner without triggering complications such as feeding intolerance and NEC.[62,63]

One of the key functions of human milk-based fortifiers is to compensate for the variability in macronutrient content found in human milk, which can make precise calorie calculations difficult. Studies show that human milk samples in NICUs frequently contain less than 20 kcal/oz, meaning the actual calorie intake may be lower than estimated.[52] This variability, whether the milk source is MOM or DHM, highlights the importance of fortification to ensure adequate nutrition.[64–66] Additionally, fat and nutrients can be lost during the transfer of human milk due to adherence to surfaces and tubing in the feeding apparatus.[67,68] Human milk-based fortifiers that are processed in a manner that best preserves bioactivity, such as vat pasteurization, help mitigate the loss of bioactive factors commonly seen in the processing of DHM.[69] This fortification not only provides essential macronutrients but also supports developmental support beyond its macronutrient content.

Given all these benefits, it comes as no surprise that the use of human milk-based fortifiers has been shown to reduce complications and improve outcomes for VLBW infants fed human milk while still promoting optimal growth.[50,51,54,55,70–74]

Finding the Right Protocol

To fully harness the benefits of an EHMD, fortification must be part of a thoughtful, evidence-based feeding protocol. Research has shown that early initiation of human milk-based fortifier, at less than 60 ml/kg/day, leads to better outcomes, compared with later fortification.[62] Similarly, proactive use of a human milk fat modular has shown improved growth metrics and reduced malnutrition rates.[75] A recently completed randomized trial in Japan involving 146 VLBW infants receiving an EHMD demonstrated excellent growth with early fortification at 50 ml/kg/day with no increase in mortality or morbidity above the already excellent outcomes seen in Japanese NICUs.[76]

VLBW infants require an individualized approach to nutrition management. While standardized fortification provides a starting point, adjustments based on the infant's growth or direct measurements of calorie and protein intake through targeted fortification are essential. Careful observation and close monitoring are paramount, and factors such as fat loss during milk transfer and feeding infusion must be carefully managed to ensure optimal nutrition and healthy development. Given the natural variability in human milk composition, fortification protocols must be optimized to address both macronutrient and micronutrient gaps.

Defining Healthy Growth: Evaluating Nutritional Metrics for VLBW Infants on an EHMD

How do we know if a VLBW infant on an EHMD is growing appropriately? Fenton et al recommend against using "extrauterine growth restriction" and "postnatal growth failure" among VLBW preterm infants, as these arbitrary cut-offs fail to account for the normal weight loss that occurs when moving to an extrauterine environment.[77] To accurately assess healthy growth, it is important to consider both the variability in nutritional intake and the specific metrics used to track growth and development.

Guidelines on neonatal malnutrition offer valuable insights into assessing growth in VLBW infants. Rather than relying solely on comparisons to in-utero fetal growth rates, it is more meaningful to evaluate growth using a combination of metrics. These include changes in weight-for-age z-scores, the number of days needed to regain birth weight, head circumference growth, linear growth velocity, and length-for-age z-scores.[35,42] The StRONNG checklist was developed to standardize how nutritional intake and growth outcomes are reported. This tool considers factors such as growth velocity, head circumference, assessment duration, and calculation methods, while promoting international standards for evaluating growth, body composition, and nutrient intake.[44]

Despite the ability to standardize nutritional calculations, the macronutrient content of human milk can vary significantly. It is often estimated at 20 kcal/oz, but in reality, the calorie content can be much lower, contributing to slower growth rates in some infants. This variability, whether the milk source is MOM or DHM, underscores the importance of fortification to increase the odds that VLBW infants will receive adequate nutrition.[64–66]

Micronutrients such as sodium, vitamin D, and iron also play a crucial role in supporting healthy growth, yet their concentrations in human milk can vary widely. When growth targets are not met, potential contributors such as total body sodium depletion or conditions that increase metabolic demand should be considered.[78] Moreover, standardized feeding guidelines do not account for differences in micronutrient levels between MOM and DHM. Notably, DHM has been shown to be deficient in sodium, a gap not fully addressed by most standard fortification protocols.[79] Micronutrient deficiencies can compound growth challenges and must be addressed alongside macronutrient fortification to ensure balanced development.

If we shift our focus to consider the *quality* of growth rather than just quantity, it is evident that premature infants

grow best on an EHMD when paired with an appropriate fortification protocol. Several studies have demonstrated that while EHMD-fed infants may experience slower weight gain velocity, they also exhibit healthier body composition characterized by longer and leaner bodies.[55,72,80] Notably, Lucas et al observed similar gains in weight and length among VLBW infants fed with an EHMD, compared to those receiving cow milk-based fortifier, but the EHMD group had greater gains in head circumference.[74]

Ultimately, the definition of healthy or ideal growth must be tied to meaningful outcomes. Current evidence consistently demonstrates that VLBW infants on an EHMD experience fewer complications and better long-term outcomes even when slower weight gain may be observed.[49–51,53–55,71,73,81]

Conclusion

Human milk remains the gold standard for infant nutrition, offering lifesaving benefits for VLBW infants whose survival and long-term development depend on optimized nutritional care. While human milk alone provides essential bioactive components that promote immunity, gut maturation, and brain development, it must be fortified to meet the concentrated nutritional needs of VLBW infants. With the widespread availability of DHM in US NICUs, an EHMD has become increasingly accessible, allowing clinicians to focus on tailoring fortification protocols rather than overcoming supply limitations. By combining MOM or DHM with fortifiers made exclusively from human milk, an EHMD provides the ideal nutritional foundation for healthy growth and improved developmental outcomes. When growth is evaluated holistically—not just by weight gain but by considering length, head circumference, and body composition—it becomes clear that infants fed an EHMD exhibit improved outcomes compared with those fed cow milk-based products. As clinical guidelines continue to evolve, the focus must remain on supporting the quality of growth in VLBW infants to ensure they thrive both in the NICU and beyond.

About the Authors

Melinda Elliott, MD, FAAP, is Chief Medical Officer at Prolacta Bioscience, Inc. She serves as the voice of the patient, working to ensure that the needs of premature infants are being articulated and that relevant treatment and product opportunities are identified. She also has over 30 years experience as a neonatologist and continues to serve as a clinical neonatologist with the Pediatrix Medical Group.

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regions of the US, as well as in international markets. These partnerships underscore the platform's ability to standardize and individualize care, reducing variability and supporting clinicians in making data-driven decisions regarding both the escalation and de-escalation of care in the ICU setting. The company forged strategic alliances with two top 10 global med tech companies, paving the way for comprehensive solution bundles, including cardiogenic shock management. These collaborations enhance Etiometry's platform, which already leverages FDA-cleared risk algorithms to provide near real-time insights for ICU teams to get ahead of patient deterioration. Etiometry launched ADK 2.0 in 2024, a groundbreaking Algorithm Development Kit designed to empower clinician researchers to develop, validate, and deploy custom algorithms for high-acuity care. Built on the same FDA-validated infrastructure that supports Etiometry's platform, ADK 2.0 streamlines the path from research to clinical application, reinforcing Etiometry's commitment to powering a "Learning Health System" within ICUs. Etiometry plans to build on its momentum with: Expansion of automated clinical pathways for acute respiratory distress syndrome (ARDS), cardiogenic shock, hemodynamic management after cardiac surgery, and ventilation weaning, further enhancing its capability to standardize care across ICUs. Development of new FDA-cleared algorithms and advancement of the utility of existing algorithms to address emerging challenges in critical care. Sustained focus on harnessing the platform to drive enhanced condition management across cardiogenic shock, hemodynamic management, respiratory failure and acute kidney injury (AKI). Deeper integration with electronic health records (EHR) systems to provide seamless workflows and better decision support. "We're in a great place to build on the incredible momentum we've established in 2024," said Cooke. "The strides we've made set a strong foundation for 2025 to ensure the Etiometry platform becomes even more comprehensive, progressively integrative and increasingly informative—enabling care teams to navigate the complexities of critical care with confidence."

Study Supports Vat Pasteurization

Prolacta Bioscience, the world's leading hospital provider of 100% human milk-based nutritional products for critically ill and premature infants, announced that the journal Foods has published a study demonstrating that vat pasteurization preserves most native characteristics of unprocessed human milk fat globules (MFG), compared to other processing methods for donor human milk. MFG comprises 98% of the fat in human milk. Human milk fat and fatty acids provide most of an infant's energy intake necessary for growth and development. The milk fat globule membrane provides antimicrobial protection and plays a role in shaping the gut microbiome to support healthy development of the infant's immune system. The study, "Investigating Milk Fat Globule Structure, Size, and Functionality After Thermal Processing and Homogenization of Human Milk," compared the effects of vat pasteurization (Vat-PT), retort sterilization (RTR), and ultra-high-temperature (UHT) processing, with and without homogenization, on human milk fat. The authors used these three methods with pilot-scale equipment to mimic industrial conditions to process and study 250 liters of human milk, using raw human milk as the control. "Our findings provide an increased understanding of how current processing methods affect human MFG, which is critical for optimizing processing conditions to preserve human milk bioactivity,"
Continued on page 37…

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Enhancing Safety and Comfort in Intravenous Infusions — With Coiled Tubing

Constance Girgenti, MSN, RN, VA-BC

Introduction

In the realm of healthcare, ensuring patient safety and comfort during intravenous (IV) therapy is paramount, particularly for vulnerable populations such as NICU/pediatrics and oncology patients to mention a few. Traditional IV tubing poses challenges, including the risk of tripping/falls (for healthcare workers, family and patients), the potential for infection, and limitations on mobility. Addressing these concerns, coiled extension tubing emerges as a promising solution, offering both practical advantages and enhanced patient well-being.

Benefits of the Vygon Coiled Extension Tubing

The coiled Extension Tubing has several key benefits that significantly improve the administration of IV therapy for our youngest to oldest patients:

Fall Prevention: One of the primary advantages of this innovative tubing is its coil design, which keeps the tubing elevated off the floor. By minimizing contact with the ground, the risk of accidental tripping and subsequent falls is dramatically reduced. This feature is particularly crucial in environments where patient mobility is limited or compromised. Keeping the tubing off the floors also reduces risks for the healthcare team.

Infection Prevention: Keeping IV tubing off the floor is essential for infection control, especially in the NICU/PICU and oncology settings where patients may have compromised immune systems. The elevated coil design minimizes contact with potentially contaminated surfaces, thereby reducing the risk of microbial transmission and nosocomial infections. This proactive approach aligns with best practices for infection prevention and contributes to overall patient safety.

Enhanced Mobility: The flexibility and stretchability of the coil tubing accommodate the patient's movements, allowing for greater freedom of mobility during IV therapy. This feature is especially beneficial for pediatric patients and active individuals who may struggle with traditional, rigid tubing. Patients can engage in daily activities and play without being hindered by the constraints of their IV line, promoting a sense of normalcy and well-being.

Customization and Adaptability: Coiled extension tubing can be easily adjusted to suit individual patient needs and treatment protocols. Healthcare providers can tailor the length and configuration of the tubing to optimize patient comfort and clinical efficacy. This adaptability ensures that patients receive personalized care while minimizing potential complications associated with standard IV tubing.

Conclusion

Incorporating innovative technologies such as coiled Extension Tubing into clinical practice represents a proactive step towards enhancing patient safety and comfort during intravenous infusions. By addressing common challenges such as fall risks and infection prevention, this advanced tubing solution offers tangible benefits for patients, caregivers, and healthcare facilities alike. Moving forward, healthcare providers must prioritize the adoption of such technologies to elevate the standard of care and ensure the well-being of all patients, particularly those with unique healthcare needs such as NICU/PICU and oncology patients.

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Constance Girgenti is an influential nurse leader renowned for her expertise in NICU care, particularly in advocating for human milk and advancing vascular access. She is a sought-after speaker at conferences worldwide and has authored publications on vascular access. Connie has received prestigious awards, including the AVA 2016 "Impact Award" and the Lasallian Nursing Graduate Award in 2021. She is also a distinguished member of Sigma Global Nursing Excellence.

Barcode Scanning Versus Manual Processes for Infant Feedings and Recipe Calculations Improves Safety, Reduces Errors, and Enhances Staff Efficiency

Caroline Steele, MS, RD, IBCLC, FAND and Suzanne Smith, MS, RD, IBCLC, LDN

Introduction

Safe handling of enteral nutrition (EN) including human milk and formulas for infants in the hospital setting is critical. Processes should be in place to prevent contamination, ensure preparation accuracy, and prevent misadministration. Misadministration (defined as providing the wrong human milk, fortifier/additive, or formula) is a patient safety concern. Provision of the wrong human milk is considered a reportable bodily fluid exposure and poses the risk of passing along viruses or exposing a different infant to medications or drugs from another person's milk. Concerns around human milk misadministration are well-recognized and the use of bar code scanning for human milk at the time of feeding is widespread. However, fewer organizations are scanning human milk at other steps in the preparation process. Furthermore, scanning fortifiers, additives, and formulas is not universally a standard of care suggesting that the risks of providing the wrong formula or fortifier as well as an expired or recalled formula or fortifier are not fully appreciated.

Regulatory standards and best practice recommendations suggest that verification of expressed human milk (EHM), pasteurized donor human milk (DHM), and enteral formulas prior to administration prevents errors and promotes patient safety. The Joint Commission National Patient Safety Goal 01.01.01 indicates that two patient identifiers should be verified before human milk is administered.[1] It also indicates that clinicians should verify a minimum of two patient identifiers when providing care, treatment, and services.[1] Because hospitals require an order from the provider to administer infant feedings, many consider the provision of enteral feedings as part of the patient's care/treatment. Consequently, confirming identifiers prior to administering formulas ensures this standard is met. The American Academy of Pediatrics Standards for Levels of Neonatal Care recommends that hospitals have procedures in place for accurate verification and administration of not only human milk, but formula as well to prevent misadministration.[2] The Institute for Safe Medication Practices (ISMP) notes that "organizations must ensure proper verification of EN products prior to preparation and administration, regardless of the feeding components (i.e., human milk, fortifiers, formulas, modulars)."[3]

Verification of feedings may occur through two methods: through a two-person double visual check of a minimum of two patient identifiers or by using bar code scanning technology. The purpose of this study was to compare the efficiency of manual two-person verification versus the use of bar code scanning technology.

Methods

A simulation laboratory was set up and two registered dietitians were used to conduct the verification for each appropriate step in the human milk and formula preparation and administration processes. Verification was performed manually during phase I and via bar code scanning using the Timeless Medical Nutrition Platform (Timeless Medical Systems, Prince Edward Island, Canada) in phase II. Verification steps in phases I and II are outlined in Figures 1 and 2, respectively. The time required for each step of the verification process was recorded by an observer. Only the time required for verification tasks was recorded. The time required for the actual feeding preparation tasks was not recorded as it was determined that the feeding preparation time itself would be similar in both phases. All calculations and tasks were based on a scenario where feedings were prepared for 12-hour time frames and unit-dosed.

Results

Verification tasks for human milk feedings averaged 4.03 minutes per patient for manual processes versus 2.71 minutes per patient using bar code scanning, a time savings of 33%. Time savings for verification tasks for formula feedings averaged 3.24 minutes per patient for manual processes versus 1.62 minutes per patient using bar code scanning resulting in a 50% time savings. While the minutes per patient may seem insignificant, for a hospital feeding 25 infants per day, this time savings equates to 200 to 246 hours per year. When looking at a large neonatal intensive care unit that may be feeding 100 patients per day, this time savings equates to over 800 hours per year. This may be further compounded if a hospital elected to use bar code scanning technology for enteral nutrition for patients of all ages.

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Suzanne Smith is a neonatal registered dietitian and international board certified lactation consultant with 25 years of clinical experience. Her evidence-based approach to neonatal care has been an asset to clinical outcomes and invaluable in setting the standard of care for neonatal nutrition.

Figure 1: Manual Enteral Nutrition Verification Steps (Phase I)

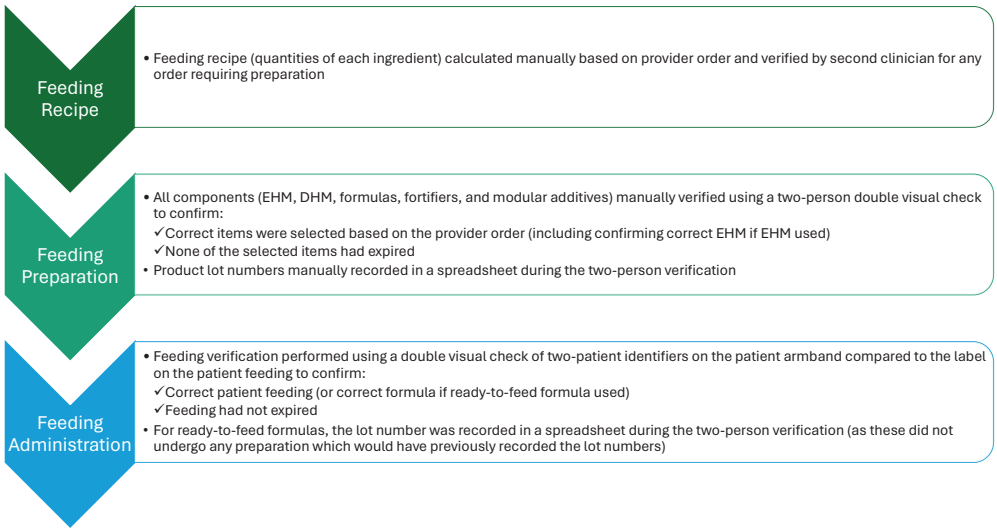
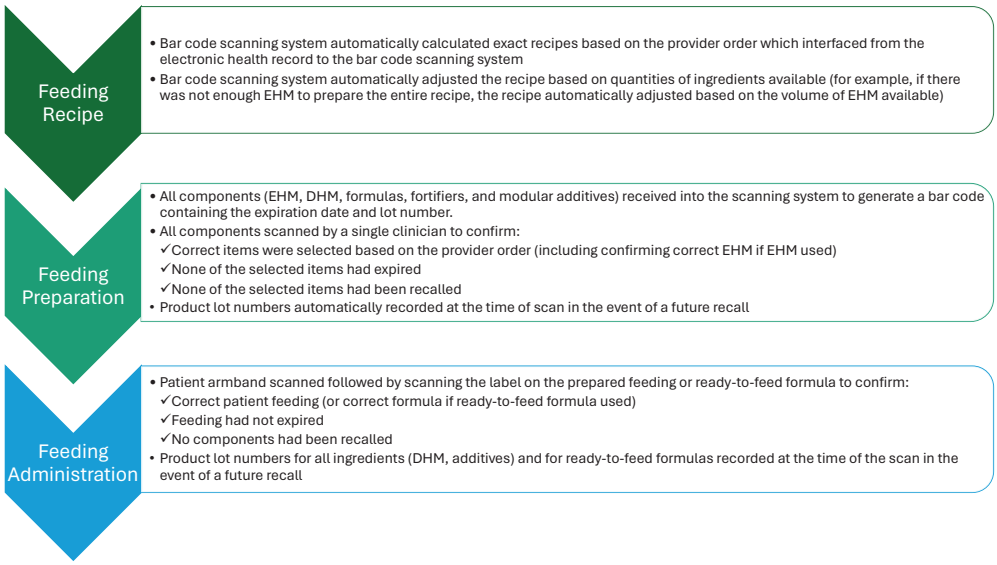


Figure 2: Bar Code Scanning Enteral Nutrition Verification Steps (Phase II)



Discussion

In addition to the actual time saved for verification tasks, there are additional time savings related to staffing needs. Many of the tasks require two individuals to be present solely for the purpose of performing the manual verification. The use of bar code scanning could allow centralized feeding preparation operations to have fewer staff working, particularly at non-peak preparation times, as they would not need to be conducting two-person manual verifications. One children's hospital published time savings in their preparation room of 1,052 hours per year because they did not have to double staff at certain times of the day which allowed them to eliminate a 20-hour per week technician.[4]

However, the benefits of using bar code scanning in lieu of performing a manual two-person verification extend beyond the time savings. Patient safety is the primary reason for choosing technology over manual processes. After conducting a failure mode and effects analysis (FMEA) on human milk handling, one hospital identified that 55% of potential failure points were unlikely to be detected by their manual processes before implementing bar code scanning.[5] This facility noted that the addition of bar code scanning improved safety by eliminating manual calculations and the potential for human error at each manual verification step.[5] Their concerns about potential for human error are supported by the literature.[5-9] There is little evidence that using a double visual check in the clinical setting is associated with significant reduction in errors.[6-9] Studies show that effectiveness is limited due to confirmation bias, the fact that both individuals may be affected by the same factors that can lead to errors, and that the practice may become a "mindless routine" over time.[10] Therefore, many professional organizations suggest the use of bar code scanning technology over manual processes for human milk and formula verification throughout the preparation and administration process.[3,11,12]

In addition to ensuring the correct feedings and feeding components reach the correct patient, verification should also confirm the feedings (or any of their components) are not expired or recalled. The safe practice recommendations from ISMP recommend the use of bar code scanning to alert the clinician if an incorrect, expired, or recalled item is scanned and that hospitals should ensure the technology can document the product's lot number and expiration date in the event of a

future recall.[3] Guidelines published by the American Society for Parenteral and Enteral Nutrition (ASPEN) also suggest the use of bar code scanning technology to reduce risk of providing incorrect enteral nutrition products and to track lot numbers in the event of a recall.[11,12] While manual verification could include steps to confirm both correct items and to ensure nothing has expired, there is no realistic way to confirm with each feeding preparation and administration that none of the ingredients has been recalled. The use of bar code scanning technology would be needed for that purpose.

Finally, verification of human milk and formula sample products at discharge is an important process that is not always considered. To guarantee patient safety and legal compliance, it is imperative that the correct human milk is dispensed to the intended family. Scanning each bottle of human milk at discharge is crucial in preventing misadministration and ensuring adherence to the Health Insurance Portability and Accountability Act (HIPAA). Furthermore, lot number documentation of formula sample(s) provided at discharge are needed to ensure follow up care in the event of a recall. One of the challenges many facilities face during widespread infant formula recalls is identifying patients who received samples of these products upon hospital discharge. Unless dispensed samples are scanned or lot number manually recorded, clinicians will not know which families received the recalled lot numbers.[13] For lot numbers manually recorded, the effort involved in reviewing manual logs to identify impacted patients could be extensive. Organizations should seek to implement processes where lot numbers are tracked throughout the infant feeding process through discharge. Having such robust systems in place improves patient safety by reducing the risk of a patient receiving a recalled product and provides the ability to track data in the event of a future recall.

Conclusions

While many hospitals verify human milk at the time of feeding, verification of all feeding components (EHM, DHM, fortifiers, formulas, and modulars) at the time of preparation, feeding, and discharge is not common when bar code scanning is not used. Hospitals using manual verification may not be verifying mathematical calculations for feeding recipes, nor checking expiration dates or tracking lot numbers. In addition, manual processes likely cannot easily confirm that none of the components have been recalled.

Furthermore, two-person manual verification has a high potential for human error and requires that two individuals be present solely for the purpose of performing a double visual check, even if one individual could otherwise perform the necessary duties.

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Nurturing Bonds: Transformative Power of a Mother's Voice

Anduin Anderle, RN

Introduction

Expectant mothers dream of bonding with their babies before they are born. The mother-baby bond is a fundamental aspect of human development, with bonding critical to baby's growth and mother's well-being

However, some births may not go as planned and a baby may end up requiring care in the neonatal intensive care unit (NICU). While NICU care may be essential to preserve life, the circumstances create barriers to physical and emotional bonding.

We cannot underestimate the presence of a mom to her infant. There are unseen chemical bonds that are forged when mom holds her baby—when baby smells mom and hears her voice. The human heart feels the importance of the mother-baby connection. But can we use science to truly understand and quantify the impact of nurturing these bonds even for the sickest babies in the neonatal care environment?

Emerging, evidence-based interventions aimed at fostering mother-baby attachment and connection include use of the mother's voice as a therapeutic tool in the NICU. Whether the mother is speaking directly to her baby, or her voice is recorded and played to the infant during the NICU stay, the cognitive, socioemotional and physical development benefits are well documented.

The NICU Challenge: Developing "Normally" in an "Abnormal" Environment

For babies born healthy at full gestational age (after 37 weeks in utero) and placed into the care of their mothers, the mother-infant attachment begins at birth and continues after they head home.

The baby in this fortunate situation can progress "normally," being held by their mother, gazing into her eyes and hearing her voice, all which are critical to cognitive, socioemotional and physical development.[1] Conversely babies requiring admission to the NICU following birth, "are challenged to develop normally without constant contact with their parents, particularly their mother, as their primary caregiver."[2]

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Mothers of neonates admitted to the NICU are shown to suffer negative impacts as well, including stress, anxiety, depression and post-traumatic stress syndrome (PTSD), because of the "inability to prevent their infant's pain, limited ability to care for the infant and feelings of helplessness."[3]

NICU teams not only bear the responsibility of caring for the physical and neurodevelopmental health of the babies in their units, but also providing emotional and physical support to the babies' mothers and other caregivers at their bedsides.

Mother's Voice Interventions

Based on the decades of research into the importance of maternal-infant attachment, neonatal therapists have at their disposal a variety of interventions they can leverage to support physical and emotional connections between mothers and babies in the NICU. A common and well-known example is encouraging mother/baby skin-to-skin contact, referred to as Kangaroo Care.[4]

Another key intervention that neonatal therapists can employ, even when a baby's mother is not physically by the bedside, is the application of the maternal voice as a therapeutic agent.[5]

The impact of sounds in the NICU has been well documented, with research correlating elevated noise with negative impacts on NICU babies' neurodevelopmental environment, sleep and brain development.[6] These findings have driven healthcare organizations to apply design principles and technologies to minimize harmful noise in the NICU, including incubators such as Draeger's Babyleo TN500 with integrated light and sound monitoring.

While some sounds are harmful to NICU babies, the mother's voice has been proven beneficial when applied, according to evidence-based guidelines.[7] Researchers have documented the positive impacts of both:[8]

- A mother's voice spoken live at their baby's bedside
- An audio recording of the mother's voice played to the baby

Audio Recordings Offer Flexibility and Consistency of Contact

A key benefit of recording the mother's voice is that it can be played to the baby when the mother is unable to be at the bedside. As the authors of a study on mothering in the NICU wrote, "NICU visitations required leaving employment, childcare, and other household or caregiving responsibilities behind."[9]

"Parents often struggle with coordinating their availability between their personal lives and the predetermined visiting hours set by the hospital, even with open visitation many NICUs still may have times when parents cannot visit, such as during nursing report or medical rounds." Some parents may have limited access to transportation and/or other children at home to care for and this can limit their time in the NICU as well.[10]

The researchers added how infants born in hospitals without NICUs but requiring neonatal critical care are transferred to hospitals that can provide this level of care. For the baby's mother, this could mean traveling an even greater distance from home and work to visit their babies.

Infectious disease outbreaks further restrict mothers' abilities to visit their babies in the NICU. This was the case during the height of the COVID-19 pandemic when hospitals and their NICUs "significantly reduced parental and family visitation privileges."[11]

Technology Supports Mother-Baby Connection in the NICU

Connecting the recording of the mother's voice to her biological sounds (e.g., heartbeat) or skin-to-skin holding (Kangaroo Care) has proven to be most effective in aiding the infant in maintaining autonomic stability and weight gain."[12]

The Dräger Babyleo® TN500 IncuWarmer features a safely integrated audio stimulation function providing the opportunity to play a mother's voice or heartbeat at safe low decibel levels to soothe and stabilize the baby. Babyleo's Kangaroo Mode allows parents to practice skin-to-skin care with minimal alarms and continuous temperature monitoring (using skin sensor monitors) while the incubator settings are kept stable for baby's return.

The Power of a Mother's Voice

Selena Williamson, BSN, RN and Jacqueline M. McGrath, PhD, RN, FNAP, FAAN published the results of their systematic search

Mother's Voice in Practice at Advent Health

Narendra Dereddy, MD and his team of researchers at AdventHealth for Children in Orlando, Florida, collaborated with the hospital's music therapy department on a maternal voice intervention for NICU patients.

The aim was to study how playing mother's recorded voice to extremely preterm infants in the NICU impacted the mothers' mental health, as measured by the Depression, Anxiety and Stress Scale –21 (DASS-21) questionnaire.

"It is a well-known fact that moms who have babies in the NICU are at higher risk for postpartum depression and anxiety than having a healthy baby," said Dr. Nereddy.[17]

Since this was a pilot study, a convenient sample size of 20 mothers in each group was chosen. While the study was conducted with extremely premature babies, other recommendations suggest older gestational babies for positive sounds stimulation.

Mothers of NICU babies created voice recordings, which included the mother speaking to her child (i.e., reading a book, expressing her love and hopes for the future) or singing to her child. Each mother could choose the voice recording subject matter for speaking and from a list of available books/songs for reading or singing.

The AdventHealth for Children NICU team cares for their babies in Dräger Babyleo® TN500 IncuWarmers featuring an integrated audio stimulation function. Neonatal therapists played each mother's recording to their baby through the Babyleo® audio port, which allows sound to be played inside the incubator at no more than 55 dB (within the recommended range).

Per the evidence-based guidelines, each recording was 30 minutes long and was played four times per day at a time the clinical team determined was appropriate for the baby and when visitors were not present. There was a 30-minute period of silence after the recording was played.

Dr. Dereddy and his team found the mothers' knowledge that they had provided their own audio to their babies helped reduce their anxiety scores. Additionally, the babies tolerated maternal voice played into the incubator directly well, without any adverse changes in vital signs. This finding assured the researchers in the safety of conducting a future trial.

Dr. Raena Baptiste-Boles, an Orlando psychologist whose daughter Riley spent the first three months of her life in the NICU at AdventHealth, participated in the study. She recorded herself singing and reading books, with the recording played to Riley's in the Dräger Babyleo® TN500. She commented on the experience: [18]

"My hope was that she would recognize it once she comes out, and she did. I've noticed as she got older, when I sing to her, she calms down and I think a lot of it has to do with the fact that she recognizes my voice from the singing in the isolette."

"It helps with feeling like a mom, feeling like you didn't do anything wrong, like you are doing the best way you can," Baptiste-Boles added.

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and synthesis of literature on the use of maternal voice as a therapeutic agent in the NICU.

The resulting *Evidence Based Practice Brief*, *What Are the Effects of the Maternal Voice on Preterm Infants in the NICU*, offers documented evidence of the power of a mother's recorded voice and biological sounds. Benefits of this intervention include:[13]

- **Better feeding tolerance:** Babies experienced fewer episodes of feeding intolerance when played a recording of their mother's voice reciting nursery rhymes twice a day
- **Greater weight gain:** Infants exposed to the maternal sounds gained significantly more weight
- **Improved physiological measures:** Babies' oxygen saturation increased, and heart rates and respiration decreased when recordings of their mother's voice were played
- **Fewer respiratory events:** Infants who were played a recording of their mother reading and singing along with their mother's heartbeat (with sounds filtered together to mimic how they would sound in the womb) experienced a lower number of critical respiratory events (CREs)
- **Increased stability and attending behaviors:** There was an increase in babies' stability behaviors (foot clasp, handclasp, sigh, ooh face, open face, flexion, grasping and smile) and attending behavior (eyes wide, eyes brightening, eyes toward source, suckling, stilling, visual locking, hand to face/mouth) when maternal recordings were played

With regards to the question of whether a baby in the NICU can differentiate between their mother's voice and that of another female caregiver, research revealed babies' right and left frontal lobes were activated when hearing a nurse's voice recording, but only their left frontal lobe was activated when hearing their mother's voice. Furthermore, the activity level was increased in response to the mother's voice recording as compared with the nurse's recording.[14]

> "One strategy to combat this shared stress [baby and mother] is increasing parental participation, particularly through the use of their voices whether parents are present or not."[15]

The Positive Impact on NICU Moms

Research into the use of mother's voice audio recordings in the NICU demonstrate benefits not only to the babies but to their mothers as well. Williamson and McGrath wrote in their Evidence Based Practice Brief: [16]

"Recordings serve as a parenting participation strategy that the mothers can control, reducing not only their anxiety but also reinforcing their attachment to their child and alleviating their fear or discomfort of not being able to more fully participate in the care of their child."

Evidence Based Recommendations for NICU Teams

While Williamson and McGrath's literature found "use of maternal voice did not appear to produce any negative effects or outcomes for the preterm infants; even in the cases where the interventions did not produce significant results," there is the potential for harm when any intervention is applied incorrectly."

Neonatal therapists play a central role in developing, tailoring and administering positive sound stimulation care for NICU babies in accordance with evidence-based recommendations and guidelines. They must consider the importance of minimizing toxic sound while enhancing therapeutic sound at the right times, at the right duration and at the appropriate gestational age.

As with evidence-based recorded music guidelines for premature infants in the NICU, therapeutic sound using the mother's voice should be administered with consideration of baby's gestational age in no more than 20–30-minute intervals.[19]

Williamson and McGrath offer these evidence-based recommendations for playing maternal voice recordings to NICU babies:[20]

- Use engaging "motherese" tone for recording (soothing tone as if they were speaking to their baby directly)
- Use recordings during periods of no parental contact (rounds, report)
- Use recordings during feedings and caregiving activities
- Use recordings before, during and after painful procedures (heel lance, surgeries)
- Do not choose all the above; target intervention choice to best support the individual needs of infant

Conclusion

The NICU experience presents profound challenges for both babies and their families, yet it also offers opportunities for transformative care. Harnessing the therapeutic potential of the mother's voice underscores the resilience of the maternal-infant bond, even in the most trying circumstances.

By implementing evidence-based strategies, such as recordings of maternal speech and biological sounds, and encouraging skin-to-skin contact, NICU teams are not only fostering improved outcomes for infants but also empowering mothers to participate in their child's care, alleviating their stress and reinforcing attachment.

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said the study's lead author, Gulustan Ozturk, Ph.D., who was at the University of California, Davis when the study was performed and is now assistant professor at the University of Wisconsin-Madison. Key highlights from this study: Vat-PT and RTR processing resulted in similar-sized MFG as unprocessed human milk while UHT processing resulted in smaller MFG diameter. The RTR treatment completely inactivated xanthine oxidase activity, a marker of MFG bioactivity, while UHT reduced its activity by 93%. In contrast, Vat-PT retained 28% of xanthine oxidase activity. Prolacta's human milk-based nutritional products are vat pasteurized using time and temperature specifications defined by the US Food and Drug Administration (FDA) to ensure pathogen inactivation and the highest level of safety while retaining as much of the natural bioactivity of the milk as possible. Bioactivity is thought to support infants' immunity, development, growth, and long-term health. "This study builds on previous research showing that Prolacta's vat pasteurized human milk-based nutritional products maintain higher bioactivity compared to fortifiers with other processing methods," said Melinda Elliott, MD, FAAP, chief medical officer at Prolacta. "Prolacta's fortifiers containing bioactive components have demonstrated a reduction in the risk of serious complications, including necrotizing enterocolitis (NEC)."

Fifty Years Later: Preterm Birth Shows Complex Pattern of Cardiovascular Outcomes

Adults aged 50 years who were born preterm have a higher risk for hypertension but lower risk for cardiovascular events than those born at term, with similar risks for diabetes, prediabetes, and dyslipidemia between groups. The researchers conducted a prospective cohort study of the Auckland Steroid Trial—the first randomized trial of antenatal corticosteroids (betamethasone) for women who were at risk for preterm birth, conducted in Auckland, New Zealand, between December 1969 and February 1974. They analyzed 470 participants, including 424 survivors recruited between January 2020 and May 2022 and 46 participants who died after infancy. The outcomes for 326 participants born preterm (mean age, 49.4 years) and 144 participants born at term (mean age, 49.2 years) were assessed using either a questionnaire, administrative datasets, or both. The primary outcome was a composite of cardiovascular events or risk factors, defined as a history of a major adverse cardiovascular event or the presence of at least one cardiovascular risk factor, including diabetes mellitus, prediabetes, treated dyslipidemia, and treated hypertension. The secondary outcomes included respiratory, mental health, educational, and other health outcomes, as well as components of the primary outcomes. The composite of cardiovascular events or risk factors occurred in 34.5% of participants born preterm and 29.9% of participants born at term, with no differences in the risk factor components. The risk for cardiovascular events was lower in participants born preterm than in those born at term (adjusted relative risk [aRR], 0.33; P = .013). The participants born preterm had a higher risk for high blood pressure (aRR, 1.74; P = .007) and the composite of treated hypertension or self-reported diagnosis of high blood pressure (aRR, 1.63; P = .010) than those born at term. From randomization to the 50-year follow-up, death from any cause was more common in those born preterm than in those born at term (aRR, 2.29; P < .0001), whereas the diagnosis or treatment of a mental health disorder was less common (P =

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Enhancing Upper Airway Function: Tools and Techniques for Patients With Tracheostomies

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The anatomy of the upper airway consists of the nasal cavity, oral cavity, pharynx, and larynx. The upper airway serves many functions including air warming and humidification, olfaction, respiration, swallowing, and speech.[1] All these functions may be compromised once a patient receives a tracheotomy.

Tracheotomy is a common procedure performed in medical settings for both pediatric and adult patient populations when concerns arise for respiratory distress or compromise. Over 100,000 adult patients receive a tracheotomy annually in the US.[2] Approximately 4,800 pediatric patients have a tracheostomy performed, with approximately 33% of them occurring in neonates.[3] There are a few reasons a patient may need a tracheotomy, some of which include prolonged intubation, upper airway obstruction, secretion management, and prevention of upper airway damage.[4] In the neonatal population, most tracheostomies performed are secondary to chronic respiratory failure or upper airway obstruction. [5]

Effects of a Tracheotomy on Upper Aerodigestive Function

Regardless of age, once a patient receives a tracheotomy, there will be many changes in their upper airway physiology. A tracheostomy tube disrupts respiration. Instead of airflow passing through the trachea to and from the upper airway, a tracheostomy tube becomes the access point for breathing. By redirecting airflow through the tracheostomy tube and reducing or eliminating airflow in the upper airway, many physiological changes occur.

Pressure. A primary change that occurs is the natural pressures in the aerodigestive system. The aerodigestive system requires subglottic pressure for voice production, breathing, swallowing, and pulmonary function.[6,7] Typically, in a person without a tracheostomy, the vocal cords play a major role in creating this pressure by opening and closing as needed to stop the flow of air and subsequently build pressure. However, a tracheostomy tube is placed below the level of the vocal cords and creates an open aerodigestive system. This open aerodigestive system may cause patients with tracheostomies to be unable to generate the pressure they need for many necessary functions.

Dysphagia. The changes that are seen in upper airway physiology post-tracheotomy may also have a negative effect on swallow function. Normal swallow function can be broken down into three main phases: oral, pharyngeal, and esophageal phases.[7]

1) The *oral phase* consists of preparing the food or liquid, also called the bolus, for entry into the pharynx by suck/swallow/breathe sequences, sucking, mastication (chewing), or manipulation. After the oral phase, the bolus enters the *pharyngeal phase*.
2) The *pharyngeal phase* serves two primary functions: to direct the bolus to the esophagus and to assist with protecting the airway from aspiration. The pharyngeal phase begins with the soft palate elevating to seal the nasopharynx, preventing pressure from escaping the nasal cavity. During the pharyngeal phase, a small period of apnea occurs, during which the vocal cords will close, and the arytenoids tilt forward to help protect the airway and to assist with opening the esophagus. The bolus then passes through the upper esophageal sphincter and into the esophagus, entering the last phase of the swallow, the *esophageal phase*.
3) The *esophageal phase* occurs once the bolus enters the esophagus. It is propagated inferiorly through peristalsis until it passes through the lower esophageal sphincter and into the stomach.[8]

When a patient's swallow function is negatively altered, this is referred to as dysphagia. Many patients who undergo a tracheotomy may also have dysphagia. Dysphagia can lead to many complications including dehydration, malnutrition, pneumonia, or airway obstruction.[9] However, it is important to note that the presence of a tracheostomy tube does not cause dysphagia, but it may exacerbate some issues. Each patient, pediatric or adult, must be evaluated individually.

Communication. Verbal communication may also be negatively affected by the disruption in airflow to the upper airway. For phonation to occur, the vocal cords vibrate while airflow moves through the glottis allowing for the production of voice.[10] However, with a tracheostomy tube in place, especially with an inflated cuff, there will be limited to no airflow to the upper airway. Without airflow to the upper airway, patients will be unable to communicate verbally. Loss of voice is detrimental

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to the well-being of patients. Freeman-Sanderson et al. (2016) found that patients with tracheotomies experience anxiety, fear, powerlessness, and futility due to the loss of voice.[11] In pediatrics, having access to functions necessary to meet developmental milestones for language may be a concern. Without access to crying, vocalizing, cooing, and babbling in infancy, there is a risk of delayed development and negative impacts on parent-child bonding.

Humidification. Another difficulty that patients with tracheostomies face is improper humidification. During normal breathing, the upper airway naturally humidifies, warms, and filters inspired gases.[12] With a tracheostomy tube in place, patients are no longer able to use the upper airway to heat and humidify the air they breathe. This can result in dry secretions, dry airways, increased work of breathing, and even damage to the mucosa.[12]

Tools for Enhancing Upper Airway Function

Because patients who receive a tracheotomy have the potential for multiple negative effects on their upper airway function, it is imperative to provide rehabilitation to the upper airway to restore normal physiological functions.

Speaking Valve. One of the best tools for restoring airflow to the upper airway and improving upper airway function is the use of a speaking valve. Having a speaking valve in place redirects airflow to the upper airway during exhalation instead of the air exiting out the tracheostomy tube. The Passy-Muir Tracheostomy & Ventilator Swallowing and Speaking Valve (PMV) is a one-way valve that restores the natural exhalation pathway and facilitates a reclosure of the aerodigestive system. With this Valve, a patient still breathes in through the tracheostomy tube but the closed-position, no-leak design redirects 100% of the exhalation up and out through the mouth and nose. Once the Valve is in place, airflow is restored to a patient's upper airway and assists with the rehabilitation of more normal physiologic functions. With restored airflow to the upper airway, respiration, swallow function, and verbal communication may be improved.[13]

Heat Moisture Exchanger. Another tool used to help restore a patient's upper airway function is a Passy-Muir heat-moisture exchanger (HME). An HME serves as a substitute for humidifying inspired gases by retaining moisture from every exhaled breath and returning moisture to the patient on the next inspired breath.[12] However, with an HME, the patient is primarily inhaling and exhaling out the tracheostomy tube. Reengagement of the upper airway is limited. HMEs have been shown to improve pulmonary function, patient satisfaction, and quality of life.[14]

Techniques for Enhancing Upper Airway Function

Once the tools have been employed, it is time to put the techniques to use. Breathing through a tracheostomy tube allows for less respiratory effort and a decrease in the work of breathing for patients. This decrease in the work of breathing is due to a drop in resistance following a change in the patient's exhalation pathway being out through the tracheostomy tube.[15] Because breathing through the tracheostomy tube requires less effort, some patients may experience some disuse atrophy of their respiratory muscles. Newborn infants are especially prone to respiratory muscle dysfunction due to limited functional reserves.[16]

Using a PMV®007 to close the system and restore pressure to assist with trunk support and vocalizations.

Respiratory Muscle Training. A very important component of rehabilitation will be to improve the use and function of a patient's respiratory muscles. Older children and adult patients who have a tracheostomy tube may do expiratory muscle strength training (EMST) if capped or using a PMV. EMST has been shown to improve upper airway muscle strength, reduce the risk of aspiration, and reduce respiratory morbidity.[17-19]

While EMST may not be feasible for neonatal patients, there has been research suggesting that inspiratory muscle strength training (IMST) is also beneficial and can be performed successfully with neonatal patients who are mechanically ventilated. The studies utilized an inspiratory-resistive load to improve infants' respiratory strength and endurance with positive outcomes.[20] Various devices address respiratory muscle function. Depending on the goals of therapy, one may use a pressure threshold device or a resistive device. The pressure threshold allows the clinician to increase the load on the system while a resistive device increases the resistance to flow. These devices may address expiratory and inspiratory needs.

Considerations for Dysphagia

While improving respiration techniques are crucial, we also must keep swallow function in mind. Providing rehabilitation for swallow function will be essential for patients with tracheostomies who experience dysphagia. Doing so will ensure safe and effective swallowing, reduce aspiration risk, and improve overall health.[21] Speech-Language Pathologists (SLPs) assess, diagnose, and treat various speech, communication, cognitive linguistic, and swallowing disorders.[22] As an essential part of the management of patients with tracheostomies, regardless of age, SLPs employ various maneuvers, exercises, and diet modifications to promote swallow function. The appropriate interventions are dependent on the patient's age, medical history, and underlying disease processes.[23]

Considerations for Communication

In addition to respiration and swallow function, it is critical to improve communication for patients with tracheostomies.

Communication is essential for all as it directly impacts autonomy, patient rights, and psychological well-being. Restoring communication will allow patients with tracheostomies to make decisions about their healthcare and advocate for their individual needs.[11] Patients also have the right to communicate; the ADA requires all medical facilities to provide patients with effective communication.[24] Restoring communication directly impacts quality of life; studies have shown improving communication improves self-esteem, mood, and cheerfulness.[11] Access to communication also impacts patient safety. It has been shown that adverse events, including safety with infants and children, are more frequent for patients without ready access to communication. Many indications of pain, hunger, and other biological needs occur through vocalizations, cries, and verbalizations.

Often in the NICU, restoring patients' verbal communication is something that gets disregarded as these patients are not able to use language. However, it is especially important to address communication, even for patients in the neonatal population. Restoring communication for these patients means allowing them to hear their vocalizations and crying. Studies have shown self-stimulation with sound is extremely valuable for development.[25]

Once the PMV is in place, airflow will be restored to the upper airway, and this should allow patients to phonate. However, some patients may have underlying conditions that cause dysphonia or difficulty speaking. Patients who are diagnosed with dysphonia will require additional therapy. SLPs are critical to providing voice therapy which involves vocalizations, manipulations, and breathing exercises that are designed to retrain the laryngeal muscles and system to produce sound.[26]

Conclusion

Patients who undergo tracheotomies experience physiological changes. It is imperative to restore airflow to the upper airway and close the aerodigestive system to restore and improve patients' breathing, swallow function, and phonation. Airflow can easily be restored with the use of the Passy-Muir Valve. Once the Valve is in place, techniques can be used to further enhance a patient's upper airway function and allow them to get back to a more normal physiology.

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.007); no differences were observed between the groups for other outcomes. "Those aware of being born preterm also may be more likely to seek preventive treatments, potentially resulting in a reduced risk of cardiovascular disease but a greater prevalence of risk factors if defined by a treatment such as treated dyslipidemia or treated hypertension," the authors wrote. "In this cohort, the survival advantage of the term-born control group abated after infancy, with a higher all-cause mortality rate compared with that of the group born preterm," wrote Jonathan S. Litt, MD, MPH, ScD, and Henning Tiemeier, MD, PhD, in a related commentary.

RSV Vaccines and Treatments Face Global Access Hurdles

Almost 70 years after the discovery of the respiratory syncytial virus (RSV), vaccines and preventive treatments are giving babies a chance to beat the potentially deadly childhood infection. As doctors turn to monoclonal antibody therapies and governments plan vaccination programs, clinical researchers are asking whether these measures will reduce the spread of the virus. Will fewer babies die from RSV, and fewer children develop permanent wheezing? Fabio Midulla, an associate professor of pediatrics at Sapienza University of Rome in Rome, Italy, said that the pharmaceutical industry is poised to push governments to use vaccines and monoclonal antibodies for even more children. "Such a push might work," he said at the European Respiratory Society (ERS) 2024 Congress, "given that several studies have already demonstrated that their use can improve outcomes for children who do become infected and reduce societal costs by reducing hospitalizations." But Mariëlle WH Pijnenburg, a pulmonary specialist at Erasmus University Rotterdam in Rotterdam, the Netherlands, said at the Congress that greater rollout would require governments to force industry to lower prices. If treatments remain beyond the reach of lower-income countries—where the burden of RSV is the greatest—the death toll from this common childhood infection will remain stubbornly high, and the prospect of global elimination will remain forever out of reach, she said. Nirsevimab, a long-acting monoclonal antibody given to newborns to prevent severe infection, was approved by the European Medicines Agency (EMA) in October 2022 and the US Food and Drug Administration (FDA) in July 2023. And Abrysvo, a vaccine given to older adults and pregnant women to stop them from passing the virus to babies from birth through 6 months of age, was approved by the FDA and the EMA in 2023. RSV is responsible for over 33 million lung infections in children younger than 5 years annually, with more than 4 million hospitalizations and nearly 200,000 deaths. According to the Centers for Disease Control and Prevention, every year, 2.1 million children younger than 5 years old visit a healthcare provider because of an RSV infection and between 58,000 and 80,000 children younger than 5 years old are hospitalized in the United States. The burden of severe RSV disease is also high among adults, with an estimated 123,000-193,000 hospitalizations, 24,400-34,900 ICU admissions, and 4680-8620 in-hospital deaths occurring annually among US adults. While the virus affects all age groups, it is particularly severe in infants, swelling their airways and causing them to struggle for breath. Infection in infancy can lead to later complications, such as the development of wheezing, a condition that causes breathlessness and a feeling of tightening in the chest, and possibly also asthma. Studies have shown that children and preterm infants infected with RSV who were given monoclonal antibodies experienced less post-infection wheezing,
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The Association Between Self-Reported Total Gestational Weight Gain by Pre-Pregnancy Body Mass Index and Moderate to Late Preterm Birth

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Background

Preterm birth, defined as birth before 37 weeks of gestation, is one of the leading causes of neonatal morbidity and mortality.[1,2] Currently, preterm birth occurs in approximately 8.2% of pregnancies in Canada,[3] and this rate increased over the past decades.[4,5] Moderate to late preterm births between 32-<37 weeks of gestation constitute 86% of all preterm births.[6] Medically induced preterm birth due to pregnancy complications are a contributor to the rise in moderate to late preterm birth.[7-9] However, higher pre-pregnancy body mass index (BMI) and advanced maternal age have also become more common, which are risk factors for spontaneous preterm birth.[10,11] For most preterm births, the causes are complex and largely unknown.[12]

Inadequate, recommended, and excessive gestational weight gain (GWG) were defined by the Institute of Medicine (IOM) in 2009 and are based on pre-pregnancy BMI.[13] In Canada, only about one-third of pregnan- cies meet the recommended GWG, while approximately half are considered excessive and fewer than 20% are considered inadequate.[14-16] While excessive GWG occurs among pregnant people in all BMI categories, it is most prevalent among those who are overweight or have obesity, which also increase the risk of pregnancy complications.[14,17-20] The IOM found evidence for a U-shaped association among underweight and healthy weight people, with both inadequate and excessive GWG increasing the risk of preterm birth, and that high GWG was associated with preterm birth among all pre-pregnancy BMIs.[13] However, the literature often demonstrates inconsistencies, and not all studies account for gestational duration when defining GWG. For example, a systematic review found that inadequate GWG was associated with increased odds of preterm birth, and excessive GWG was associated with decreased odds of preterm birth.[21] The association is less understood for those with a BMI in the obesity range. The 2009 IOM recommendations acknowledge that more research is needed to understand healthy GWG among people with obesity, specifically among severe obesity subgroups.[13] Many studies of GWG have only evaluated the categorical variable (inadequate, recommended, or excessive weight gain); however, evaluating risk across a continuous measure of total GWG would contribute valuable new evidence regarding risk thresholds. Additionally, few studies have evaluated the moderate to late preterm birth category.

The primary objective of this study was to evaluate the association between IOM-defined total GWG categories (inadequate, excessive, recommended) and moderate to late preterm birth and assess variation in the association by pre-pregnancy BMI category. Our secondary objectives were to evaluate the association between continuous total GWG and moderate to late preterm birth by pre-pregnancy BMI, and to evaluate subgroup analyses by child sex, family income, maternal age at birth, and gestational diabetes and/or hypertension status.

Methods

Cohort selection

We conducted an analysis of cross-sectional data from The Applied Research Group for Kids (TARGet Kids!). TARGet Kids! is a primary care practice based research network with an open longitudinal cohort.[22] Children younger than 6 years of age were recruited through primary care paediatric and family medicine clinics, primarily in the Greater Toronto Area, Ontario, Canada, during regularly scheduled health supervision visits.[22] Children with health conditions affecting growth (e.g., failure to thrive or cystic fibrosis), chronic conditions (except asthma), severe developmental delay, gestational age < 32 weeks, and families not fluent in English were excluded from enrollment.[22] All children that met the eligibility criteria were invited to participate in TARGet Kids!, and parents completed a baseline questionnaire that collected health and demographic information. Data was based on recall. Ethics approval was provided by Clinical Trials Ontario with the board of record as the Research Ethics Board at The Hospital for Sick Children (#2063). Informed, written consent was obtained from parents/ caregivers of all participating children. For this study, participants who completed the TARGet Kids! baseline questionnaire from January 2011 to March 2020 were eligible. Non-biological children (e.g., adopted) were excluded. Only singleton births were included as separate GWG recommendations exist for twin pregnancies;

no recommendations currently exist for other multiple pregnancies.[13]

Exposures

The primary exposure was self-reported total GWG defined as a 3-level categorical variable as inadequate, recommended, and excessive, based on the 2009 IOM recommendations for each pre-pregnancy BMI category.[13] Pre-pregnancy BMI was calculated as self-reported pre-pregnancy weight in kilograms divided by mean maternal height in meters squared (kg/m^2) and categorized into 4 groups according to the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) classification.[23,24] We calculated observed total GWG by subtracting self-reported pre-pregnancy weight from self-reported end-of-pregnancy weight. Using standardized measurement protocols, parent height was measured by trained research assistants.[22] Most parents had repeated height measures obtained during follow-up visits, and for data cleaning purposes we compared the observed height to a calculated mean maternal height for each participant. We excluded participants if the difference between mean height across all TARGet Kids! visits and observed height at baseline was ≤−10 cm or ≥ 10 cm, or if mean height was < 121 cm. Participants with a calculated BMI < 15 kg/ m^2 or > 70 kg/m^2 (n = 7) or with a calculated GWG <−30 kg or > 50 kg (n = 15) were excluded.[25-27] Participants with gestational weight loss and implausible end-of-pregnancy weight were also excluded (n = 2) (Fig. 1).

Since total GWG increases with gestational duration, we accounted for gestational age at birth when determining whether participants had inadequate, recommended, or excessive GWG, using methods previously described.[25,28-31] Given that the IOM recommendations apply to full-term births, we determined expected GWG at 40 weeks of gestation for each pre-pregnancy BMI category using the formula, recommended first trimester weight gain + (gestational age – 13 weeks) × (recommended weight gain rate during second and third trimesters). Expected GWG at 40 weeks of gestation was defined as 100% of the IOM recommendations. To determine the percentage of recommendations that corresponded to the upper and lower limits of the IOM's total GWG recommendations, we divided the IOM lower and upper limits for each pre-pregnancy BMI category by the respective expected GWG and multiplied by 100%. Thus, the recommended GWG percentage ranges were 79–114% for underweight, 86–120% for healthy weight, 81–134% for overweight, and 77–140% for obesity. We calculated expected GWG for 32, 33, 34, 35, 36, and 37 weeks of gestation for each pre-pregnancy BMI category. To determine the percentage of recommendations met for each participant, we divided observed GWG by expected GWG for the respective gestational age and pre-pregnancy BMI category and multiplied by 100%. Participants were classified into the recommended GWG group if the percentage fell within the range based on pre-pregnancy BMI. If the percentage was less or greater than the ranges, participants were classified as inadequate GWG or excessive GWG, respectively. The IOM recommendations for BMI-specific first trimester weight gain, second and third trimester weight gain, and total GWG,[13] as well as the details for the calculations[25,28-31] are provided in Supplementary Table 1.

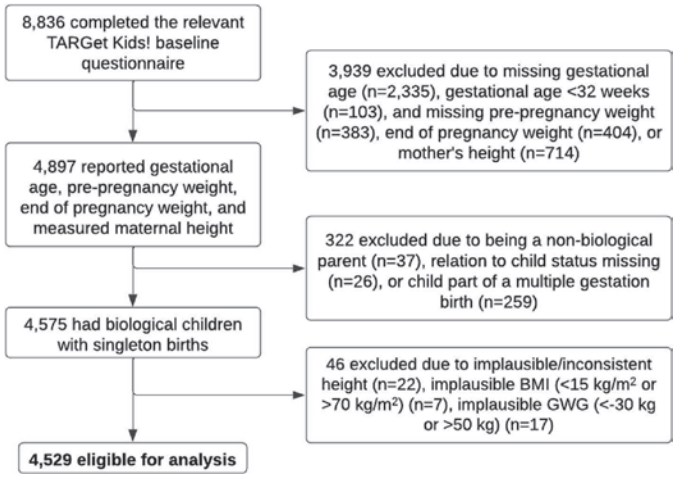

Figure 1. Flowchart of study participants from the TARGet Kids! research network in the Greater Toronto Area, Canada and study exclusion criteria.

We also assessed self-reported total GWG defined as an 8-level categorical variable (Supplementary Table 2) to observe the association among various subgroups of inadequate and excessive GWG, similar to previous literature.[28] Continuous total GWG was also evaluated as an exposure. Both variables were expressed as the percentage of recommendations met to account for gestational duration.

Outcome

The outcome was gestational age at birth. Parents were asked about their child's gestational age in the baseline questionnaire, in which response options included < 32, 32, 33, 34, 35, 36, 37, 38–41, and > 41. Previous analysis of TARGet Kids! data found that parent-reported gestational age at birth categories, including term, late preterm, and moderately preterm birth had high sensitivity and specificity > 80% using administrative healthcare data as the criterion standard.[32] For some participants, electronic medical record data was available for gestational age and were used in our analysis when available. To be consistent with the exclusion criteria, a few children with a gestational age < 32 weeks that were inadvertently enrolled were excluded. Gestational age was categorized as term (≥ 37 weeks of gestation), and moderate to late preterm (32-<37 weeks of gestation). The moderate to late preterm category was further subdivided in secondary analysis according to clinical definitions, including late preterm (34-<37 weeks of gestation), and moderately preterm (32-<34 weeks of gestation).[33,34]

Confounders and effect modifiers

All variables were collected from parent-reported data on the baseline questionnaire. The following potential confounders were selected a priori based on literature and variables that were hypothesized to be related to the exposure and outcome and not on the causal path: maternal ethnicity (European; East, South, or Southeast Asian; African; or Arab, Latin American, mixed ethnicity, or other), family income (<$60,000, $60,000 to $149,999, or ≥$150,000), maternal education level (less than university or university degree or higher), cigarette use during pregnancy (yes or no), alcohol use during pregnancy (yes or no), maternal age at birth, and parity (1 child or ≥ 2 children). Child sex (male or female) was also included in adjusted models as a potentially important predictor of the outcome. Complications during pregnancy including gestational hypertension and gestational diabetes were hypothesized to be on the causal pathway between GWG and moderate to late preterm birth and thus, were not adjusted for in our analysis.[35]

To explore important subgroup differences and potential for effect modification, we performed subgroup analysis by pre-pregnancy BMI, child sex, family income, maternal age at birth, and a combined variable of gestational hypertension and/or diabetes status (yes or no). These variables were selected because they are important health equity variables, and it was plausible that there were differences among these subgroups.

Statistical analysis

We evaluated the prevalence of inadequate, recommended, and excessive GWG for each pre-pregnancy BMI category. Binomial logistic regression models with generalized estimating equations (GEE) were used to calculate unadjusted and adjusted odds ratios (aORs) and 95% confidence intervals (CIs) for the association between total GWG categories and moderate to late preterm birth. For the relationship between total GWG categories and clinically relevant categories of preterm birth, including moderately preterm and late preterm birth, we used GEE multinomial logistic regression models to estimate unadjusted and aORs and 95% CIs. GEE with independent correlation structure were used to account for 559 parents with more than one child enrolled in the TARGet Kids! cohort, who also met the criteria for this study. The recommended GWG group was the referent category in models with categorical GWG as the exposure. For the analysis of continuous GWG, adjusted predicted probabilities were calculated using logistic regression by pre-pregnancy BMI using restricted cubic splines,[36] and plotted against GWG expressed as the percentage of recommendations met. Statistical analyses were conducted using SAS, version 9.4 (SAS Institute Inc, Cary NC).

Models were adjusted for confounders identified a priori as described above. Confounders had less than 15% missingness and were considered missing at random. The PROC MI procedure in SAS, version 9.4 (SAS Institute Inc) was used to perform multiple imputations with a total of 20 imputations using the fully conditional specification (FCS) method. To understand potential effect modification and explore differences by health equity variables, we performed subgroup analyses by pre-pregnancy BMI, child sex, family income, maternal age at birth, and gestational diabetes and/or hypertension status. We also conducted type 3 tests with Wald statistics for the interaction and reported p-values for the multiplicative interaction terms. For our subgroup analyses, underweight and healthy weight BMI categories were combined due to a small number of underweight parents in our study sample.

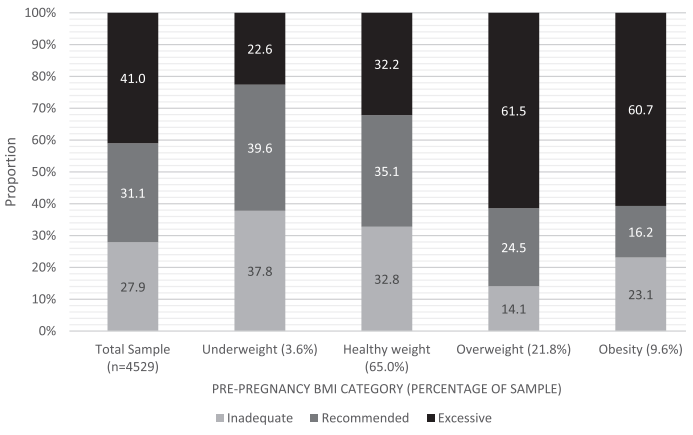

Figure 2. Prevalence of inadequate, recommended and inadequate GWG overall and by pre-pregnancy BMI category.

Results

A total of 4,529 participants were available for the analysis (Fig. 1). The prevalence of inadequate, recommended, and excessive GWG overall and for each pre-pregnancy BMI category is displayed in Fig. 2. Overall, 31.1% had GWG within the IOM recommendations, 41.0% had excessive GWG and 27.9% had inadequate GWG. More than 60% of participants with overweight or obesity had excessive GWG.

Distribution of study participant characteristics by GWG

A total of 8.2% of children were born moderate to late preterm; 6.6% born late preterm and 1.6% born moderately preterm (Table 1). The moderate to late preterm birth rate was 6.3% among parents with recommended GWG, 7.4% among parents with inadequate GWG, and 10.3% among parents with excessive GWG. Most parents had a university degree or higher (75.6%) and were < 35 years of age at birth (61.0%) (Table 1).

Association between GWG and moderate to late preterm birth

Excessive versus recommended GWG was associated with increased odds of moderate to late preterm birth compared to term birth (aOR 1.68, 95% CI 1.29, 2.19), while there was insufficient evidence of an association between inadequate vs. recommended GWG and moderate to late preterm birth (aOR 1.10, 95% CI 0.81, 1.50). When the outcome was further categorized into late preterm and moderately preterm, the association with inadequate and excessive GWG remained similar for both preterm categories (Table 2).

After subgroup analysis by pre-pregnancy BMI, among parents with an underweight/healthy BMI, both inadequate (aOR 1.44, 95% CI 1.01, 2.07) and excessive GWG (aOR 2.13, 95% CI 1.52, 3.00), compared to recommended GWG, were associated with increased odds of moderate to late preterm birth (Table 2). Among parents who were overweight, inadequate GWG was associated with decreased odds of moderate to late preterm birth compared to recommended (aOR 0.39, 95% CI 0.16, 0.97). Additionally, there was no evidence of an association between excessive vs. recommended GWG and moderate to late preterm birth (aOR 1.13, 95% CI 0.67, 1.91). Among parents with obesity, insufficient evidence of an association was found between inadequate (aOR 0.41, 95% CI 0.15, 1.22) or excessive (aOR 0.65, 95% CI 0.27, 1.55) vs. recommended GWG.

When we plotted the adjusted predicted probability for moderate to late preterm birth across continuous GWG, variations existed by pre-pregnancy BMI category. A U-shaped association was observed for those with underweight/healthy weight (Fig. 3). Among parents with overweight or obesity, the risk of moderate to late preterm birth did not substantially increase until GWG exceeded 200% of the recommendations. This would be equivalent to a total GWG that exceeds 9.4–12.9 kg for parents with obesity and 12.6–17.1 kg for overweight, depending on gestational age between 32 and 40 weeks. Similar results using the 8-level GWG variable to calculate ORs are shown in Supplementary Table 3. For those with overweight/obesity, weight gain slightly lower than the recommendations had a protective effect on moderate to late preterm birth (aOR 0.33, 95% CI 0.11, 0.95), while the highest GWG level showed a strong positive association with the outcome (aOR 2.05, 95% CI 1.06, 3.95).

Table 1 Sample characteristics of eligible participants enrolled in TARGet Kids! overall and by GWG category

Characteristic	All Participants *N* (%)	Inadequate *n* (%)	Recommended *n* (%)	Excessive *n* (%)
Total Participants	4,529	1,265 (27.9%)	1,409 (31.1%)	1,855 (41.0%)
Total gestational weight gain, mean (SD)	13.5 (6.6)	6.7 (5.2)	12.8 (2.6)	18.6 (5.1)
Gestational age category	4,529			
Term (≥37 weeks)	4,156 (91.8%)	1,171 (92.6%)	1,321 (93.8%)	1,664 (89.7%)
Moderate to late preterm (32 to <37 weeks)	373 (8.2%)	94 (7.4%)	88 (6.3%)	191 (10.3%)
Late preterm (34 to <37 weeks)	299 (6.6%)	75 (5.9%)	70 (5.0%)	154 (8.3%)
Moderately preterm (32 to <34 weeks)	74 (1.6%)	19 (1.5%)	18 (1.3%)	37 (2.0%)
Pre-pregnancy BMI category (kg/m^2)	4,529			
Underweight (<18.5)	164 (3.6%)	62 (4.9%)	65 (4.6%)	37 (2.0%)
Healthy (18.5 to <25)	2,943 (65.0%)	964 (76.2%)	1,032 (73.2%)	947 (51.1%)
Overweight (25 to <30)	989 (21.8%)	139 (11.0%)	242 (17.2%)	608 (32.8%)
Obesity (≥30)	433 (9.6%)	100 (7.9%)	70 (5.0%)	263 (14.2%)
Pre-pregnancy BMI, mean (SD)	24.0 (4.7)	23.4 (4.8)	23.1 (3.8)	25.2 (5.0)
Maternal education level	4,086			
Less than university	998 (24.4%)	351 (30.8%)	211 (16.4%)	436 (26.3%)
University degree or higher	3,088 (75.6%)	789 (69.2%)	1,077 (83.6%)	1,222 (73.7%)
Annual family income	4,019			
Less than $60,000	814 (20.3%)	281 (25.3%)	198 (15.5%)	335 (20.5%)
$60,000 to $149,999	1,566 (39.0%)	433 (39.0%)	483 (37.8%)	650 (39.8%)
$150,000 or more	1,639 (40.8%)	395 (35.6%)	597 (46.7%)	647 (39.6%)
Maternal ethnicity	4,137			
European	2,280 (55.1%)	528 (46.4%)	760 (57.9%)	992 (58.8%)
East, South, or Southeast Asian	942 (22.8%)	319 (28.0%)	295 (22.5%)	328 (19.4%)
Arab, Latin American, Mixed ethnicity, other	570 (13.8%)	149 (13.1%)	181 (13.8%)	240 (14.2%)
African	345 (8.3%)	142 (12.5%)	76 (5.8%)	127 (7.5%)
Child sex	4,529			
Male	2,377 (52.5%)	639 (50.5%)	726 (51.5%)	1,012 (54.6%)
Female	2,152 (47.5%)	626 (49.5%)	683 (48.5%)	843 (45.4%)
Parity	4,114			
1 Child	1,971 (47.9%)	535 (46.7%)	614 (47.5%)	822 (49.1%)
≥2 Children	2,143 (52.1%)	611 (53.3%)	679 (52.5%)	853 (50.9%)
Maternal age at birth	4,434			
<35 years	2,706 (61.0%)	746 (60.4%)	824 (59.5%)	1136 (62.6%)
≥35 years	1,728 (39.0%)	489 (39.6%)	561 (40.5%)	678 (37.4%)
Maternal age at birth in years, mean (SD)	33.2 (4.5)	33.1 (4.8)	33.5 (4.1)	33.0 (4.7)
Gestational diabetes and/or hypertension	4,502			
Yes	563 (12.5%)	169 (13.4%)	146 (10.5%)	248 (13.4%)
No	3,939 (87.5%)	1,089 (86.6%)	1,251 (89.6%)	1,599 (86.6%)
Parent-reported birthweight	4,482			
<2.5kg	310 (6.9%)	104 (8.3%)	89 (6.4%)	117 (6.4%)
≥2.5kg to <4kg	3,749 (83.7%)	1,078 (86.3%)	1,182 (85.0%)	1,489 (80.8%)
≥4kg	423 (9.4%)	67 (5.4%)	120 (8.6%)	236 (12.8%)
Cigarette use during pregnancy	4,440			
Yes	75 (1.7%)	22 (1.8%)	11 (0.8%)	42 (2.3%)
No	4,365 (98.3%)	1,220 (98.3%)	1,370 (99.2%)	1,775 (97.7%)
Alcohol use during pregnancy	4,440			
Yes	253 (5.7%)	70 (5.6%)	91 (6.6%)	92 (5.1%)
No	4,187 (94.3%)	1,172 (94.4%)	1,290 (93.4%)	1,725 (94.9%)

Abbreviations: *GWG* gestational weight gain, *BMI* body mass index, *SD* standard deviation, *kg* kilograms, *m* meters

Lastly, we performed subgroup analyses by child sex, family income, maternal age at birth, and gestational diabetes and/or hypertension status (Table 3). Among those < 35 years of age at birth, both inadequate and excessive GWG, compared with recommended, were associated with increased odds of moderate to late preterm birth (inadequate: aOR 1.66, 95% CI 1.08, 2.55; excessive: aOR 2.16, 95% CI 1.46, 3.19). However, among those 35 years of age or older, the aOR for inadequate GWG was 0.69 (95% CI 0.43, 1.12) and the aOR for excessive GWG was 1.35 (95% CI 0.93, 1.97). There was also evidence of effect modification among the lowest and highest income subgroups. For those with a family income ≥$150,000, excessive vs. recommended GWG had a 2.7-fold increased odds of moderate to late preterm birth (aOR 2.72, 95% CI 1.70, 4.35). For those with a family income <$60,000, excessive vs. recommended GWG had an aOR of 0.92 (95% CI 0.53, 1.60). There was no evidence of effect modification for child sex. Differences were observed by gestational diabetes and/or hypertension status, such that associations were strong and consistent only among those who had no gestational diabetes and/or hypertension (Table 3).

Discussion

Our analysis showed that the association between self-reported total GWG and moderate to late preterm birth varied by pre-pregnancy BMI. Overall, excessive GWG was strongly associated with increased odds of moderate to late preterm birth. When we performed subgroup analysis by pre-pregnancy BMI, there was a U-shaped association among those with underweight/healthy weight, such that both inadequate and excessive GWG increased the risk of moderate to late preterm birth. For parents who were

Table 2 Odds ratios and 95% confidence intervals for the associations between inadequate or excessive GWG and moderate to late preterm birth, late preterm birth, and moderately preterm birth, compared to term birth, overall and by pre-pregnancy BMI category, using recommended GWG as the referent group

	Moderate to Late Preterm (32-<37 weeks)		Late Preterm (34-<37 weeks)		Moderately Preterm (32-<34 weeks)	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Overall[a]						
Inadequate	1.21 (0.89, 1.63)	1.10 (0.81, 1.50)	1.21 (0.86, 1.70)	1.09 (0.77, 1.54)	1.19 (0.62, 2.28)	1.14 (0.59, 2.21)
Recommended	Reference	Reference	Reference	Reference	Reference	Reference
Excessive	1.72 (1.33, 2.24)	1.68 (1.29, 2.19)	1.75 (1.31, 2.33)	1.70 (1.27, 2.28)	1.63 (0.93, 2.88)	1.60 (0.89, 2.88)
Pre-pregnancy BMI (kg/m^2)[ab]						
Underweight/ Healthy weight (<25)						
Inadequate	1.59 (1.12, 2.27)	1.44 (1.01, 2.07)	1.60 (1.08, 2.39)	1.43 (0.95, 2.15)	1.56 (0.74, 3.28)	1.48 (0.70, 3.13)
Recommended	Reference	Reference	Reference	Reference	Reference	Reference
Excessive	2.17 (1.55, 3.04)	2.13 (1.52, 3.00)	2.18 (1.50, 3.16)	2.11 (1.45, 3.08)	2.17 (1.07, 4.40)	2.18 (1.07, 4.55)
Overweight (25 to <30)						
Inadequate	0.50 (0.21, 1.21)	0.39 (0.16, 0.97)	0.61 (0.25, 1.49)	0.47 (0.18, 1.20)	NA	NA
Recommended	Reference	Reference	Reference	Reference	Reference	Reference
Excessive	1.14 (0.69, 1.87)	1.13 (0.67, 1.91)	1.15 (0.67, 1.97)	1.16 (0.66, 2.03)	1.11 (0.35, 3.51)	1.02 (0.31, 3.38)
Obesity (≥30)						
Inadequate	0.43 (0.15, 1.29)	0.41 (0.15, 1.22)	0.37 (0.10, 1.32)	0.36 (0.10, 1.32)	0.65 (0.09, 4.73)	0.65 (0.08, 5.18)
Recommended	Reference	Reference	Reference	Reference	Reference	Reference
Excessive	0.65 (0.28, 1.48)	0.65 (0.27, 1.55)	0.69 (0.28, 1.72)	0.74 (0.27, 1.97)	0.51 (0.09, 2.84)	0.42 (0.07, 2.46)

Abbreviations: *GWG* gestational weight gain, *BMI* body mass index, *kg* kilograms, *m* meters, *OR* odds ratio, *CI* confidence interval

[a] Models were adjusted for child sex, parity, family income, cigarette use during pregnancy, alcohol use during pregnancy, maternal age at birth, maternal ethnicity, and maternal education level

[b] GWG*BMI $p = 0.016$; interaction p-value was calculated from fully adjusted binomial model

overweight or had obesity, the risk did not increase substantially until far beyond the recommended upper limit of the IOM weight gain guidelines, and a broad range of GWG appeared to have a low risk of moderate to late preterm birth. In addition to variations in the association by pre-pregnancy BMI, there was also evidence of effect modification by maternal age at birth and family income. Both inadequate and excessive GWG were associated with increased odds of moderate to late preterm birth among parents < 35 years of age at birth. For those with a family income ≥$150,000, excessive GWG was most strongly associated with moderate to late preterm birth.

Our study makes important contributions to the literature. Given the narrow range of recommended GWG for those with obesity, and the high prevalence of excessive GWG among those with overweight or obesity, an important finding of our study was the broad range of GWG that was associated with a low risk of moderate to late preterm birth for these groups.

Similar to our findings, two studies found that excessive GWG compared to recommended was associated with increased odds of preterm birth, while the association for inadequate GWG and preterm birth was not significant.[15,37] However, several studies have found differing results.[20,21,38-41] Notably, a systematic review and meta-analysis found that inadequate GWG was associated with increased odds of preterm birth and excessive GWG decreased the odds of preterm birth.[21] Differences among published studies could be due to not accounting for gestational duration when determining total GWG, which may result in a spurious association with inadequate GWG.[35] Additionally, there may be unmeasured or unaccounted confounding factors.

Similar to our results, other studies have also suggested that wider GWG ranges may be acceptable for the association with preterm birth among parents with high BMI, and that the risk of preterm birth increased at GWG beyond the current upper limit.[28,42,43] While one study differentiated between spontaneous and medically induced preterm birth, some results were comparable to our results for those with overweight or obesity. Notably, for medically induced preterm birth, a substantial increase in risk did not occur until quite high GWG.[28] However, for spontaneous preterm birth, weight loss displayed the greatest risk among those with class I obesity and the risk was U-shaped among those with class II obesity.[28] Our results may deviate from this finding due to our inability to distinguish between spontaneous and induced preterm birth. More research is needed to determine if lower than recommended GWG can be safely recommended to pregnant people with overweight or obesity and ensure that gaining less weight or weight loss is not harmful to maternal and infant pregnancy outcomes, as demonstrated in other research.[44-46] However, recent literature has also showed that lower than recommended GWG or weight loss did not increase the risk of adverse maternal and infant outcomes among those with obesity, especially among those with class III obesity.[47] Studies have also suggested that overweight or obesity are independent risk factors of preterm birth regardless of GWG.[18,48,49]

Another unique aspect of our study was our subgroup analysis to examine the association between GWG and moderate to late preterm birth by maternal age at birth, family income, and child sex. To our knowledge, no other studies evaluated family income subgroups, or found that excessive GWG was associated with increased odds of moderate to late preterm birth among higher income families. While the reasons for this are unknown, previous literature has suggested that the effects of low income can significantly increase the rates of preterm birth.[6] Previous literature has also suggested that parents with lower income are more likely to enter pregnancy with overweight or obesity,[50] and this would be consistent with our results by pre-pregnancy BMI. Another study found differences in the association among maternal age subgroups.[41] Our findings might suggest that

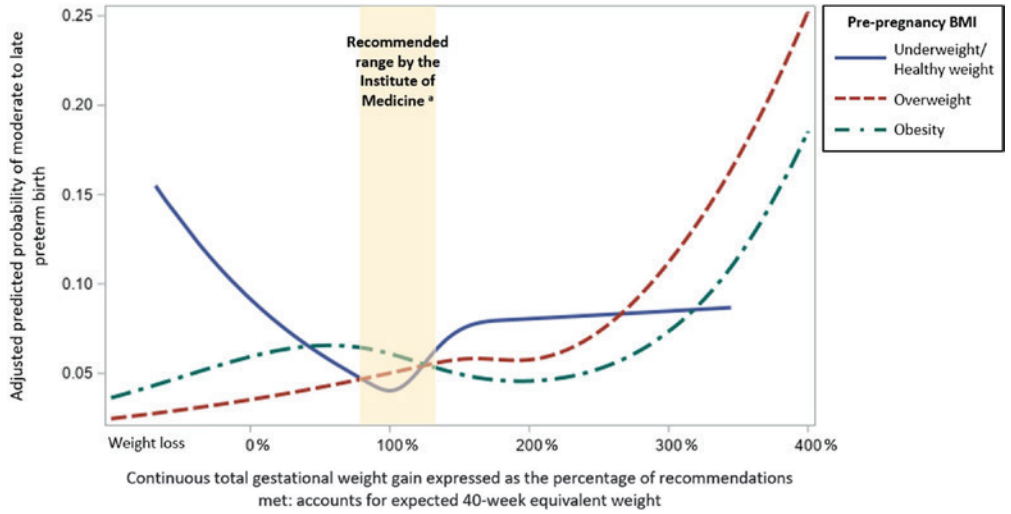

Fig. 3 Adjusted predicted probability of moderate to late preterm birth across continuous total GWG expressed as the percentage of recommendations met by pre-pregnancy BMI category

A recommended range varies by pre-pregnancy BMI. The range is 79%-114% for underweight, 86%-120% for healthy weight, 81%-134% for obesity, and 77%-140% for obesity

Model was adjusted for child sex, parity, family income, cigarette use during pregnancy, alcohol use during pregnancy, maternal age at birth, maternal ethnicity, and maternal education level

GWG ≤-100% or ≥400% were combined

advanced maternal age at birth alone is a risk factor of preterm birth, as described by other literature.[11] More studies are needed to determine if these factors increase the risk of preterm birth regardless of GWG.

Strengths and limitations

Strengths of this study include adjustment for important confounders and accounting for gestational duration in the exposure. We also explored the association using continuous GWG, which has not been frequently explored in the literature. We had a subgroup analysis among our ethnically diverse cohort, which included maternal and socioeconomic health determinants to address research gaps.

This study also has limitations. We were unable to assess GWG longitudinally at multiple time points during pregnancy. The findings were based on self-reported pre-pregnancy weight and end-of-pregnancy weight, with potential for misclassification among pre-pregnancy BMI and GWG categories. However, previous literature has suggested that pre-pregnancy and delivery weight are often underestimated, although this error did not largely bias associations with birth outcomes.[51] Our cohort consisted of primarily healthy children and did not include neonatal deaths or children born < 32 weeks of gestation. However, in our cohort that excluded births < 32 weeks of gestation and multiples, the proportion of children born preterm was higher than the provincial average. Our higher rate of preterm birth may be due to geography (Toronto area only), or possibly due to recruitment from both pediatric and family practice sites participating in the TARGet Kids! research network. Our sample was also relatively small, especially when subdivided into late preterm and moderately preterm separately in the subgroup analyses. Additionally, there is the potential for selection bias and the results may not be generalizable to other populations, as the cohort consisted of a non-random sample which included families with relatively high incomes and post-secondary education. While we accounted for gestational duration in the determination of our exposure variables, there is potential for bias in the measure used.[52,53] We were unable to differentiate between sub-types of preterm birth including spontaneous and induced. Previous literature has found different associations between GWG and spontaneous vs. medically induced preterm birth.[28,39,54,55] We were also unable to evaluate obesity subgroups, and the 2009 IOM guidelines acknowledge that more research is needed to understand healthy GWG among obesity subgroups.[13] While many potential confounders have been accounted for, there may still be some residual confounding such as prior preterm birth influencing the results.[56] Additionally, there was a lack of evaluation and analysis of maternal complications and biochemical indicators during pregnancy because it was not collected in TARGet Kids!.

Conclusion

Our results suggest that the association between self-reported total GWG and moderate to late preterm birth differs according to pre-pregnancy BMI. Among those with a BMI in the underweight/healthy weight range, there was a U-shaped association with moderate to late preterm birth. For those with a BMI in the overweight or obesity range, GWG > 200% of the recommendations was associated with higher risk. Parents with a higher BMI may have a broader range of GWG with low moderate to late preterm birth risk. This research is particularly important given that over 50% of people of child-bearing age are overweight or have obesity,[57] and that there is a high prevalence of excessive GWG among this group. Prospective studies with validated measures are needed to verify the accuracy of the results. This and future research may inform new guidelines for the prevention of preterm birth among parents with overweight or obesity.

Acknowledgements

We thank all of the participating families for their time and involvement in TARGet Kids! and are grateful to all practitioners who are currently involved in the TARGet Kids! practice-based research network.Members of the TARGet Kids! Collaboration: Co-Leads: Catherine S. Birken, MD, and Jonathon L. Maguire,

Table 3 Odds ratios and 95% confidence intervals for the associations between inadequate or excessive GWG and moderate to late preterm birth, late preterm birth, and moderately preterm birth, by maternal age at birth, family income, and child sex, using recommended GWG as the referent group

	Moderate to Late Preterm (32-<37 weeks)		Late Preterm (34-<37 weeks)		Moderately Preterm (32-<34 weeks)	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Maternal age at birth[a]						
(GWG*age p= 0.042)[e]						
<35 years						
Inadequate	1.78 (1.17, 2.71)	1.66 (1.08, 2.55)	1.80 (1.12, 2.89)	1.66 (1.03, 2.69)	1.70 (0.69, 4.17)	1.68 (0.69, 4.09)
Recommended	Reference	Reference	Reference	Reference	Reference	Reference
Excessive	2.20 (1.50, 3.23)	2.16 (1.46, 3.19)	2.19 (1.43, 3.36)	2.13 (1.38, 3.29)	2.27 (1.01, 5.09)	2.22 (0.98, 5.01)
≥35 years						
Inadequate	0.78 (0.50, 1.24)	0.69 (0.43, 1.12)	0.78 (0.47, 1.30)	0.69 (0.41, 1.16)	0.78 (0.30, 2.08)	0.74 (0.26, 2.07)
Recommended	Reference	Reference	Reference	Reference	Reference	Reference
Excessive	1.39 (0.96, 2.01)	1.35 (0.93, 1.97)	1.46 (0.97, 2.18)	1.41 (0.93, 2.13)	1.12 (0.48, 2.59)	1.14 (0.48, 2.71)
Family income[b]						
(GWG*income p= 0.059)[e]						
<$60,000						
Inadequate	0.82 (0.46, 1.48)	0.80 (0.44, 1.43)	0.91 (0.47, 1.75)	0.87 (0.45, 1.70)	0.49 (0.13, 1.76)	0.48 (0.13, 1.77)
Recommended	Reference	Reference	Reference	Reference	Reference	Reference
Excessive	0.93 (0.54, 1.62)	0.92 (0.53, 1.60)	0.91 (0.49, 1.72)	0.87 (0.46, 1.64)	0.89 (0.30, 2.53)	0.94 (0.32, 2.77)
$60,000 to 149,999						
Inadequate	1.08 (0.65, 1.78)	0.98 (0.59, 1.65)	0.98 (0.56, 1.72)	0.89 (0.50, 1.58)	1.47 (0.47, 4.53)	1.39 (0.45, 4.32)
Recommended	Reference	Reference	Reference	Reference	Reference	Reference
Excessive	1.54 (1.00, 2.36)	1.51 (0.98, 2.33)	1.47 (0.91, 2.36)	1.45 (0.90, 2.34)	1.75 (0.63, 4.85)	1.66 (0.60, 4.60)
≥$150,000						
Inadequate	1.56 (0.89, 2.72)	1.50 (0.85, 2.62)	1.61 (0.84, 3.08)	1.53 (0.80, 2.91)	1.67 (0.54, 5.20)	1.66 (0.54, 5.10)
Recommended	Reference	Reference	Reference	Reference	Reference	Reference
Excessive	2.70 (1.69, 4.29)	2.72 (1.70, 4.35)	3.01 (1.79, 5.07)	3.03 (1.79, 5.13)	2.21 (0.84, 5.82)	2.25 (0.84, 6.04)
Child sex[c]						
(GWG*sex p= 0.280)[e]						
Female						
Inadequate	0.99 (0.63, 1.55)	0.88 (0.55, 1.39)	0.90 (0.55, 1.50)	0.81 (0.48, 1.35)	1.40 (0.52, 3.79)	1.23 (0.45, 3.38)
Recommended	Reference	Reference	Reference	Reference	Reference	Reference
Excessive	1.78 (1.21, 2.60)	1.73 (1.17, 2.55)	1.72 (1.14, 2.61)	1.67 (1.09, 2.56)	2.06 (0.85, 5.01)	2.02 (0.82, 4.97)
Male						
Inadequate	1.42 (0.94, 2.14)	1.31 (0.86, 1.99)	1.53 (0.97, 2.43)	1.39 (0.87, 2.23)	1.06 (0.45, 2.51)	1.04 (0.43, 2.52)
Recommended	Reference	Reference	Reference	Reference	Reference	Reference
Excessive	1.67 (1.17, 2.40)	1.67 (1.16, 2.40)	1.77 (1.18, 2.66)	1.77 (1.18, 2.66)	1.36 (0.65, 2.86)	1.36 (0.64, 2.89)
Gestational diabetes and/or hypertension[d]						
(GWG*gestational diabetes/hypertension p=0.042)[e]						
Yes						
Inadequate	0.58 (0.30, 1.11)	0.55 (0.28, 1.08)	0.59 (0.28, 1.23)	0.58 (0.27, 1.24)	0.53 (0.15, 1.93)	0.45(0.11, 1.73)
Recommended	Reference	Reference	Reference	Reference	Reference	Reference
Excessive	1.20 (0.70, 2.05)	1.21 (0.70, 2.07)	1.25 (0.69, 2.28)	1.26 (0.69, 2.29)	1.02 (0.36, 2.86)	1.01 (0.35, 2.88)
No						
Inadequate	1.42(1.003, 2.01)	1.34 (0.94, 1.90)	1.41 (0.96, 2.07)	1.32 (0.90, 1.94)	1.47 (0.69, 3.15)	1.46(0.68, 3.12)
Recommended	Reference	Reference	Reference	Reference	Reference	Reference
Excessive	1.84 (1.36, 2.50)	1.82 (1.34, 2.48)	1.84 (1.32, 2.57)	1.83 (1.30, 2.56)	1.84 (0.93, 3.64)	1.82 (0.91, 3.64)

Abbreviations: *GWG* gestational weight gain, *BMI* body mass index, *OR* odds ratio, *CI* confidence interval

[a] Models were adjusted for child sex, parity, family income, cigarette use during pregnancy, alcohol use during pregnancy, maternal ethnicity, and maternal education level

[b] Models were adjusted for child sex, parity, alcohol use during pregnancy, maternal age at birth, maternal ethnicity, and maternal education level. Cigarette use during pregnancy was not adjusted for due to convergence issues

[c] Models were adjusted for parity, family income, cigarette use during pregnancy, alcohol use during pregnancy, maternal age at birth, maternal ethnicity, and maternal education level

[d] Models were adjusted for child sex, parity, family income, cigarette use during pregnancy, alcohol use during pregnancy, maternal age at birth, maternal ethnicity, and maternal education level

[e] Interaction p-values were calculated from fully adjusted binomial models

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Conceptualization and Study Design: AMP, LNA, GMM, AF, CSB, JLM, CDGKS. Analysis and Interpretation: AMP, LNA, CDGKS. Writing – Original Draft: AMP, LNA. Writing - Review and Editing: AMP, LNA, GMM, AF, CSB, JLM, CDGKS.

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Data availability

Data are available upon request by contacting https://www.targetkids.ca/ contact. The full data are not freely available to respect the confidentiality of our participants, ensure data integrity, and avoid scientific overlap between projects. Once initial contact has been made, we request a short research pro- posal which will be subject to review by the TARGet Kids! Scientific Committee and approval by institutional IRBs.

Declarations

Ethics approval and consent to participate

Ethics approval was provided by Clinical Trials Ontario with the board of record as the Research Ethics Board at The Hospital for Sick Children (#2063). Informed, written consent was obtained from parents/caregivers of all partici- pating children. TARGet Kids! adhered to the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Abbreviations

aOR	Adjusted odds ratio
BMI	Body mass index
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
FCS	Fully conditional specification
GEE	Generalized estimating equation
GWG	Gestational weight gain
IOM	Institute of Medicine
kg	Kilograms
m	Meters
SD	Standard deviation
TARGet Kids!	The Applied Research Group for Kids
WHO	World Health Organization

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A Term Neonate With 1p36 Deletion Syndrome and 16p12 Deletion: A Case Report and Literature Review

Surasak Puvabanditsin, MD, Amrryn Halari, MBBS, Jenny Choi, Sutharsanam Balaji, MD, Su Young Park, MD, Rajeev Mehta, MD

Abstract

Monosomy 1p36 is a known delineated multiple congenital anomalies/mental retardation syndrome characterized by hypotonia, mental retardation, growth delay, epilepsy, congenital heart defects, characteristic facial appearance, and precocious puberty. It is considered to be one of the most common subtelomeric microdeletion syndrome. The majority of 1p36 deletions occur de novo with <1% recurrent risk. We report new findings of imperforate anus, gall bladder cyst, and choroid plexus cysts in a patient who had terminal deletion of chromosome 1p36.33 and interstitial deletion of 16p12.2 with a brief review of the literature.

Introduction

1p36.3 deletions account for as much as 0.5-0.7% of idiopathic mental retardation. The prevalence is estimated to be one in 5,000-10,000 newborns, making it the most common terminal deletion syndrome. So far about 600 cases of monosomy 1p36 have been reported.[1-3] The main clinical manifestations other than mental retardations are distinctive facial anomalies, microcephaly, congenital heart defects, cardiomyopathy, brain malformations, hearing loss, short stature, and behavioral disorders.

16p12.2 deletion is characterized by variable clinical findings that do not constitute a recognizable syndrome. It was usually noted in clinical chromosomal microarray analysis of individuals with intellectual disability, developmental delay and schizophrenia. Other clinical findings included hearing loss, dental abnormalities, renal anomalies, male genital anomalies and cleft palate ± cleft lip.[3]

We report a term male newborn with periventricular cysts secondary to periventricular hemorrhage, gastrointestinal and genitourinary malformations. We establish a theory of brain malformation seen in a patient with deletions of chromosome 1p36 and 16p12.2 and report a new finding of the liver abnormality. We review the literature.

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Case Report

This is a 1620-g male neonate was born at 37 weeks of gestation to a 29-year-old primigravida Indian mother by cesarean section because of severe intrauterine growth retardation (IUGR). Apgar scores were 8 and 9 at 1 and 5 minutes respectively. Prenatal care was complicated with IUGR. The family history was unremarkable and there is no consanguinity. Prenatal sonogram revealed enlarged choroid plexuses and bilateral ventriculomegaly. The fetus karyotype was normal 46 XY on amniocentesis. Birth weight was 1620 g (<10th centile), length 42 cm (<10th centile), and head circumference was 31.5 cm (10th centile). The physical findings at birth were small for gestation age appearing neonate, dysmorphic facies, an enlarged anterior fontanelle, epicanthal folds, high arch palate, hypoplasia of the middle phalange of the fifth finger (single crease), glandular hypospadias (Figure 1), imperforate anus and perineal fistula. Echocardiography was normal. Abdominal ultrasound showed a cyst (3x3 mm) near the gall bladder representing a choledochal cyst (Figure 2). Neurosonogram (day of life #1) showed hypoechoic density of ependymal region of the left lateral ventricles with multiple septation in both lateral ventricles (Figure 3a, 3b). MRI (day of life # 31) of the head revealed left lateral periventricular cystic encephalomalacia (Figure 4a, 4b). He underwent a colostomy on day of life #2. He was discharged from the hospital after 35 days of hospitalization.

Cytogenetic and Molecular Studies

Whole genome SNP (Single Nucleotide Polymorphisms) microarray analysis was performed using the SNP oligonucleotide micro array analysis (SOMA) CytoScan HD

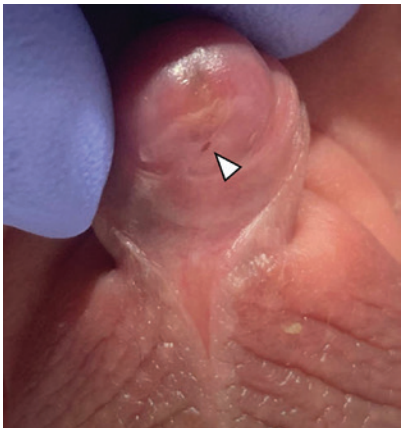

Figure 1. Photo showed penile hypospadias (arrow).

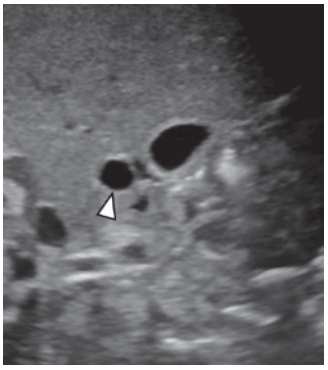

Figure 2. Abdominal ultrasound showed a cystic structure adjacent to the gall bladder and common bile duct representing a choledochal cyst (arrow).

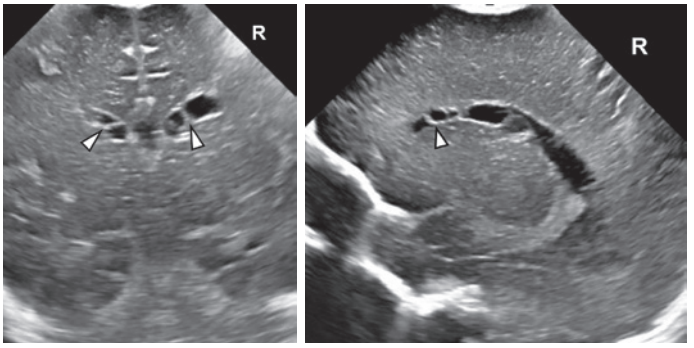

Figure 3a, 3b. Coronal and saggital views of cranial ultrasound soon on the first day of life showed resolving bilateral intraventricular hemorrhage with intraventricular septations (arrows).

platform which uses over 743,000SCN probes and 1,953,000 NPCN probes with median spacing of 0.88 kilobase (kb). Total genomic DNA was extracted from the patient's blood sample and digested with NspI and the ligated to NspI adaptors. Polymerase chain reaction (PCR) products were purified and quantified. Purified DNA was fragmented and biotin labeled and hybridized to the Cytoscan HD Genechip. The data was analyzed using chromosome Analysis Suite which is based on the GRCh37/hg19 assembly. There was a 6.79 megabase (MB) terminal deletion of the short arm of chromosome 1: arr [hg19] 1p36.33p36.23 (849,466-7,638,032) x1 and 257 kilobase (Kb) interstitial deletion in the short arm of chromosome 16p12.2 (21,596,299-21, 852,932) x1. The SNP microarray analysis identified a considerable size and number of genes in terminal deletion of chromosome segment 1p, includes numerous OMIM genes [proximal gene[*CAMTA1*], consistent with 1p36 deletion syndrome.

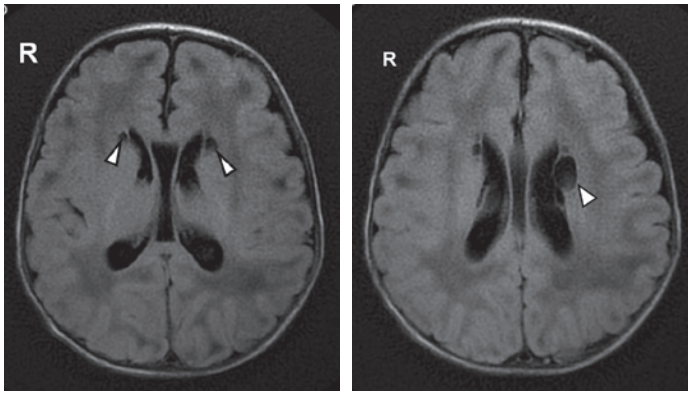

Figure 4a, 4b. Cranial MRI T2 showed bilateral ventriculomegaly and encephaloma Lacia (arrows).

Also microarray analysis detected an interstitial deletion of chromosomal segment 16p12.2, this interval includes 3 OMIM genes (*METTL9*, *IGSF6*, *OTOA*). Mutations in *OTOA* have been associated with autosomal recessive deafness (OMIM: 607039).[4]

Discussion

Brain neuroimaging in 1p36 deletion syndrome has documented cerebral atrophy, ventricular dilatation, ventricular asymmetry, hydrocephalus, corpus callosum abnormalities, delay in myelination, focal cortical dysplasia, periventricular nodular heterotopia, and a leukodystrophic picture.[2,5,6,21] Our patient has new clinical findings of brain abnormalities involving periventricular and intraventricular hemorrhage resulting in ventriculomegaly and encephalomalacia. Our case revealed the possible pathogenesis of the ventriculomegaly reported in the literature on the patients with 1p36 deletions. The findings of intraventricular septation and hemorrhage at birth signified in-utero event leading to the ventriculomegaly and brain abnormality (encephalomalacia). There is a report case of choroid plexus hyperplasia associated with 1p36.3 deletion patient.[5] We postulated that the abnormality of choroid plexus would risk infant with 1p36 deletion to develop periventricular/intraventricular hemorrhage (PVH/IVH) leading to ventriculomegaly. Our patient developed ventriculomegaly and the encephalomalacia as the result of PVH/OH as well as. Recent published data showed 66% of patients with 1p36.3 deletion had brain malformations, 13/62 patients with abnormal corpus callosum, and 12/62 patients with ventriculomegaly.[6]

While this syndrome has been increasingly studied over the years, linking of specific anatomic and physiologic defects to gene deletions is yet to be fully achieved, leaving clinicians to rely on reports of previously identified abnormalities. Recent reports of association of 1p36 deletion syndrome with specific gastrointestinal (GI) abnormalities including duodenal atresia, intestinal malrotation, annular pancreas, and anomalous arrangement of pancreaticobiliary duct presenting as pancreatitis, hepatic steatosis, biliary atresia, bilobed gall bladder, anal atresia, rectovaginal fistula[6,7,8,9,10,11] To our knowledge, our patient is the first report of choledochal duct cyst and the second case report of anal atresia and rectoperineal fistula in a patient with 1p36 deletion syndrome. Currently, there are no reports of genes in the region of chromosome 1p that have been linked to cause bile duct abnormality, an area that should be explored, given the mounting number of GI abnormalities seen in association with 1p36 deletion syndrome.

There are variable clinical findings that characterizes individuals with a 16p12.2 microdeletion, no recognizable syndrome has been established. Findings commonly observed in children with this deletion include: developmental delay, cognitive impairment, growth impairment, cardiac malformations, epilepsy, and psychiatric and/or behavioral problems. Other findings include: hearing loss, dental abnormalities, renal anomalies and genital anomalies in males, and cleft palate with or without cleft lip. The frequency is about 1 in 2,000 newborns have a 16p12.2 microdeletion and show signs and symptoms of the condition. Abnormal brain imaging was reported in 56%-63% of individuals with 16p12.2 microdeletion including cerebellar and cerebral atrophy, decreased white matter, unspecified periventricular changes, and agenesis of the corpus callosum.[12,13] Individuals with a 16p12.2 microdeletion who have neurological or behavioral problems often have an additional chromosomal abnormalities.

In conclusion, we described widening phenotypic spectrum of a neonate with monosomy 1p36 and monosomy 16p12.

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suggesting that RSV prophylaxis could prevent the development of wheezing bronchitis. A study conducted in Galicia, Spain, showed that only 0.3% of infants who received prophylaxis with Nirsevimab were hospitalized for RSV-related lower respiratory tract infections. "This is very promising," Yvonne Maldonado, MD, professor of pediatrics and epidemiology and population health at Stanford University in Stanford, California, said. "But this virus is ubiquitous. It's found everywhere. It comes around every winter season. And immunity is not long-lasting." Older children who are not receiving monoclonal antibodies still experience RSV-related hospitalizations, suggesting the virus continues to circulate at high enough levels in the community. "The vaccine and monoclonal antibodies can reduce the risk of hospitalization and more severe disease in young kids, but they won't eliminate the virus," Maldonado said. "Right now, the goal is to prevent serious infection, not to prevent the spread of the virus completely." Currently, the RSV vaccine and monoclonal antibodies are only given in the United States, Europe, United Kingdom, and Canada to newborns, children at risk for severe disease, and pregnant women. However, Midulla said that pharmaceutical companies are pushing to broaden the rollout to a broader population within these countries. Yet, he said, over 99% of RSV infection-related deaths occur in the Global South. No pharmaceutical company has sought approval in low-income countries such as those in Africa.

Early-Onset Asthma May Slow Memory Development

Children with asthma scored significantly lower than those without asthma on measures of episodic memory, based on longitudinal data from nearly 500 individuals. Animal models have shown associations between asthma and memory problems, but data for children are lacking, wrote Nicholas J. Christopher-Hayes, MA, of the University of California, Davis, and colleagues. "Asthma is very frequent among children, and there is mounting evidence from rodent models that asthma may result in neural injury in the hippocampus, which in turn may cause memory loss," Christopher-Hayes said in an interview. "Although there is also a good amount of research with older adults, very little research has been done with children, the period that is most frequently linked to asthma onset," he said. Therefore, the researchers leveraged a large national study on child development to examine development of memory as a function of asthma exposure. In this study published in JAMA Network Open, the researchers conducted both a longitudinal and cross-sectional analysis of data from the Adolescent Brain Cognitive Development Study, which began in 2015. Children were enrolled at ages 9-10 years with a follow-up assessment 1-2 years later. The participants were categorized as early childhood-onset asthma (asthma at baseline and follow-up), later childhood-onset asthma (asthma at follow-up only), or no asthma history. The primary outcome of the longitudinal analysis was episodic memory. Approximately half of the participants were boys, and slightly more than half were White. Among 474 children reviewed in the longitudinal analysis, 135 had early-onset asthma, 102 had later-onset asthma, and 237 had no asthma and served as control individuals. Overall, those with early-onset asthma showed significantly lower rates of longitudinal memory improvements at follow-up compared with the comparison group ($P < .01$). Developmental memory improvement in children with later-onset asthma was not significantly different from the control individuals.

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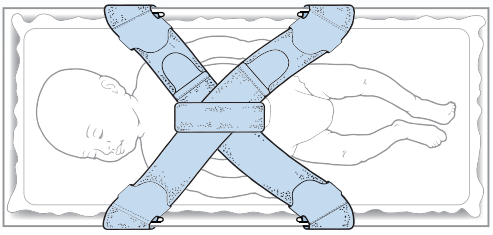

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