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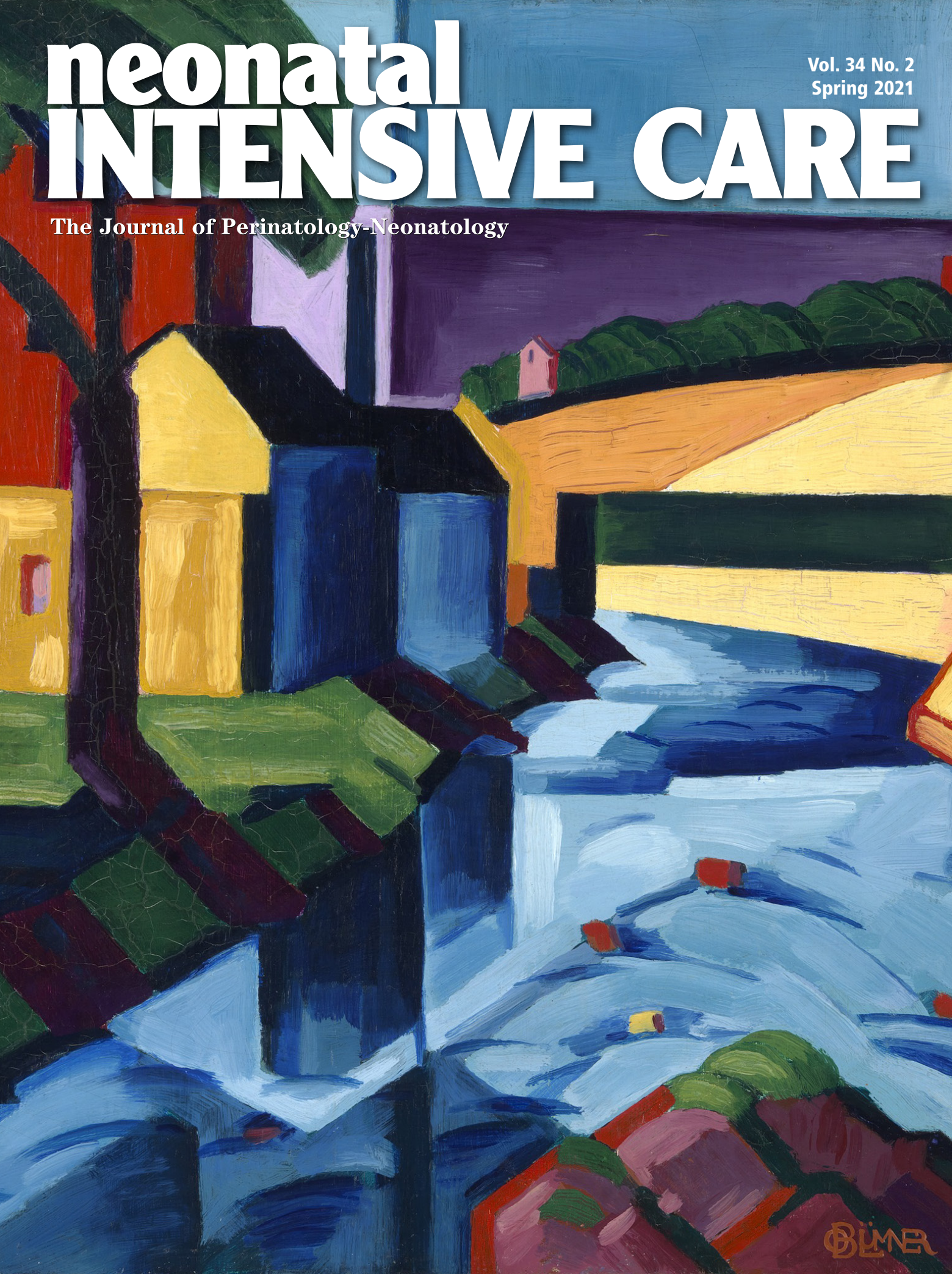

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[1] Castillo A et al. Prevention of Retinopathy of Prematurity in Preterm Infants through Changes in Clinical Practice and SpO2 Technology. *Acta Paediatr*. 2011;100(2):188-92.) [2] Chow et al. Can changes in clinical practice decrease the incidence of sever retinopathy of prematurity in very low birth weight infants? *Pediatrics*. 2003;111(2):339-345. [3] de-Wahl Granelli A et al. Impact of pulse oximetry screening on the detection of duct dependent congenital heart disease: a Swedish prospective screening study in 39,821 newborns. *BMJ*. 2009;8;338. [4] Ewer AK et al. NIHR Health Technology Assessment Programme: Executive Summaries. 2012.

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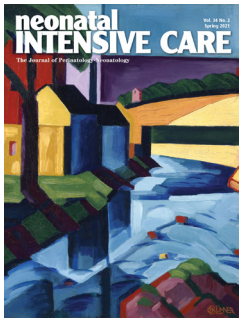

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Maternal Caffeine Consumption May Reduce Neonatal Size

For pregnant women, just half a cup of coffee a day may reduce neonatal birth size and body weight, according to a prospective study involving more than 2,500 women. That's only 50 mg of a caffeine day, which falls below the upper threshold of 200 mg set by the American College of Obstetricians and Gynecologists, lead author Jessica Gleason, PhD, MPH, of the Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, Md, and colleagues reported. "Systematic reviews and meta-analyses have reported that maternal caffeine consumption, even in doses lower than 200 mg, is associated with a higher risk for low birth weight, small for gestational age (SGA), and fetal growth restriction, suggesting there may be no safe amount of caffeine during pregnancy," the investigators wrote in JAMA Network Open. Findings to date have been inconsistent, with a 2014 meta-analysis reporting contrary or null results in four out of nine studies. Dr Gleason and colleagues suggested that such discrepancies may be caused by uncontrolled confounding factors in some of the studies, such as smoking, as well as the inadequacy of self-reporting, which fails to incorporate variations in caffeine content between beverages, or differences in rates of metabolism between individuals. "To our knowledge, no studies have examined the association between caffeine intake and neonatal anthropometric measures beyond weight, length, and head circumference, and few have analyzed plasma concentrations of caffeine and its metabolites or genetic variations in the rate of metabolism associated with neonatal size," the investigators wrote. Dr Gleason and colleagues set out to address this knowledge gap with a prospective cohort study, including 2,055 non-smoking women with low risk of birth defects who presented at 12 centers between 2009 and 2013. Mean participant age was 28.3 years and mean body mass index was 23.6. Races and ethnicities were represented almost evenly even across four groups: Hispanic (28.2%), White (27.4%), Black (25.2%), and Asian/Pacific Islander (19.2%). Rate of caffeine metabolism was defined by the single-nucleotide variant rs762551 (CYP1A2*1F), according to which, slightly more women had slow metabolism (52.7%) than fast metabolism (47.3%). Women were enrolled at 8-13 weeks' gestational age, at which time they underwent interviews and blood draws, allowing for measurement of caffeine and paraxanthine plasma levels, as well as self-reported caffeine consumption during the preceding week. Over the course of six visits, fetal growth was observed via ultrasound. Medical records were used to determine birth weights and neonatal anthropometric measures, including fat and skin fold mass, body length, and circumferences of the thigh, arm, abdomen, and head. Neonatal measurements were compared with plasma levels of caffeine and paraxanthine, both continuously and as quartiles (Q1, ≤ 28.3 ng/mL; Q2, 28.4-157.1 ng/mL; Q3, 157.2-658.8 ng/mL; Q4, > 658.8 ng/mL). Comparisons were also made with self-reported caffeine intake. Women who reported drinking 1-50 mg of caffeine per day had neonates with smaller subscapular skin folds (beta = –0.14 mm; 95% confidence interval, –0.27 to —0.01 mm), while those who reported more than 50 mg per day had newborns with lower birth weight (beta = –66 g; 95% CI, –121 to –10 g), and smaller circumferences of mid-upper thigh (beta = –0.32 cm; 95% CI, –0.55 to –0.09 cm), anterior thigh skin fold (beta = –0.24 mm; 95% CI, –0.47 to -.01 mm), and mid-upper arm (beta = –0.17 cm; 95% CI, –0.31 to –0.02 cm). Caffeine plasma concentrations supported these findings. Compared with women who had caffeine plasma concentrations in the lowest quartile, those in the highest quartile gave birth to neonates with shorter length (beta = –0.44 cm; P = .04 for trend)

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10940 Wilshire Blvd., Suite 600
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Phone: 310-443-4109
Fax: 310-443-4110
E-mail: s.gold4@verizon.net
Web: www.nicmag.ca

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Steve Goldstein

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Cover: Evening Tones. Artist: Oscar Bluemner, born Prenzlau, Germany 1867-died South Braintree, MA 1938

and lower body weight (beta = –84.3 g; P = .04 for trend), as well as smaller mid-upper arm circumference (beta = -0.25 cm; P = .02 for trend), mid-upper thigh circumference (beta = –0.29 cm; P = .07 for trend), and head circumference (beta = –0.28 cm; P < .001 for trend). A comparison of lower and upper paraxanthine quartiles revealed the similar trends, as did analyses of continuous measures. "Our results suggest that caffeine consumption during pregnancy, even at levels much lower than the recommended 200 mg per day of caffeine may be associated with decreased fetal growth," the investigators concluded.

First wearable device can monitor jaundice-causing bilirubin and vitals in newborns

Researchers in Japan have developed the first wearable devices to precisely monitor jaundice, a yellowing of the skin caused by elevated bilirubin levels in the blood that can cause severe medical conditions in newborns. Jaundice can be treated easily by irradiating the infant with blue light that breaks bilirubin down to be excreted through urine. The treatment itself, however, can disrupt bonding time, cause dehydration and increase the risks of allergic diseases. Neonatal jaundice is one of the leading causes of death and brain damage in infants in low- and middle-income countries. To address the tricky balance of administering the precise amount of blue light needed to counteract the exact levels of bilirubin, researchers have developed the first wearable sensor for newborns that is capable of continuously measuring bilirubin. In addition to bilirubin detection, the device can simultaneously detect pulse rate and blood oxygen saturation in real time. Led by Hiroki Ota, associate professor of mechanical engineering in Yokohama National University's Graduate School of System Integration, and Shuichi Ito, professor of department of Pediatrics in Yokohama City University's Graduate School of Medicine, the team published their results on March 3 in *Science Advances*. "We have developed the world's first wearable multi-vital device for newborns that can simultaneously measure neonatal jaundice, blood oxygen saturation and pulse rate," Ota said, noting that jaundice occurs in 60 to 80% of all newborns. "The real-time monitoring of jaundice is critical for neonatal care. Continuous measurements of bilirubin levels may contribute to the improvement of quality of phototherapy and patient outcome." Currently, medical professionals use handheld bilirubinometers to measure bilirubin levels, but there is not a device that can simultaneously measure jaundice and vitals in real time. "In this study, we succeeded in miniaturizing the device to a size that can be worn on the forehead of a newborn baby," Ota said. "By adding the function of a pulse oximeter to the device, multiple vitals can easily be detected." Held to the baby's forehead by a silicone interface, the device has a lens capable of efficiently transmitting lights to neonatal skin via battery-powered light-emitting diodes, commonly known as LEDs. "At the present stage, coin cell batteries are used, and the overall shape is very thick," Ota said. "In the future, it will be necessary to further reduce the thickness and weight by using thin-film batteries and organic materials." The researchers tested the device on 50 babies, and they found that the device is not currently accurate enough to suffice for clinical decision-making. According to Ota, they will reduce the thickness and increase the flexibility of the device, as well as improve the silicone interface to facilitate better skin contact. In the future, the researchers plan to develop a combined treatment approach that pairs a wearable bilirubinometer with a phototherapy device to optimize the amount and duration of light therapy based on continuous measurements of bilirubin levels.

COVID-19 Isolation and an Infant's Immune System

Queirra Fenderson, a first-time mom in Fort Washington, MD, gave birth to her daughter, Arya, at the end of December 2019. On the advice of their pediatrician, she and her husband spent the first month of their daughter's life living in a "bubble" with only a few close family and friends seeing their baby to protect her from germs during cold and flu season. Right about the time the new parents were ready to start exposing Arya to more people and germs, the pandemic hit. So a year later, their 14-month-old still remains in that bubble. "There are still people to this day, some are my closest friends, who haven't met her yet. It's crazy," Fenderson says. She says she and her husband have often wondered how this isolation is impacting their daughter's developing immune system. They've even considered day care to boost her immunity, but balancing that against the risk of COVID-19 has led them to still keep her home. "Arya hasn't been sick her whole entire life, and I want her to get more exposure to germs to boost her immunity. But in my gut, I'm afraid of the exposure to COVID, too," Fenderson says. "Pandemic parenting is hard." Simone Christensen of California agrees. She's been very cautious with her 9-week-old daughter, Scout, who has seen only a few family members since she was born. Christensen has asthma, and their pediatrician has stressed the need to be cautious about COVID-19. But she and her husband also worry how isolation is impacting their daughter's immune system. "Scout hasn't really been exposed to much at this point, which seems crazy because I feel like at this age, I was probably sucking on a table at McDonald's," she says with a laugh. "Anytime you talk to someone who raised their child pre-pandemic, they always tell you how important it is to expose babies to germs so their immune system starts to build up, and I always thought I'd be the kind of mom who does that. But everything is different because of COVID. The risks are so much greater, and trying to figure out what's best in a pandemic is scary and hard." Leana Wen, MD, is an emergency room doctor and a public health expert. She's also a mom whose second child — a 10-month-old girl — was born during the pandemic. She says there's good reason to be cautious with babies and what you expose them to early in life. "Newborns are highly susceptible to illnesses," she says. "They don't have much of an immune system of their own, so even pre-pandemic, we advised people to be very careful to germ exposure with newborns, understanding that they develop more robust immune systems over time." But many others, like B. Brett Finlay, PhD, a Canadian microbiologist and professor of microbiology at the University of British Columbia, also stress that early exposure to microbes has been shown to help a baby's immune system develop well. "We've learned over the last decade or so that the normal development of the immune system absolutely requires the presence of normal microbes," says Finlay, co-author of *Let Them Eat Dirt: Saving Your Child from an Oversanitized World*. "It makes a difference in childhood development, and lack of exposure to these good microbes affects allergies, asthma, eczema, obesity, and more,"

We don't know everything about how the immune system is built, "but we do know the end result is you need these early life microbes to get normal immune system development." This question, often referred to as the hygiene hypothesis, was first raised in 1989, and it has long caused controversy and debate. It argues that the developed world's focus on clean environments through the use of disinfectants, sanitizers, and bleach has a negative impact on the immune system. The FDA points out it is one of many explanations for "for asthma being the most common chronic disease in the developed world." But plenty of others aren't so sure. Researchers who published a study

in 2016 found "no good evidence that hygiene, as the public understands, is responsible for the clinically relevant changes to microbial exposures." The study, published in *Perspectives in Public Health*, says a combination of things, including "natural childbirth, breast feeding, increased social exposure through sport, other outdoor activities, less time spent indoors, diet and appropriate antibiotic use, may help restore the microbiome and perhaps reduce risks of allergic disease." The hygiene hypothesis theorizes that cleanliness and lack of exposure to microbes have led to increased allergies, asthma, and other conditions.

Continuous Glucose Monitoring Curbs Hyperglycemia, Hypoglycemia in Preemies

In preterm infants, continuous glucose monitoring (CGM) reduced prolonged or severe hyperglycemia and hypoglycemia in an international randomized controlled trial. Both conditions "are associated with long-term harm," Dr Kathryn Beardsall of the University of Cambridge, UK, said. "Another recent paper has shown that the intervention is cost effective, which supports the use of CGM to become an established part of clinical care, not simply a valuable research tool." "We have been working with the clinical team and the Addenbrooke's Charity Trust to ensure that real-time CGM is now part of the standard of care for our extremely preterm babies," she said. "Children and babies deserve technology that has been designed and tested appropriately for their use, not dependent on off-license use."

As reported in The Lancet Child and Adolescent Health, the study was done in 13 neonatal intensive care units in the UK, Spain, and the Netherlands. Included infants were within 24 hours of birth, had a birthweight of no more than 1,200 grams (2.6 pounds), and a gestational age up to 33 weeks plus six days. Infants were randomly assigned to real-time CGM or standard care (with masked CGM for comparison). The main efficacy outcome was the proportion of time the sensor glucose concentration was 2.6-10 mmol/L in the first week of life. Safety outcomes were related to hypoglycemia (glucose concentrations <2.6 mmol/L), also in the first week of life.

Seventy infants randomized to real-time CGM and 85 receiving standard care were included in the primary analysis. Compared with the standard care group, infants managed with CGM had more time in the 2.6-10 mmol/L glucose concentration target range (mean proportion of time, 94% vs 84%; adjusted mean difference 8.9%, equivalent to 13 hours). More infants receiving standard care experienced at least one episode of a sensor glucose concentration <2.6 mmol/L for more than one hour (15% vs. 6%). The authors state, "This study supports the clinical use of CGM in preterm infants to optimize nutritional delivery alongside improving glucose monitoring and management." Dr Beardsall added, "We would encourage other centers to consider learning to use CGM, but acknowledge that these devices are not ideally designed for use in extremely preterm infants. Their use requires training and some experience, but we would consider it worth the investment... With this in mind, we are exploring the next steps in design solutions for these babies that we hope will encourage wider use."

Masimo Monitoring Solutions Promote Newborn and Maternal Safety

Masimo provides a variety of innovative monitoring solutions designed to improve maternal and newborn safety during childbirth and the critical first minutes of life. Masimo SET pulse oximetry's ability to measure during motion and low perfusion

has helped newborns, neonates, and pediatric patients like no other pulse oximetry. Not only has Masimo SET helped clinicians reduce retinopathy of prematurity (ROP) and improve screening for critical congenital heart disease (CCHD), but it has helped push the standard of care for babies to new heights—the evidence from CCHD studies with SET, for example, has been used in the establishment of screening guidelines used around the world. On International Women's Day, it is especially important to recognize that, as UNICEF reports, "newborns and mothers are still dying in appalling numbers." Every day, approximately 7,000 babies in the first month of life die, and approximately 810 women die, from preventable complications related to childbirth or pregnancy. Similarly, according to the WHO, "Although important progress has been made in the last two decades, about 295,000 women died during and following pregnancy and childbirth in 2017. The most common direct causes of maternal injury and death are excessive blood loss, infection, high blood pressure, unsafe abortion, and obstructed labor, as well as indirect causes such as anemia, malaria, and heart disease." Masimo's first and ongoing focus has been helping neonatologists, pediatricians, OB-GYNs, and midwives around the world provide the best care possible for newborns and their mothers. The Masimo Newborn Sensor, the first and still the only sensor of its kind, was introduced in 2004 and is designed to provide accurate arterial oxygen saturation (SpO_2) and pulse rate (PR) measurements in the fastest time possible during hectic neonatal resuscitation scenarios. Alongside Newborn Sensors, Pathway, introduced in 2019 for the Root platform, helps clinicians visualize their preferred SpO_2 and PR protocol during neonatal resuscitation. Eve, a software application introduced in 2014, simplifies and automates the CCHD screening process, which Masimo SET enabled. The Blue Sensor, introduced in 2004, provides accurate monitoring in cyanotic children at low SpO_2 levels to help clinicians care for them and was validated specifically on infants with cyanotic disease. rainbow SpHb, noninvasive hemoglobin monitoring, introduced in 2008, can measure hemoglobin levels during pregnancy and alert clinicians to the possibility of excessive blood loss during delivery. Adding to the significant body of clinical evidence demonstrating the utility of SET pulse oximetry and other Masimo newborn and maternal solutions, a new study published in the *Journal of Clinical Neonatology* investigated the use of comparing Masimo perfusion index (Pi) pre- and post-ductal values on pre-term infants to aid clinicians in diagnosing hemodynamically significant patent ductus arteriosus (hsPDA). Dr Melek Büyükeren and colleagues at Hacettepe University in Ankara, Turkey found that the difference in right-hand and right-leg Pi values obtained using Masimo SET pulse oximetry was significantly higher in pre-term infants with hsPDA, leading them to conclude that the difference in Pi "has diagnostic value in hsPDA and can assist diagnosis when echocardiography is not available." Marcelo Cardetti, MD, said, "As Head of the Neonatology Service of the Clinic and Maternity of the Center for Endocrinology and Human Reproduction (CERHU) in San Luis, Argentina, we have been using Masimo pulse oximetry monitors with SE for approximately 8 years in all high-risk newborns and also for newborn resuscitation. In addition, we use Masimo SET monitors for the detection of CHD and hypoxemia in all newborns in the mother-infant unit. Furthermore, our neonatal department is engaged in a research protocol on regional cerebral oxygenation (O3) with neonatal sensors for Masimo Root—to know what happens with cerebral oxygenation during routine clinical procedures in the NICU. This monitoring, in addition to SpO_2 and perfusion index (Pi), perfectly shows us what is happening with oxygenation of seriously ill newborns in real-time and in a noninvasive way. Masimo SET's innovative technology far overcomes the limitations of conventional oximetry and the Pi is an important clinical tool in the care of sick neonates. This monitor and the special neonatal RD sensors have been of great value for the prevention of ROP and for successful and quick, accurate, and reliable steps needed in resuscitation in the delivery room." Hernando Baquero, MD, commented, "I am a pediatrician, neonatologist, clinician, educator and researcher in a major university in Colombia, with several publications on noninvasive neonatal SpO_2 monitoring and oxygenation. The introduction in the Latin American market of Masimo SET technology dramatically improved neonatal care in our countries. In contexts with serious resource limitations, as is the case in most neonatal units in our countries, it was vital to be able to provide quality care to the most vulnerable population due to their health conditions (eg hypoperfusion) or their biological characteristics (eg prematurity). Having reliable, fast, and stable readings as provided by SET and its neonatal sensors improved the chances of many of our newborns." Anne de-Wahl Granelli, PhD, Biomedical Scientist, RDCS(PE), Medical Centre Manager, Sweden, said, "The integration of pulse oximetry into the CCHD screening process has made a significant impact on the detection of congenital heart disease and neonatal health. In clinical studies, the use of pulse oximetry screening with SET technology significantly improved the detection of duct dependent heart disease before hospital discharge. In 2011, the US Department of Health and Human Services added pulse oximetry screening of newborns for CCHD to the Recommended Uniform Screening Panel. Today pulse oximetry has become a global standard of care when screening newborns for CHD." Sergio Golombek, MD, MPH, FAAP, Member of the Board and Past President of the Ibero-American Society of Neonatology (SIBEN), said, "I have authored and published several scientific studies in relation to newborn oxygenation and screening for CCHD. Masimo SET and new innovations and sensor development like RD sensors for noninvasive monitoring represent excellent technology that we can trust, that work promptly and accurately when we need it the most, and are designed specifically with ill newborn babies in the NICU in mind. SET technology allows us also to do the pulse oximetry test or CCHD screening on newborn babies in our units, knowing well that we can fully trust the results. The technology is very easy to use and understand, and makes us deliver better clinical care." Katsuyuki Miyasaka, MD, PhD, Executive Advisor, Wayo Women's University Graduate School, Tokyo and Professor Emeritus, St. Luke's International University, Tokyo, said, "As a critical care pediatric anesthesiologist, reliable and accurate pulse oximetry is paramount to optimal patient outcomes. Some suggest pulse oximetry is the fifth vital sign. Clinicians can rely on the sensitivity and specificity provided by Masimo's measure-through-motion technology in the management of children in the PICU. The use of pulse oximetry can lead to fewer adverse events in the recovery room by capturing accurate readings even during movement such as shivering in critically ill or unstable patients." Mark Ansermino, MBBCh, MMed, Director of the Center for International Child Health and Professor, Department of Anesthesiology, Pharmacology & Therapeutics at the University of British Columbia, Canada, said, "Anemia is a significant public health problem that especially affects the quality of life, health status, and survival of mothers and children around the world. Having access to continuous hemoglobin monitoring technology can help provide visibility to hemoglobin levels. The noninvasive nature of the SpHb solution makes it

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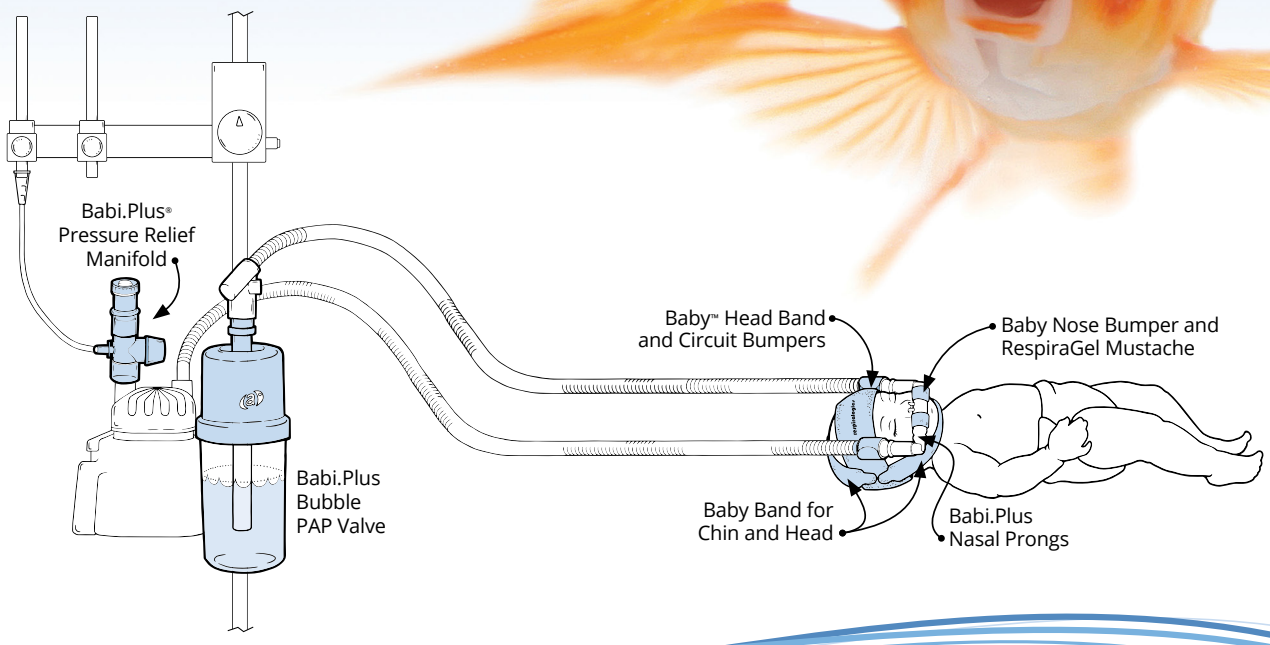

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comfortable for the mother and child and makes monitoring during childbirth feasible even in low-resource settings." Asrat Dibaba Tolossa, MD, MPH, is Chief of Party for the Global Affairs Canada ENRICH (Enhancing Nutrition Services to Improve Maternal and Child Health) Program, a multi-year, multi-country initiative designed to improve the health and nutrition of mothers, newborns, and children. As part of the program, ENRICH has been conducting a study in central Tanzania, where maternal and child care services are often overburdened, using the Masimo Rad-67 Pulse CO-Oximeter, which provides spot-check SpHb measurements. Dr Tolossa commented, "In our field experimentation with the Rad-67, we found out that the device can be used easily by lower-level health workers in the communities for screening and referral of patients to health facilities for further assessment and treatment. There was also a high acceptance rate by community members as the method is noninvasive." Joe Kiani, Founder and CEO of Masimo, said, "From our inception, we have been committed to improving outcomes for the youngest and most fragile patients. Our foundational SET pulse oximetry was designed with newborns in mind. With rainbow Pulse CO-Oximetry, we have made the noninvasive monitoring of child and mother clinically more meaningful. While we stand behind the fact that we have the best pulse oximetry for all patients, especially the most fragile patients, we continue to seek new ways to help clinicians provide newborns and their mothers with the best care possible. On this International Women's Day, we thank the caregivers who have dedicated themselves to the health of newborns and their mothers, as well as women everywhere, for their achievements, their sacrifices, and for nurturing us all." SpHb is not intended to replace laboratory blood testing. Clinical decisions regarding red blood cell transfusions should be based on the clinician's judgment considering, among other factors, patient condition, continuous SpHb monitoring, and laboratory diagnostic tests using blood samples. Noninvasive, continuous SpHb has CE clearance for all patients and in the US has received FDA clearance for patients >3 kg but is not currently indicated for patients <3 kg. As part of its US FDA 510(k) clearance, spot-check SpHb on Rad-67 is contraindicated for use on pregnant patients and not indicated for use on pediatric patients or patients with renal disease. Eve has not obtained FDA clearance and is not available in the United States.

Reassuring' Data on COVID-19 Vaccines in Pregnancy

Pregnant women can safely get vaccinated with the Pfizer-BioNTech and Moderna vaccines for COVID-19, surveillance data from the US Centers for Disease Control and Prevention (CDC) suggest. More than 30,000 women who received these vaccines have reported pregnancies through the CDC's V-Safe voluntary reporting system, and their rates of complications are not significantly different from those of unvaccinated pregnant women, said Tom Shimabukuro, MD, MPH, MBA, deputy director of the CDC Immunization Safety Office. "Overall, the data are reassuring with respect to vaccine safety in pregnant women," he said. Shimabukuro presented the data during a March 1 meeting of the Advisory Committee on Immunization Practices (ACIP), a group of health experts selected by the Secretary of the US Department of Health and Human Services. The CDC has included pregnancy along with other underlying conditions that qualify people to be offered vaccines in the third priority tier (Phase 1c). "There is evidence that pregnant women who get COVID-19 are at increased risk of severe illness and complications from severe illness," Shimabukuro explained. "And there is also evidence that pregnant persons who get COVID-19 may be at increased risk for adverse pregnancy outcomes." The American College of Obstetrics and Gynecology recommends that "COVID-19 vaccines should not be withheld from pregnant individuals." By contrast, the World Health Organization recommends the vaccines only for those pregnant women who are "at high risk of exposure to SARS-CoV-2 (eg, health workers) or who have comorbidities which add to their risk of severe disease." Not enough information was available from the pivotal trials of the Moderna and Pfizer vaccines to assess risk in pregnant women, according to these manufacturers. Pfizer has announced a follow-up trial of its vaccine in healthy pregnant women. To better assess whether the Pfizer or Moderna vaccines cause problems in pregnancy or childbirth, Shimabukuro and colleagues analyzed data from V-Safe and the Vaccine Adverse Event Reporting System (VAERS). The CDC encourages providers to inform people they vaccinate about the V-Safe program. Participants can voluntarily enter their data through a website, and may receive follow-up text messages and phone calls from the CDC asking for additional information at various times after vaccination. It is not a systematic survey, and the sample is not necessarily representative of everyone who gets the vaccine, Shimabukuro noted. At the time of the study, V-Safe recorded 55,220,364 reports from people who received at least one dose of the Pfizer or Moderna vaccine through February 16. These included 30,494 pregnancies, of which 16,039 were in women who received the Pfizer vaccine and 14,455 in women who received the Moderna vaccine.

Placenta's Role in Schizophrenia 'Bigger Than We Imagined'

Schizophrenia-related genes in the placenta are predictive of the size of a baby's brain at birth and the rate of cognitive development. In a complicated pregnancy, such genes could raise the risk of developing schizophrenia later in life, new research suggests. "This is further evidence that early life matters in schizophrenia, and the placenta plays a bigger role than we imagined," Daniel R Weinberger, MD, director and CEO, Lieber Institute for Brain Development, and professor of neurology, psychiatry, and neuroscience, Johns Hopkins University School of Medicine, Baltimore, Maryland, said in a news release. "The holy grail would be to identify, based by complicated pregnancies and placental risk scores, who is at maximum risk for schizophrenia from very early in life, and these individuals could be followed more carefully," Weinberger said. The study was published online February 8 in *Proceedings of the National Academy of Sciences.* The same group of researchers reported that genes associated with schizophrenia are activated in the placenta during a complicated pregnancy, increasing a child's risk of developing schizophrenia later in life. In this latest study, they further explored the biological interplay between placental health and neurodevelopment. They found that a higher placental genomic risk score for schizophrenia, in conjunction with early-life complications during pregnancy, at labor/delivery, and early in neonatal life, is associated with changes in early brain growth and function, particularly in males. "The higher the placental schizophrenia gene risk score, the smaller the brain size at birth, and this was associated with slower cognitive development over the first 2 years of life, particularly in the first year of life," said Weinberger. This research defines a "potentially reversible neurodevelopmental path of risk that may be unique to schizophrenia," the researchers write. Although most individuals on this altered neurodevelopmental path likely

"canalize" back toward normal development, some may not be rescued and instead "decanalize" toward illness, they add. To date, prevention of schizophrenia from early life has seemed "unapproachable if not unimaginable, but these new insights offer possibilities to change the paradigm," Weinberger said in the news release. "Measuring schizophrenia genetic scores in the placenta combined with studying the first two years of cognitive developmental patterns and early life complications could prove to be an important approach to identify those babies with increased risks," he added.

Low-Dose Aspirin Did Not Reduce Preterm Birth Rates, but Don't Rule It Out Yet

Women at risk of preterm birth who took daily low-dose aspirin did not have significantly lower rates of preterm birth than those who did not take aspirin, according to preliminary findings from a small randomized controlled trial. There was a trend toward lower rates, especially among those with the highest compliance, but the study was underpowered to detect a difference with statistical significance, said Anadeijda Landman, MD, of the Amsterdam University Medical Center. Landman presented the findings Jan. 28 at a meeting sponsored by the Society for Maternal-Fetal Medicine. Preterm birth accounts for a third of all neonatal mortality, she told attendees. Among 15 million preterm births worldwide each year, 65% are spontaneous, indicating the need for effective preventive interventions. Dr Landman reviewed several mechanisms by which aspirin may help reduce preterm birth via different pathways. The researchers' multicenter, placebo-controlled trial involved 8 tertiary care and 26 secondary care hospitals in the Netherlands between May 2016 and June 2019. Starting between 8 and 15 weeks' gestation, women took either 80 mg of aspirin or a placebo daily until 36 weeks' gestation or delivery. Women also received progesterone, cerclage, or pessary as indicated according to local protocols. The study enrolled 406 women with singleton pregnancy and a history of preterm birth delivered between 22 and 37 weeks' gestation. The final analysis, after exclusions for pregnancy termination, congenital anomalies, multiples pregnancy, or similar reasons, included 193 women in the intervention group and 194 in the placebo group. The women had similar baseline characteristics across both groups except a higher number of past mid-trimester fetal deaths in the aspirin group. "It's important to realize these women had multiple preterm births, as one of our inclusion criteria was previous spontaneous preterm birth later than 22 weeks' gestation, so this particular group is very high risk for cervical insufficiency as a probable cause," Landman told attendees. Among women in the aspirin group, 21.2% delivered before 37 weeks, compared with 25.4% in the placebo group (P = .323). The rate of spontaneous birth was 20.1% in the aspirin group and 23.8% in the placebo group (P = .376). Though still not statistically significant, the difference between the groups was larger when the researchers limited their analysis to the 245 women with at least 80% compliance: 18.5% of women in the aspirin group had a preterm birth, compared with 24.8% of women in the placebo group (P = .238). There were no significant differences between the groups in composite poor neonatal outcomes or in a range of prespecified newborn complications. The aspirin group did have two stillbirths, two mid-trimester fetal losses, and two extremely preterm newborns (at 24+2 weeks and 25+2 weeks). The placebo group had two mid-trimester fetal losses. "These deaths are inherent to the study population, and it seems unlikely they are

related to the use of aspirin," Landman said. "Moreover other aspirin studies have not found an increased perinatal mortality rate, and some large studies indicated the neonatal mortality rate is even reduced." Although preterm birth only trended lower in the aspirin group, Landman said the researchers believe they cannot rule out an effect from aspirin. "It's also important to note that our study was underpowered as the recurrence risk of preterm birth in our study was lower than expected, so it's possible a small treatment effect of aspirin could not be demonstrated in our study," she said. "And, despite the proper randomization procedure, many more women in the aspirin group had a previous mid-trimester fetal loss. This indicates that the aspirin group might be more at risk for preterm birth than the placebo group, and this imbalance could also have diminished a small protective effect of aspirin."

Epidural Analgesia During Labor Might Increase Autism Risk

Women who receive epidural anesthesia during labor seem to stand an increased chance of having a child with autism, a new study has found. But the study was not designed to prove cause and effect and does not suggest that epidurals cause autism. Multiple professional organizations weighed in critically on the work. The study "does not provide credible scientific evidence that labor epidurals for pain relief cause autism," say the Society for Obstetric Anesthesia and Perinatology, American Society of Anesthesiologists, Society for Pediatric Anesthesia, American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine in a joint statement. "This study should not alter the analgesia currently offered to women in labour," says a statement from the Royal College of Anaesthetists. The prevalence of autism among the children of women who received an epidural is low: 1.9 percent, compared with 1.3 percent among the children of women who did not receive an epidural. That difference corresponds to a 0.6 percent increase in the odds of having a child with autism for the epidural group. The results were published yesterday in *JAMA Pediatrics*. "There may be many other factors that could explain that small increase," says co-lead researcher Anny Xiang, director of biostatistics research in the Department of Research and Evaluation at Kaiser Permanente Southern California in Pasadena. Such factors — which the study did not account for — could include a family history of psychiatric or neurologic conditions, or differences in the women's propensity to seek an autism diagnosis for their children, says Brian Lee, associate professor of epidemiology and biostatistics at Drexel University in Philadelphia, Pennsylvania, who was not involved in the work. "The major concern is that there are unobserved characteristics between" women who receive epidurals and those who do not, he says. "It's quite possible other differences exist beyond that which is seen."

Hospital Survey Finds Reasons for Both Optimism and Concern About COVID-19 and Newborns

Nebulized Surfactant Shows Promise in Large Cohort

Nebulized delivery of surfactant reduced the need for intubation and liquid surfactant administration by half among newborns with signs of respiratory distress syndrome, according to results from a large randomized, multicenter trial. Neonatologists have long sought alternatives to intubation for administering surfactant to newborns with respiratory distress syndrome (RDS). An effective noninvasive aerosolized treatment has remained elusive, with small clinical trials that have produced mixed results. In research published in Pediatrics, James J Cummings, MD, of Albany (NY) Medical Center, and colleagues, randomized 457 infants (mean 33 weeks' gestational age) with signs of RDS to either usual care or a nebulized bovine surfactant. Infants were recruited at 22 neonatal ICUs in the United States. Investigators were not blinded to treatment allocation and the decision to intubate was left up to the individual treating physician, because to do so, the authors wrote, would add "pragmatic strength" to the study, and "be ethically compliant with the infant's best interest." Infants in the study received usual care or up to three treatments 4 or more hours apart of 35 mg/mL calfactant suspension, 210 mg phospholipid/kg body weight delivered into the mouth through a nebulizer modified with a pacifier. Dr Cummings and colleagues found that intubation and liquid surfactant administration within the first 4 days after birth was 26% in the intervention group and 50% in the usual care group ($P < .001$). The results remained significant after investigators adjusted for gestational age, birth weight, age when randomized, sex, delivery mode, and antenatal steroids. Rates of intubation for surfactant administration were lower for infants in the intervention group in all gestational age brackets except the youngest (23-24 weeks); all of these infants needed intubation. Respiratory support at days 3, 7, and 28 did not differ between study groups. "Our study is the first to reveal the efficacy of an aerosolized surfactant delivery system that does not require a respiratory circuit interface," the investigators wrote. In previous trials of aerosolized surfactants, they noted, treatment was delivered with nasal continuous positive airway pressure. "By using a separate, pacifier interface, both the aerosol delivery and [nasal continuous positive airway pressure] flow can be managed independently, which should allow for safer patient care."

Prolonged Central Line in Preemies Tied to Fewer Needle Sticks

Premature infants who have central lines maintained for more than 14 days have fewer needle pokes that break the skin and more thalamus growth than infants with lines in place for shorter periods of time, a new study suggests. Researchers studied two groups of extremely preterm neonates born at less than 28 weeks' gestation with arterial line and central venous line (AC/CVL) used for a prolonged period of at least 14 days (n=86) or for a restricted period of less than 14 days (n=57). The median number of skin breaks from needle pokes was 34 with prolonged AC/CVL use, compared with a median of 91 skin breaks with restricted AC/CVL use. The neonates who had prolonged AC/CVL also had larger thalamic volume on MRI scans within a few weeks after birth than those with restricted AC/CVL. After adjusting for sex, age at birth, and age at MRI scan, the neonates who had prolonged AC/CVL use had a mean thalamic size of 1,233 cubic millimeters (mm3), compared to 1,110 mm3 in neonates who had restricted AC/CVL use. While the study didn't examine the reason for the association, it's possible more pain impacts the development of neuronal morphology or synaptic connectivity in the thalamus, leading to slower growth, said senior study author Dr Steven Miller, a professor of pediatrics at the University of Toronto and a senior scientist at the SickKids Research Institute. "We recognize from this study, and others, that the thalamus is an important brain structure for motor skills and cognitive function," Dr Miller said. "In these babies born extremely preterm, increased growth of the thalamus in the first weeks of life predicted better developmental function at school age." Neuropsychological exams done for a total of 118 children (83%) at a median age of 4.9 years found that children with a larger thalamus size as infants achieved higher scores on

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cognitive and motor assessments than their counterparts with a smaller thalamus size in infancy. On the Movement Assessment Battery for Children, second edition (MABC-2), scores ranged from the 1st to the 90th percentiles. The median score for the kids who had received prolonged AC/CVL as neonates was 31st percentile, compared with 25th percentile for those who had restricted AC/CVL as neonates. On the Wechsler Preschool and Primary Scale of Intelligence, third edition (WPPSI), the median score was 104 for those who had prolonged AC/CVL compared with 96 with restricted AC/CVL. It's not clear from the study results whether reducing needle pokes or invasive procedures during infancy might promote more brain growth or lead to improved outcomes on motor or cognitive assessments later in childhood, the study team notes in Neurology. "The finding that thalamic health is negatively impacted by pain in the first weeks of life suggests that activation of pain pathways in some manner leads to a disruption of thalamic maturation," said Dr Brenda Banwell, chief of child neurology at the Children's Hospital of Philadelphia and a professor of neurology and pediatrics at the University of Pennsylvania.

New Case Suggestive of in Utero SARS-CoV-2 Transmission

A new report of mother-to-fetus transmission of SARS-CoV-2 through umbilical cord blood adds to a small but growing body of evidence that the virus can be transmitted in utero. Further, this case suggests such infections may not be easily detectable in neonates until days after birth. In a report published in the Journal of The Pediatric Infectious Diseases Society, Isabelle Von Kohorn, MD, PhD, of Holy Cross Health in Silver Spring, Md., and colleagues, described a case of neonatal infection with SARS-CoV-2 in a boy delivered by C-section at 34 weeks to a mother diagnosed with COVID-19 some 14 hours before. The newborn was immediately removed to a neonatal ICU and reunited with his mother a week later, once the mother had recovered. Dr Von Kohorn and colleagues reported that, while the infant's nasopharyngeal swab test for SARS-CoV-2 was negative at 24 hours after birth, repeat molecular tests (using different assays) from 49 hours on were positive and indicated an increasing viral burden, although the infant never developed symptoms of COVID-19. In addition to being found in the nasopharynx, viral RNA also was detected in cord blood and in urine. No viral RNA was found in the placenta. The circumstances of the birth, and the care taken to keep mother and her infant at a safe distance along with masking of the mother, made it "extremely unlikely" that the infant acquired his infection by the respiratory route, Dr Von Kohorn and colleagues wrote. "While we cannot rule out microscopic maternal blood contamination of cord blood in this or any other delivery, cord blood collection procedures are designed to avoid gross contamination with maternal blood. Microscopic contamination would not explain the RNA levels observed in our patient's cord blood," they wrote. Clinicians should note that a neonate born to a mother with COVID-19 may take time to test positive for SARS-CoV-2, the investigators argued, though the current recommendation of the American Academy of Pediatrics is to test nasopharyngeal secretions of well newborns at 24 and 48 hours but not again in the absence of symptoms. "This case suggests that some cases of SARS-CoV-2 in newborns may be detectable only after 48 hours of life." The authors hypothesized that virus transmitted by cord blood "seeded the nasopharynx and required 2 days for incubation and replication sufficient for detection."

Halting Antiseizure Medication Poses No Harm in Infants

Maintaining antiseizure medication in infants who have had acute symptomatic neonatal seizures has been standard practice, but a prospective, observational, comparative effectiveness study calls that practice into question, providing evidence that discontinuing therapy at discharge poses no harm to children and has no effect on the development of epilepsies. "The balance of evidence supports discontinuing antiseizure medication after resolution of acute symptomatic neonatal seizures and before discharge home from the neonatal seizure admission," said Hannah C. Glass, MDCM, MAS, of the University of California, San Francisco, Benioff Children's Hospital, co-principal investigator, who presented results of the study at the 2020 CNS-ICNA Conjoint Meeting, held virtually this year. Renee Shellhaas, MD, MS, clinical associate professor of pediatrics at CS Mott Children's Hospital, University of Michigan, was the other co-principal investigator. "Although other, smaller studies have suggested it is safe to discontinue antiseizure medication after resolution of acute symptomatic seizures, the practice of early discontinuation has been very variable and depends largely on individual provider preference," Glass said in an interview. "In our study, two-thirds of newborns with acute symptomatic seizures were maintained on antiseizure medication at the time of hospital discharge. Thus, a change to early medication discontinuation represents a major shift." The study evaluated 270 infants at nine centers enrolled in the Neonatal Seizure Registry and born from July 2015 through March 2018. Inclusion criteria were acute symptomatic seizures that occurred at up to 44 weeks postmenstrual age. In this cohort, 36% of patients had antiseizure medication discontinued after a median of 6 days; the remainder stayed on antiseizure medication after discharge at a median of 4 months. The patients were followed for 2 years.

The primary outcome was functional development measured by the Warner Initial Development Evaluation of Adaptive and Functional Skills (WIDEA-FS) assessment. The secondary outcome was epilepsy defined by International League Against Epilepsy (ILAE) criteria. Follow-up consisted of phone calls and chart reviews at 12, 18, and 24 months. "The primary outcome, functional development, was not significantly different between those children who were maintained on antiseizure medication as compared with those who were discontinued," Glass said. After propensity adjustment, the discontinued ASM group had an estimated WIDEA-FS score 4 points higher on average, she said. "The confidence intervals met our a priori noninferiority limit, indicating no harm to neurodevelopment for discontinuing antiseizure medication before discharge home from the neonatal seizure admission," Glass noted. The study also found that 13% of all participants developed epilepsy at a median of 8 months. "There was no significant difference in the frequency or timing of epilepsy between the two groups," she said. "We conclude there is no clear rationale for antiseizure medication maintenance," Glass said. "There is no benefit to neurodevelopment, it prolongs the exposure to potentially harmful antiseizure medications, it does not significantly delay the onset of epilepsy, and the earliest-onset epilepsies occur in spite of antiseizure medication."

New Tech Sheds Light on Neonatal Procedures

Sylvan Fiberoptics is introducing a new line of fiberoptic cold light transilluminators that use the latest LED light transmission technology to greatly enhance the absorption, reflection and transmission of epidermal light energy for transillumination. Utilizing discreet light energy wavelengths gives our products the highest level of transcutaneous tissue observation. This will enable successful neonatal, pediatric and general patient population IV site location, insertion of neonatal peripherally inserted central catheter (PICC) lines, diagnosing neonatal pneumothorax, detecting hydrocephalus and hydrocele. See the Sylvan Fiberoptics website at www.sylvanmed.com or contact: info@sylvanmed.com or communicate directly by calling 1-800-628-3836 (USA)/ 724-864-9350.

MS Bears No Effect on Certain Pregnancy Complications, Stillbirth, or Congenital Deformation

Multiple sclerosis (MS) may not pose a higher risk for complications in pregnant women, according to a new study published online Feb. 3 in Neurology Clinical Practice. While pregnancy and childbirth are not regarded as conditions that engender high-risk pregnancy in the MS population, previous studies evaluating the effects of MS on pregnancy and parturition have yet to fully elucidate some outcomes for pregnant women and their babies in multiple sclerosis. "Women with multiple sclerosis may be understandably concerned about the risk of pregnancy," said Melinda Magyari, MD, PhD, a consultant at the University of Copenhagen. "While previous research has shown there is no higher risk of birth defect for babies born to women with MS, we wanted to find out if women with MS are at risk for a variety of pregnancy complications." MS is regarded as a progressive, neurological disease mediated by the immune system that demands careful consideration of numerous situations and life changes including family planning. The MS population is overwhelmingly female, as women account for three out of every four cases of MS. The majority of these women range from 20 to 40 years of age at the time of being diagnosed with MS. Despite the unknown risks of pregnancy-related complications and various perinatal complications in this patient population, women who have MS are not discouraged from conceiving. This nationwide, population-based, cross-sectional study evaluated the pregnancies of 2,930 women with MS between Jan. 1, 1997, and Dec. 31, 2016, registered in the Danish Multiple Sclerosis Registry. The researchers compared pregnancy-related and prenatal outcomes to a 5% random sample of 56,958 randomly-selected pregnant women from Denmark's general population who did not have MS. They found no differences in the risks associated with several pregnancy-related complications (eg, preeclampsia, gestational diabetes, or placental complications), emergency Cesarean section (C-section), instrumental delivery, stillbirth, preterm birth, or congenital malformation. Apgar scores were low in both groups. A composite of various biometrics in newborns such as reflexes, muscle tone, and heart rate immediately following birth, the Apgar score is used to help assess the neonatal health, with a value of less than 7 considered low. Here, preterm birth is defined as delivery occurring before 37 weeks of gestation, and stillbirth describes a fetus born dead after 22 weeks of gestation. Women in the MS cohort were more likely to have elective C-sections (odds ratio, 2.89 [95% confidence interval, 1.65-2.16]), induced labor (OR, 1.15 [95%CI, 1.01-1.31]) and have babies with low birth weight based on their gestational age (OR, 1.29 [95% CI, 1.04-1.60]). Nearly 30% of babies born in the cohort (n = 851) were born to mothers who had received disease-modifying therapy (DMT). Neonates exposed to DMT weighed an average of 116 g less than babies born to mothers who had not received DMT (3,378 g vs. 3,494 g) with a slightly lower gestational age (39 weeks as opposed to 40 weeks). However, babies born to mothers with MS were less likely to show signs of asphyxia (OR, 0.87 [95% CI, 0.78-0.97]) than the comparison cohort.

New Study in Newborns Finds Nellcor Pulse Oximetry Technology Provides Fast Stable Oxygen Saturation Readings

Medtronic announced the results of an independent, prospective observational study comparing the efficacy and reliability of two pulse oximeters — Nellcor Bedside SpO_2 Patient Monitoring System and Masimo Radical-7 Pulse CO-Oximeter, both set at the highest sensitivity ("Neonatal" and "Fast" for Nellcor pulse oximetry technology and "Max" for Masimo) — with electrocardiography (ECG) monitoring following the delivery of 60 term newborns by Caesarian section. Pulse oximetry is a simple, noninvasive bedside test that can accurately detect the percentage of blood saturated with oxygen and measure heart rate. According to the study, a stable signal was obtained from all 60 newborns with the Nellcor pulse oximeter but from only 55 newborns with the Masimo pulse oximeter. Of the 55 newborns with stable signals from both monitors, the mean time to stable signal with the Nellcor pulse oximeter was 15 seconds compared with 27 seconds with the Masimo pulse oximeter. The average difference of 12 seconds between the monitors was statistically significant (P <0.001). The results of this prospective observational comparative study were published online in the *Journal of Perinatology*, the official journal of the Section on Neonatal-Perinatal Medicine of the American Academy of Pediatrics and the Neonatal-Perinatal Association of the United States. The study was conducted at the Rabin Medical Center, Petach Tikvah, Israel, a university-affiliated tertiary care center with approximately 9,000 births annually. The principal investigator of the study is Professor Ruben Bromiker, M.D., Department of Neonatology, Schneider Children's Medical Center of Israel, Petach Tikvah, Israel and Sackler Faculty of Medicine,

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Comparing The Performance Of Two Pulse Oximeters And Electrocardiography During Neonatal Transition

Chris Campbell

When it comes to the resuscitation of full-term infants, the use of a pulse-oximeter is a valuable way to monitor vital signs used for newborn evaluation after birth.

The question for those who deliver babies is: What pulse-oximeter should they use?

Schneider Children's Medical Center of Israel researchers Rasha Khoury and Gil Klinger set out to build on previous "sparse" data on the subject, comparing devices from "two companies that claim a superior performance of their POxs," according to their study, entitled: "Monitoring oxygen saturation and heart rate during neonatal transition. Comparison between two different pulse oximeters and electrocardiography."

They set out to compare the efficacy and reliability of the Masimo Radical-7 and Nellcor™ Oxymax Bedside, as well as evaluate the feasibility of routine ECG monitoring during delivery room transition.

They conducted a prospective observational comparative study and 60 newborns were connected simultaneously to both POxs and ECG monitor. Times to achieve a stable signal were compared. Heart rates were compared to simultaneous ECG.

What they found was the time for the achievement of a stable saturation reading in an uncomplicated resuscitation setting differed significantly between POxs.

Neonatal Resuscitation

According to the authors, the 2010 neonatal resuscitation program (NRP) guidelines of the American Academy of Pediatrics and American Heart Association[1] are what are followed by hospitals. These guidelines say that "resuscitation of full-term infants is initiated using an inspired fraction of oxygen (FiO2) of 21% (room air) and in preterm infants an FiO2 of 30-40%. As assessment of color has been shown to be unreliable,[2] breathing and heart rate (HR) remain important vital signs used for newborn evaluation after birth. The NRP guidelines recommend use of pulse-oximetry (POx) in the delivery room as an accurate method for estimating the FiO2 necessary to reach pre-established oxygen saturation (SpO2) targets over the first 10 min of life. POx contributes to avoid the adverse effects of exposure to low or high concentrations of oxygen.[3-6] As a consequence, POx has become essential for delivery room evaluation and monitoring of the newborn.[7,8] POx is based on photo-plethysmography, displaying pulse waves and HR required by the NRP algorithm for decision making. In 2015 the NRP guidelines were revised suggesting use of electrocardiography (ECG) monitoring for a more accurate and rapid evaluation of HR.[9] However, time to acquisition of a stable and accurate signal may be delayed, especially during critical situations such as low perfusion and motion; occasionally, the signal may even fail to appear."[10,11]

The authors write that the Masimo Radical-7 and Nellcor™ Oxymax Bedside devices have been compared in studies before,[12-14] but added that there is only "sparse data on the duration required to obtain a reliable saturation signal and on the accuracy of the HR reading."[15]

Study Methods

For the study, a convenience sample of newborns (full term and preterm) for whom consent was obtained prior to delivery was eligible for inclusion. The minimal total sample size (two tailed) of 52 subjects was calculated to achieve a power of 80% and a level of significance of 5% (two sided), for detecting an effect size of 0.4 between pairs with p value < 0.05. A resident in pediatrics (RK) approached the parents during admission before delivery in order to explain the study procedure and receive written informed consent; this required that the mother had a pain score below 3 using the (Visual Analogue Scale (VAS),[16] and both parents' emotional condition allowed them to receive the explanations.

Two POxs were simultaneously connected: Masimo Radical-7 (Masimo Corp, Irvine, CA) and Nellcor™ Oximax Bedside SpO2 (Medtronic Parkway, Minneapolis, MN) using Masimo M-LNCS™ Neo and Nellcor Neonatal-Adult SPO2 sensors respectively.

The highest sensitivity setting available was used for each POx: "Max", in the Masimo and "Neonatal" and "Fast" in the Nellcor, said the authors.

"After delivery, as soon as the newborn was placed under a radiant warmer, each of the POxs' sensors was attached to one of the newborn's feet, and then, simultaneously connected to the POxs device that was already turned on. Assignation of the device to the right or left foot was randomized by changing the side of the sensors every other patient. ECG HR was measured with Philips Efficia CM120 patient monitor (Philips, Eindhoven, Netherlands) using Neotrode® neonatal/pediatric

Chris Campbell is the Senior Editor of Neonatal Intensive Care.

ECG electrodes, (ConMed, New York, USA). ECG leads were attached to the newborns' skin following the POXs' sensors and connected to the ECG cable outlet immediately after saturation probes were connected to the POx cable outlet."

Results

Data for comparing time duration to obtain a stable signal between both POxs were available in 55 neonates.

"Nellcor POX delivered a stable signal faster than Masimo median (Interquartile range) was 8.5 (6–18) and 12 (9–34) s, respectively ($p < 0.001$)," the authors wrote. "For the Masimo pulse-oximeter, a signal from the device was obtained in 58 of 60 (96%) newborns, however a stable signal was obtained in only 55 newborns (92%). The average time to a stable signal was 27 s. In 51 newborns, simultaneous ECG records were available for comparison. Heart rate was significantly lower in POx vs ECG, Median (IQR) were 156 (121–170) vs 162 (147–172) ($p = 0.001$). In 18 of 51 (35%) newborns there was a mismatch of 12 or more beats per minute between devices, in 16 of 51 (31%) newborns the difference was of 40 or more beats per minute, (POx lower in all newborns). In all of these 18 cases the ECG (reference) showed a HR of above 100, and the baby had normal color and was crying properly."

The authors also determined that the Masimo produced false bradycardia results.

"A signal from the (Masimo) device was obtained in 58 of 60 (96%) newborns, however a stable signal was obtained in only 55 newborns (92%)," they wrote. "The average time to a stable signal was 27 s. In 51 newborns, simultaneous ECG records were available for comparison. Heart rate was significantly lower in POx vs ECG, Median (IQR) were 156 (121–170) vs 162 (147–172) ($p = 0.001$). In 18 of 51 (35%) newborns there was a mismatch of 12 or more beats per minute between devices, in 16 of 51 (31%) newborns the difference was of 40 or more beats per minute, (POx lower in all newborns). In all of these 18 cases the ECG (reference) showed a HR of above 100, and the baby had normal color and was crying properly. The HR delivered by the Pox was below 100 therefore these cases represented false bradycardia (FB)."

For the Nellcor pulse-oximeter, a signal from the device was obtained in 60 of 60 (100%) newborns and a stable value was achieved in all newborns (100%), said the authors.

"The average time to stable signal was 15 s. In 49 newborns, simultaneous ECG records were available for comparison. There was no statistical difference in HR between POx vs ECG; Median (IQR) were 158 (140–170) vs 163 (140–173) (NS) (in two there was not simultaneous ECG record at the time of stable signal reading due to electrode's detachment); in 7 cases (14%) there was a 12 beat per minute difference or higher between the devices, and in 3 of these cases the HR measured by the pulse-oximeter was higher than the HR measured by ECG."

The authors write that the American Academy of Pediatrics NRP guidelines show "ventilation is the single most important step and positive pressure should be administered to all newborns who do not breath effectively or who are apneic;[9] this would be independent of the accuracy of the HR's signal. On the other hand, during resuscitation of critically ill newborns, perfusion may be compromised and using ECG may be the only or best way of obtaining a reliable monitoring of the HR.[17] Therefore, the use of ECG during neonatal resuscitation should be evaluated based on its added value, but it comes at the expense of intervention and treatment of the newborns. An ECG monitor should be available for neonatal resuscitation and is valuable especially for those cases in which a POx does not deliver a reliable HR value. We have shown that attaching a POx does not significantly interfere with the steps of neonatal resuscitation and provides saturation and HR values within a relatively short period of time. One should be aware of the possibility of FB when POx's are used and remember that physical examination has still a crucial role in the evaluation of patients."

Conclusions

When the study authors wrapped up their report, they assessed both devices as having "relatively quick measurements" but gave a distinct edge to one device.

"Our study conclusions can be summarized as follows: Both POxs, Nellcor and Masimo provide relatively quick measurements of HR and saturation, in most cases well before the 'golden first minute' of resuscitation. We showed a statistically significant difference in the time needed to deliver a stable signal between devices in favor of Nellcor. One should be aware of the possibility of occurrence of FB during resuscitation. In general, routine connection of the ECG device to the newborn may consume valuable time (especially in centers with limited resources) without a significant effect on the management of the newborn's resuscitation, but it might be helpful in monitoring and decision making in cases of absence of a signal from a pulse-oximeter. A more user-friendly ECG device should be developed. Until then, we suggest making a selective use of ECG for resuscitation of the newborn."

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Tel Aviv University, Tel Aviv, Israel. The availability of a pulse oximeter for monitoring oxygenation and heart rate of newborns contributes to decision making during resuscitation and stabilization, and can help physicians minimize the risk of either too low or too high blood oxygen levels and associated morbidity and mortality, the authors state in the discussion section. Both the Nellcor and Masimo pulse oximeters provide relatively quick measurements of oxygen saturation and heart rate in most cases well before the so-called "golden first minute" of resuscitation. The results conclude that Nellcor showed a statistically significant difference in the time needed to deliver a stable signal between devices which could potentially impact the provision of care during neonatal resuscitation. With respect to heart rate, the study observed there was a difference of ^{3}12 beats per minute (BPM) between the Masimo monitor and the reference standard ECG in 18 of 51 (35%) newborns. In all 18 newborns, the ECG showed a heart rate >100 BPM versus <100 BPM with the Masimo monitor, which may be observed as false bradycardia with the Masimo device. In 16 of the 51 (31%) newborns, the difference in heart rate with the Masimo monitor was ^{3}40 BPM compared with the rate recorded by the comparator ECG. In contrast, the heart rate detected by the Nellcor pulse oximetry monitor correlated closely with that of the ECG, with no recording of false bradycardia and no reading having >40 BPM difference compared with the ECG. "A newborn's heart rate is a key component of physician assessment for resuscitation, and helps to identify not only those in need of intervention but also their response to treatment. Those who do not achieve a heart rate of 100 beats per minute by five minutes of life are at an increased risk of death," said Frank Chan, president, Patient Monitoring, which is reported as part of the Minimally Invasive Therapies Group at Medtronic. "This study demonstrates that physicians can rely on Nellcor pulse oximetry technology to post data quickly, offer consistency, perform well with these patients, and meet the requirements of the neonatal resuscitation program guidelines, which are especially important in the delivery room." These findings are important because, per the neonatal resuscitation program (NRP) guidelines, only one minute should be allotted for completing the initial monitoring steps to inform reevaluation and initiation of ventilation.

Maternal COVID Antibodies Cross Placenta, Detected in Newborns

Antibodies against SARS-CoV-2 cross the placenta during pregnancy and are detectable in most newborns born to mothers who had COVID-19 during pregnancy, according to findings from a study presented at the virtual Society for Maternal-Fetal Medicine (SMFM) 2021 Annual Pregnancy Meeting. "I think the most striking finding is that we noticed a high degree of neutralizing response to natural infection even among asymptomatic infection, but of course a higher degree was seen in those with symptomatic infection," Naima Joseph, MD, MPH, of the Emory University School of Medicine, Atlanta, Georgia, said. "Our data demonstrate maternal capacity to mount an appropriate and robust immune response," and maternal protective immunity lasted at least 28 days after infection, Joseph said. "Also, we noted higher neonatal cord blood titers in moms with higher titers, which suggests a relationship, but we need to better understand how transplacental transfer occurs as well as establish neonatal correlates of protection in order to see if and how maternal immunity may also benefit neonates." The researchers analyzed the amount of immunoglobulin G (IgG)
Continued on page 26…

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The Nellcor™ pulse oximetry monitoring system should not be used as the sole basis for diagnosis or therapy and is intended only as an adjunct in patient assessment.

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COVID-19 in the Pregnant and Neonatal Population: A Literature Review

Sandra Sundquist Beauman, MSN, RNC-NIC

The advent of the COVID-19 pandemic has resulted in numerous publications about occurrence, risk and risk prevention, treatment and outcomes. In the early period of the pandemic, it was thought to be a disease of very high risk only for the elderly or those with underlying chronic health conditions, in spite of case reports to the contrary. In the second wave, during the summer and fall, spikes were seen in different, often younger populations. Of particular concern is how the coronavirus affects women during pregnancy, the developing fetus and neonate. The infectious response is different during pregnancy potentially resulting in more severe manifestation of illness.[1] Newborns are known to be at increased risk of infections in general due to lack of a well-developed immune system. An increase in the incidence of COVID-19 in this population has indeed been observed over the past year with various manifestations. The purpose of this paper will be to review the available literature with focus on the occurrence of COVID-19 in pregnant women and newborns, measures recommended to prevent transmission and recommendations regarding breastfeeding when women have tested positive or are under investigation for SARS-CoV-2 infection.

A literature review was conducted utilizing keywords 'pregnancy AND COVID', 'newborn AND COVID', and 'breastfeeding AND COVID'. This was limited to English language only papers and published within the last year. Journal articles returned in PubMed were 1878, 1282 and 259 for each search respectively. While not all of these publications are included in this paper, this demonstrates the volume of information available. It is also important to focus on most recent publications since knowledge and experience have changed rapidly. Position statements from the Centers for Disease Control (CDC) and American Academy of Pediatrics (AAP) are reviewed here as those are important sources for guidance in clinical practice.

Occurrence of COVID-19 in Pregnancy

An early publication (March 2020) out of China[2] reported on the disease in 9 pregnant women. Symptoms reported in these women were similar to those seen in the general population. Many reports show more severe manifestation of symptoms in pregnant women than same-age counterparts, particularly if they are overweight or obese.[3,4] In 6 of the 9 cases, amniotic fluid, cord blood, neonatal throat swabs and breastmilk samples were tested for SARS-CoV-2 and all were negative. While this sample size was quite small, it did demonstrate that vertical transmission did not occur in these 6 patients. All 9 patients had a cesarean section delivery with typical indications with one exception. That patient had severely elevated ALT or AST as well as COVID-19 pneumonia as indication for cesarean delivery.[2]

Another report from Sweden published in Dec 2020 provided information about 67 women who were COVID-19 positive upon hospital admission.[4] In this cohort, only 2 infants were delivered due to severe maternal COVID-related symptoms, one at term and one preterm. The infants delivered to these COVID-positive mothers were tested for SARS-CoV-2 with the exception of 5. Of the 62 infants tested, three had a positive PCR test result. These three were term infants born by elective cesarean, emergency cesarean and one vaginally. These infants were not symptomatic at or soon after delivery. This study showed a much higher rate of preterm delivery in the COVID-positive cohort than is normally expected in this population for this area (3 times the rate in the general birthing population).

The AAP has a Perinatal COVID-19 registry through which many hospitals in the United States report maternal COVID-19 cases. As of the last update on February 11, 2021, over 7000 cases have been reported.[5] This registry suggests that about 2% of infants born to mothers who are SARS-CoV-2 positive will themselves test positive within 24-96 hours of delivery.

Raschetti, VIvanti, Vauloup, Loi, Benachi, and De Luca[6] performed a meta-analysis of articles that described 117 neonates who were infected by SARS-CoV-2 within the first month of life. While previous reports have virtually ruled out the likelihood of transplacental or vertical SARS-CoV-2 transmission, this meta-analysis shows that this is indeed possible, though rare. Transplacental transmission could potentially lead to miscarriage.[7] This may explain the reportedly low rates of prematurity early in the pandemic when evidence now suggests that premature birth is more likely in women with COVID-19.[3] While vertical transmission appears to be rare, early screening of neonates is a relatively new recommendation. Therefore, mode of transmission could not be further analyzed in this meta-analysis.

Some reports of cohorts of SARS-CoV-2 positive pregnant women show higher rates of cesarean delivery but indications

Sandra Sundquist Beauman has been a neonatal nurse for her entire career, spanning over 30 years. She is currently a research nurse coordinator at the University of New Mexico and an independent consultant with Medela LLC. She also provides neonatal consultation and continuing education though CNS Consulting. This article was written at the request of Medela, LLC.

for the delivery are not always detailed. Several studies show fetal distress rates similar to the occurrence of fetal distress in non-COVID patients.[4,5] The meta-analysis by Raschetti, Vlvanti, Vauloup et al[6] reported a significant association with late incidence (>72 hours of age) of SARS-CoV-2 infection and lack of mother-neonate separation from birth reinforcing the likelihood that the most common mode of transmission is likely horizontal after delivery. There was no significant association of COVID positivity in the infant with breastfeeding.

COVID-19 Symptoms in Newborns/Infants

While severity of disease caused by SARS-CoV-2 is thought to be lesser in children, particularly those under 10 years of age, infants (under 1 year) seem to be more vulnerable to this disease than the older pediatric population.[8] Symptoms seen in this population are often atypical and may not be readily recognized as SARS-CoV-2. Common symptoms identified in infants include poor feeding, diarrhea, and other mild GI symptoms. Raschetti, Vlvanti, Vauloup et al[6] reported a range of symptoms in the infant population with COVID. These included no symptoms for 45% of the 117 cases identified. Of the remaining 64 infants with symptoms, more common occurrence of fever was observed in this population with SARS-CoV-2 compared to other infectious diseases. The next most common category of symptoms was gastrointestinal (43.7%) followed by respiratory symptoms (42.2%). Other less frequently reported symptoms included neurologic and hemodynamic.

Recommendations for Perinatal Care

Early in the pandemic SARS-CoV-2 was quickly recognized as extremely contagious and the effect on various populations was only just emerging. Recommendations from the CDC changed frequently and AAP recommendations followed these. AAP recommendations from May 2020[9] included a somewhat restrained recommendation to separate mothers from their infants if mothers were infected with SARS-CoV-2. Many hospitals practiced this initially since transmission risk and severity of disease in neonates was virtually unknown but feared to be extreme. As stated in the guidance, this seemed to be the safest action at the time although it was acknowledged that separation of mother and baby is less than ideal. Even in this original document, there was recommendation to honor the wishes of the family after discussion of possible risks. Early in the pandemic when testing supplies were not readily available, infants and asymptomatic pregnant women may not have been tested. Most hospitals currently screen all pregnant women either prior to or upon admission. CDC currently recommends testing in the neonate born to SAR-CoV-2 infected mother at 24 hours and again at 48 hours if the first test is negative.[10] These measures may eventually reveal the true transmission risk.

In the most recent AAP recommendations,[5] delayed cord clamping and skin to skin care in the delivery room are recommended per usual practice but with the mother wearing a mask. Rooming in is more strongly recommended if the mother or another care giver is available but care providers are encouraged to discuss the risks and benefits with the family so that they can make an informed decision. As mentioned earlier, most infants who get SARS-CoV-2 will do so in the postnatal period. Therefore, mask wearing by those caring for the infant who are or may be COVID positive is important along with other standard measures such as good hand washing. It is further suggested that the infant may be in an incubator in the mother's room to provide another barrier of protection and reminder to mask and perform hand hygiene.[5] It is important to acknowledge that the incubator does not provide any level of isolation but rather serves as a barrier.

Breastfeeding and provision of human milk

Studies have shown the presence of SARS CoV-2 in breastmilk but it appears unlikely that any viable infectious agent is present in the milk.[11] In one case report, a 32-week infant was inadvertently fed milk from his/her mother who was COVID+ but had not yet been diagnosed as such. The infant did not become sick with COVID.[12] Salvatore et al[13] reported that when COVID+ mothers wore surgical masks during breastfeeding and washed their hands and breasts prior to feeding, all infants in the cohort of 64 tested negative at 5 to 7 days and at 14 days after birth. In addition, the COVID antibody may be present in human milk when the mother is positive. By providing this milk to the infant, additional protection may also be provided. Whether this is adequate to prevent COVID in the infant, the infant is still receiving many other immunologic advantages from mother's milk that will protect against other conditions.[14]

Provision of human milk to the infant has always been recommended, even with mothers who are known SARS-CoV-2 positive. Early guidance contained some reservation for direct breastfeeding for COVID+ mothers or those under investigation.[9]

Both direct breastfeeding, when mother is able and/or provision of human milk are now strongly recommended.[5,10] Wearing of a mask by the mother while direct breastfeeding is recommended,[10] While not mentioned in the AAP or CDC guidelines, some providers discuss assisted breastfeeding or pumping should the mother become unable to do so herself, for instance intubated and/or sedated. The health benefits of human milk are significant enough that this should be considered.

Given the many health advantages of human milk during the first months of life, the advantages of breastfeeding and/or provision of human milk are higher than any potential risk based on available evidence at this time.

Summary

There is still much that is unknown about COVID, pregnancy, transmission and infant health. To date, there have been no published analyses to determine if the stage or severity of maternal illness has any effect on the potential for transmission either prenatally or postnatally. While transplacental transmission is thought to be rare, it can and does occur.[15,16,17] Breastfeeding should be encouraged, even in the presence of COVID with proper precautions such as mask wearing by the mother and hand hygiene. In cases where the infant must be admitted to the NICU, parent visitation may need to be limited due to risk of COVID transmission to staff and other patients. However, mothers should be encouraged to pump their milk and a method provided through which it can be brought to the infant.

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Tetralogy of Fallot: Overview and Update on Surgical Wound Care

The diagnosis of Tetralogy of Fallot is frightening for parents who have infants with the disease, and rightfully so. Tetralogy of Fallot is a life-threatening condition that requires medical attention. However, there is also good reason for hope. The success rates for Tetralogy of Fallot surgery are greater than 95%. In this article, we will review the diagnosis and treatment for Tetralogy of Fallot and discuss the steps parents can take to improve outcomes after surgery.

What is Tetralogy of Fallot?

The complex term, Tetralogy of Fallot, is a bit easier to understand when it is broken down. Tetralogy simply means four (tetra-) and corresponds to the four clinical findings that occur in all patients with the disease. The defects that occur in Tetralogy of Fallot are:

1. **Ventricular septal defect (VSD)** – An opening or hole between the two ventricles (larger chambers) of the heart
2. **Overriding aorta** – The aorta is the major artery that leaves the left ventricle of the heart; an overriding aorta is caused by an enlarged aortic valve that seems to leave both the left and right ventricles
3. **Pulmonary stenosis** – A stricture in the blood vessel that carries blood from the right ventricle to the pulmonary (lung) artery
4. **Right ventricular hypertrophy** – To overcome these defects and pump at higher pressures, the muscle in the left ventricle thickens (hypertrophy)

Why Fallot? Arthur Fallot is the French doctor who first described the condition in great detail, and subsequently received credit for its name.

What are the symptoms of Tetralogy of Fallot?

The main symptoms of Tetralogy of Fallot are startling. The top of that list is cyanosis. Cyanosis is a bluing of the body. Blood (or more specifically hemoglobin) is red when it contains oxygen and blue when it does not. As the ductus arteriosus (a small, connecting blood vessel between a major artery and a major vein present during gestation and a little after birth) naturally closes, less and less blood circulates through the lungs (because of pulmonary stenosis, one of the four defects). With low oxygen levels in the blood, there is a blueish-purple tint to the skin, fingernails, lips, and tongue. The infant will be listless or (more often) irritable and fussy during one of these low oxygen

spells. The baby's body will try to get more oxygen by breathing faster; however, it is not a problem of air getting to the lungs, it is a problem of not enough blood reaching the lungs to receive oxygen. During these "Tet spells," blood oxygen will be quite low. Blood oxygen is measured through a pulse oximeter, the device that attaches to a finger or in small infants, an arm.

How is Tetralogy of Fallot diagnosed?

Tetralogy of Fallot can be diagnosed in several ways. Your doctor may be able to hear a specific heart murmur using a stethoscope. The heart murmur is caused by whooshing blood flow through the defects in the heart. The baby may need to have an echocardiogram, which is a sonogram for the heart. Other procedures may be required (eg, cardiac catheterization) to confirm the diagnosis or for surgical planning.

How is Tetralogy of Fallot treated?

The first goal in treating Tetralogy of Fallot is to stabilize the baby. One of the quickest ways to accomplish this is by administering supplemental oxygen. Supplemental oxygen by a tube in the nose or a face mask provides any blood that actually reaches the lungs to get a "superdose" of oxygen. This may or may not be enough to restore normal levels of oxygen to the blood. If it is not, a series of medications can be administered as needed. These include a pain medicine to help calm and comfort the baby and a beta blocker to slow down heart rate and ease its pumping burden. In more serious cases, a catheter may need to be inserted into the blood vessel system to temporarily improve blood flow to the lungs. The definitive treatment for Tetralogy of Fallot, however, is surgery.

Submitted for Neonatal Intensive Care by Hy Tape International. www.hytape.com.

Tetralogy of Fallot surgery

The surgery used to correct Tetralogy of Fallot is complex and technically challenging open-heart surgery, but most patients (~95%) have a successful outcome.[1] In brief, the surgeons reverse the defects of Tetralogy of Fallot; they close the ventricular septal defect with mesh, increase blood flow to the lungs, and correct the overriding aorta. As an open-heart surgery, the rib cage must be opened to access the heart and lungs, but then closed at the end of surgery. Thus, the surgical wound is relatively large (and looks especially large on a small baby) and runs vertically down the center of the chest.

Post-surgical care

Parents are responsible for quite a lot after Tetralogy of Fallot surgery. The discharge instructions and care requirements can be quite involved. It is important that parents or caregivers follow feeding and activity recommendations carefully. Certain medications will be required and should be given regularly and on time, including and especially pain medications. It is also important to watch for changes in the baby's status. Things like bluish or purplish skin, trouble breathing, unusual fussiness or signs of distress, or poor feeding should be reported to your doctor immediately. Consult your discharge instructions for a full list of worrisome symptoms.

Wound care after Tetralogy of Fallot surgery

Parents should make sure the wound that remains after Tetralogy of Fallot surgery is healing well and is free of infection. At each dressing check, check the wound for any bleeding, excess fluid, redness, or warmth. A slight redness around the surgical wound is normal soon after the surgery, but significant redness and warmth (and especially if the baby has a fever) could be signs of infection. Unless there is a drainage device left in place after surgery, the wound should be completely closed. It is normal for the surgical wound to be a little moist, but bleeding, green or yellow pus, or excessive fluid coming from the wound are all signs your doctor will want to hear about as they could indicate poor wound healing.

Dressings and dressing changes after Tetralogy of Fallot surgery

Parent or caregivers are responsible for the baby's at-home dressing changes after Tetralogy of Fallot surgery. Each dressing change is an opportunity to check the wound for signs of healing or infection. Before discharge, ask your doctor or surgical team how to perform dressing changes. In fact, you can request some dressings and medical tape to take home. Many different types of dressings are available, and your medical team or wound nurse is an excellent resource. The ideal dressing is one that retains a bit of moisture to promote wound healing, but not so much that the moisture is excessive.

Medical tape after Tetralogy of Fallot surgery

Choosing a medical tape after Tetralogy of Fallot surgery is considerably easier than choosing a dressing. The top choice of medical tape for infants and young children is called Hy-Tape. Hy-Tape — better known in pediatric circles as Pink Tape — is particularly useful for wound dressings after Tetralogy of Fallot surgery. Hy-Tape's adhesive contains zinc oxide, which is soothing to baby's skin and releases cleanly during dressing changes. In fact, the biggest advantage Hy-Tape has over other medical tapes is that it is safe and gentle on the thin skin of infants. When Hy-Tape must be removed during a dressing change, it does not cause trauma to baby's fragile skin. That said, Pink Tape is also strong enough to hold dressings in place, even when little hands try to grab and remove it.

Long term care after Tetralogy of Fallot surgery

While success rates from this type of surgery are high, close medical follow-up will be required for some time. This means visits to surgeons, cardiologists, and pediatricians. The patient may need additional surgeries and the heart may not function as well as it would have if it did not start out with the four defects. That said, almost all babies with Tetralogy of Fallot survive the procedure and life full lives.

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A New Solution to an Old Problem: Can Cervical Cerclage Prevent Umbilical Cord Prolapse in Patients with Funic Presentation?

BM Petrikovsky MD, PhD, M Terrani MD, A Dillon, RDMS, Sichinava LG, MD, DSc

The prolapse of the umbilical cord complicates 1 in 200-400 pregnancies and has been associated with a perinatal mortality rate of up to 50%[1]. Most cases of the presentation or prolapse of the umbilical cord are diagnosed during labor. The first sign of a cord prolapse is often an abnormal fetal heart rate.

A funic presentation is defined as the presence of the umbilical cord below the presenting part and can be detected by both transabdominal and transvaginal sonography. A funic presentation is a risk factor for umbilical cord prolapse. It has been reported that 18% of women in whom clinical prolapse of the umbilical cord was detected later had funic presentation.[2]

The current recommendations in cases of funic presentation are limited to frequent sonographic examinations which enhance maternal anxiety and doesn't prevent the catastrophic event — umbilical cord prolapse. We propose a new approach — the placement of a third-trimester cervical cerclage in women with persistent funic presentation. The cervical cerclage mechanically closes the cervix, which prevents the presenting umbilical cord to prolapse.[4]

Once the funic presentation was suspected, a color Doppler was used to confirm the presence of the umbilical cord, below the presenting part. If a funic presentation was detected, the follow-up sonographic examination was performed a week later to confirm its persistent nature. The risks and benefits of a late cervical cerclage were discussed with the patients. All patients signed informed consent for the placement of a cervical cerclage.

Eight patients between 27 and 34 weeks of pregnancy, with a mean of 30 ±3 weeks of pregnancy, underwent cervical cerclage. A purse-string suture was inserted with bites of the needle deep enough to suture it to the cervical stroma. Four to six bites of the needle were required to encircle the cervix, depending on its thickness. (Figure 1) The cervical cerclages were removed prior to cesarean delivery in all cases, without complications. Funic presentation was confirmed at delivery in all cases. None of the patients experienced umbilical cord prolapse. All neonates were delivered in satisfactory condition. The apgar scores varied between 7 and 10.

The authors are with the Fetal Research Fund, Ocean Perinatology, Moscow University School of Medicine.

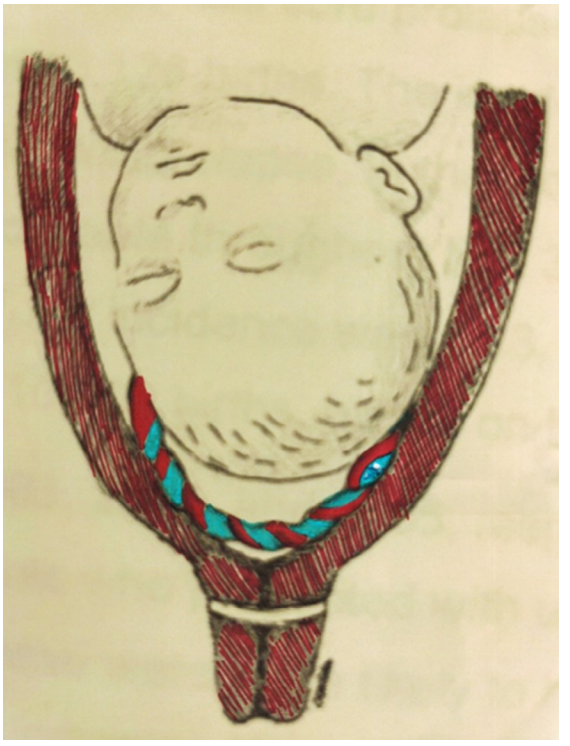

Figure 1. Illustration by Chana Rosa Bogart

Conclusion

Currently there is no strategy to prevent umbilical cord prolapse in mothers with persistent funic presentation. Current recommendations include frequent fetal surveillance and delivery by cesarean section at around 37 weeks of pregnancy.[5] However, an elective delivery at 37 weeks does not solve the problem since the majority of umbilical cord prolapses occur prior to this date.[5,6] In view of a total lack of preventative measures in cases of persistent funic presentation, the placement of cervical cerclage may be a reasonable strategy.

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Challenges…continued from page 18
and immunoglobulin M (IgM) antibodies in maternal and cord blood samples prospectively collected at delivery from women who tested positive for COVID-19 at any time while pregnant. They used enzyme-linked immunosorbent assay to assess for antibodies for the receptor binding domain of the SARS-CoV-2 spike protein. The 32 pairs of mothers and infants in the study were predominantly non-Hispanic Black (72%) and Hispanic (25%), and 84% used Medicaid as their payer. Most of the mothers (72%) had at least one comorbidity, most commonly obesity, hypertension, and asthma or pulmonary disease. Just over half the women (53%) were symptomatic while they were infected, and 88% were ill with COVID-19 during the third trimester. The average time from infection to delivery was 28 days. All the mothers had IgG antibodies, 94% had IgM antibodies, and 94% had neutralizing antibodies against SARS-CoV-2. Among the cord blood samples, 91% had IgG antibodies, 9% had IgM antibodies, and 25% had neutralizing antibodies. "It's reassuring that so far, the physiological response is exactly what we expected it to be," Judette Louis, MD, MPH, an associate professor of ob/gyn and the ob/gyn department chair at the University of South Florida, Tampa, Florida, said. "It's what we would expect, but it's always helpful to have more data to support that. Otherwise, you're extrapolating from what you know from other conditions," said Louis, who moderated the oral abstracts session. Symptomatic infection was associated with significantly higher IgG titers than asymptomatic infection (P = .03), but no correlation was seen for IgM or neutralizing antibodies. In addition, although mothers who delivered more than 28 days after their infection had higher IgG titers (P = .05), no differences existed in IgM or neutralizing response.

New NeoSmile Plus Temperature Probe Cover Available

Neotech Products announces the NeoSmile Plus Temperature Probe Cover is now available. Unlike our original NeoSmile that uses hydrocolloid for long-lasting adhesion, NeoSmile Plus features a silicone gel base. The unique, skin friendly gel allows for the temp prob cover to be repositioned with ease. "Ever since being introduced to silicone adhesives we searched for the right product to implement it. We knew that temp probe covers could be a challenge, but wanted to bring something unique to the market. We started to work with silicone adhesives for this, thus resulting in the creation of the NeoSmile Plus," said Sara Dimmitt, Manager of Business Development. The new NeoSmile Plus is a skin friendly option that can be moved or adjusted as needed. Yet, it securely holds the probe in place for reliable readings. The reflective foil cover helps protect the temperature probe from ambient and radiant heat in an incubator, and the foam layer provides added insulation. Various test users stated: "Easier to move; a more accurate reading than our current product." "Sticks better than our old one and it's smaller." "I like the thin, low profile." "Very impressed with this product."

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

Researchers at Massachusetts General Hospital (MGH), Brigham and Women's Hospital and the Ragon Institute of MGH, MIT and Harvard have found the new mRNA COVID-19 vaccines to be highly effective in producing antibodies against the SARS-CoV-2 virus in pregnant and lactating women. The study also demonstrated the vaccines confer protective immunity to newborns through breast milk and the placenta. The study, published in the American Journal of Obstetrics and Gynecology
Continued on page 40…

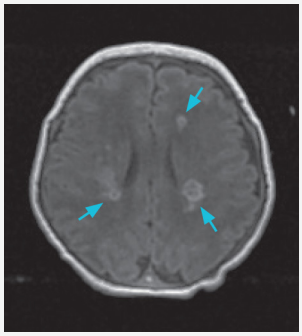
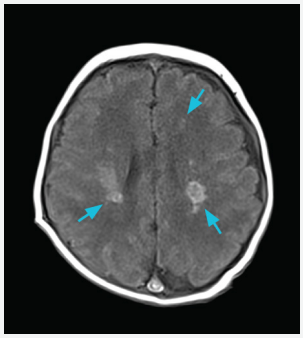
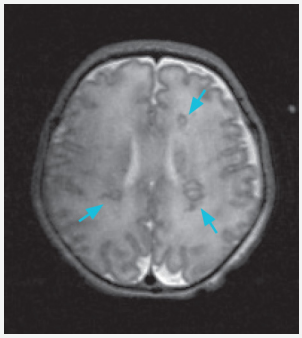
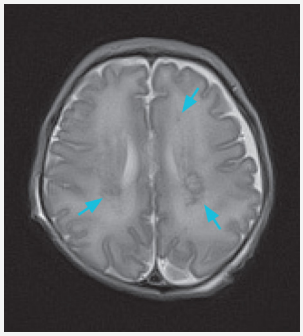
Assessing Periventricular White Matter Lesions in a 37-Week-Old Infant with Neonatal Encephalopathy

Patient History
Term infant born at 37 weeks gestation after decreased fetal movements were noted by the mother for two days. The infant had moderate encephalopathy at birth which was treated with therapeutic hypothermia for 72 hours and suffered from a complicated NICU course with multi-system organ failure, seizures and severe hypoglycemia. The infant was referred for MR on day of life 14 to assess the extent of brain injury.

Procedure
The "feed and wrap" technique was used to prepare the non-sedated infant for the MRI scan. The infant was then transported to the Embrace® Neonatal MRI system inside the NICU and placed in the temperature-controlled Embrace® patient bed. Heart rate and oxygen saturation were monitored throughout the scan with an MR-conditional wireless monitoring system and the infant's face was continuously observed through the color video monitor incorporated into the Embrace® system. Transit time to and from the Embrace® system was seven times faster compared to the off-unit MRI scanner*.

MR Protocols Used
- Axial T1
- Axial T2
- Axial Diffusion-Weighted Imaging (DWI)
- Apparent Diffusion Coefficient (ADC)
- Coronal T2
- Sagittal T2
- Sagittal T1 3D GRE

MR Findings
The MRI scan was completed at 14 days of life and showed bilateral punctate lesions in the centrum semiovale and periventricular white matter (blue arrows) as evidenced by hyperintense foci with hypointense centers on the T1-weighted images, complementary abnormal findings on the T2, and restricted diffusion on the DWI and ADC maps.

Embrace® System	1.5T MRI System
	
AX T1 SE TR/TE=600/10.4 ms voxel size=0.8 x 0.8 x 3.0 mm NSA=2, AT=2:37 min.	**AX T1 SE** TR/TE=415/11 ms voxel size=0.63 x 0.63 x 3.0 mm NSA=2, AT=2:40 min.
	
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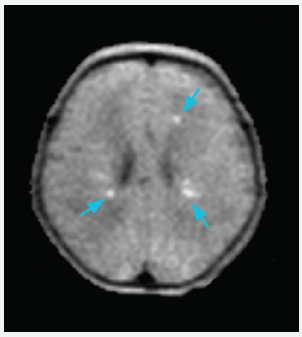
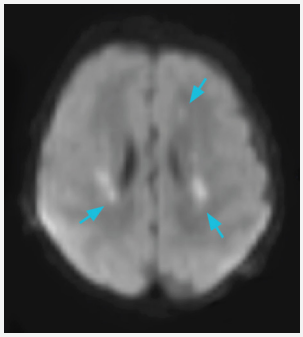
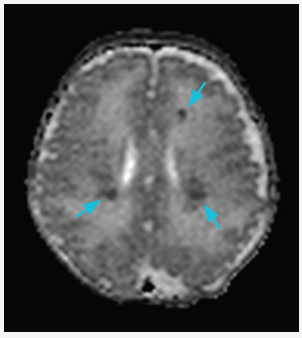
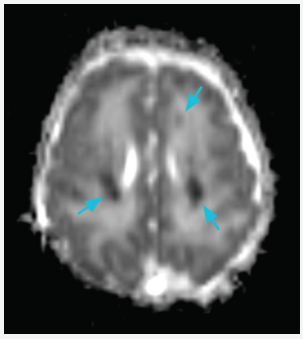
	
DWI TR/TE=13173/121.7 ms 3–directions, b-value=700 voxel size=1.5 x 1.5 x 3.0 mm NSA=3, AT=4:23 min.	**DWI** TR/TE=5600/83 ms 3–directions, b-value=700 voxel size=1.7 x 1.7 x 3.0 mm NSA=7, AT=2:55 min.
	
ADC	**ADC**

*Bin-Nun, A (2019, Feb). Global Brain Injury scores in Preterm Infants: Validation of a novel 1T Neonatal MRI vs Conventional 1.5T MRI. Podium Presentation at the 10th Annual Neonatal Brain Monitoring & Neuroprotection Conference, Tampa, FL.

For your patients with a rare and devastating genetic disorder[1,2]

With MoCD Type A, waiting is not an option[1,2]

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

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

As soon as MoCD Type A is suspected, consider NULIBRY.[1]*

INDICATION

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

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Potential for Photosensitivity

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

ADVERSE REACTIONS

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

PATIENT COUNSELING INFORMATION

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

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

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

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

Nulibry™

(fosdenopterin)
for injection

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

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

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

Visit NULIBRY.com to learn how you can give patients with MoCD Type A a fighting chance[1]

References: 1. NULIBRY [prescribing information]. Boston, MA. Origin Biosciences, Inc.; February 2021. **2.** Mechler K et al. *Genet Med*. 2015;17(12):965-970. **3.** Veldman A et al. *Pediatrics*. 2010;125(5):e1249-e1254. **4.** Durmaz MS et al. *Radiol Case Rep*. 2018;13(3):592-595.

Please see accompanying Brief Summary.

NULIBRY.com

origin
a bridgebio company

NULIBRY™ (fosdenopterin) for injection
BRIEF SUMMARY: For full prescribing information, see package insert.

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

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

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

2.2 Important Administration Information

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

2.3 Recommended Dosage and Administration

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

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

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

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

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

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

Recommendations for a Missed Dose

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

2.4 Preparation and Administration Instructions

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

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

2.5 Storage of Reconstituted Solution

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

Discard all unused reconstituted NULIBRY solution 4 hours after reconstitution.

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Photosensitivity

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

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

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Overview of Safety Evaluation

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

Adverse Reactions

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

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

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

Adverse Reactions	NULIBRY-Treated Patients (N=9) n (%)
Catheter-related complications[1]	8 (89%)
Pyrexia	7 (78%)
Viral infection	5 (56%)
Pneumonia	4 (44%)
Otitis Media	4 (44%)
Vomiting	4 (44%)
Cough/Sneezing	4 (44%)
Upper viral respiratory infection	3 (33%)
Gastroenteritis	3 (33%)
Diarrhea	3 (33%)
Bacteremia	3 (33%)
Abdominal pain	2 (22%)
Influenza	2 (22%)
Lower respiratory tract infection	2 (22%)
Viral tonsillitis	2 (22%)
Oropharyngeal pain	2 (22%)
Rash maculo-papular	2 (22%)
Anemia	2 (22%)
Eye swelling	2 (22%)
Seizure	2 (22%)
Agitation	2 (22%)

Abbreviations: MoCD = molybdenum cofactor deficiency

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

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

8.2 Lactation

Risk Summary

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

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

8.4 Pediatric Use

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

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

8.5 Geriatric Use

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

DRUG INTERACTION STUDIES

In Vitro Studies

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

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with fosdenopterin.

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

Fertility studies have not been conducted with fosdenopterin.

13.2 Animal Toxicology and/or Pharmacology

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

17 PATIENT COUNSELING INFORMATION

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

Photosensitivity

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

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

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Tracheostomy Tube Selection and Airway Patency Considerations in the Pediatric Population

Kristin A King, PhD, CCC-SLP and Laura Brooks, MEd, CCC-SLP, BCS-S

Children with complex airway problems, including those requiring tracheostomies, are a diverse patient care group requiring a multidisciplinary approach to address their needs. When a patient receives a tracheostomy tube, a critical factor for long-term management is providing access to a patent airway. Having airway patency impacts the ability to restore use of the upper airway, to access speaking valves, and to lessen the risk of airway complications. However, determining the size of the tracheostomy tube in relation to the airway size may be impacted by the underlying diagnosis. When considering the diameter of a tracheostomy tube, the considerations should include tracheal size and shape, indications for the tracheostomy, lung mechanics, upper airway resistance, and the needs of the child for speech, ventilation, and airway clearance (Sherman et al., 2000).

When selecting a tracheostomy tube, several factors should be considered—length, curvature, flexibility, and composition of the tube (Sherman et al., 2000). Additionally, tracheostomy tubes also have options for a cuffed or a non-cuffed tracheostomy tube, a fenestrated or a non-fenestrated tracheostomy tube, a tube with a straight or angled neck flange, and whether a standard tracheostomy tube will be used or a custom tracheostomy tube. There is a paucity of research data available documenting optimal choices in tracheostomy tube selection. In the pediatric population, a common standard of care for infants and young children is to use a cuffless tracheostomy tube; however, this practice is not consistent.

Kristin King, PhD, CCC-SLP: With 25 years of experience in medical, academic, and industry settings, Dr. King brings a unique perspective of medical speech pathology. Her research, publications, and teachings focus on traumatic brain injury, swallowing disorders, and critical care (tracheostomy and mechanical ventilation) for both pediatric and adult patient populations. She has been an invited speaker both domestically and internationally and has published in peer-reviewed journals. Currently, Dr. King is the Vice President of Clinical Education and Research for Passy-Muir, Inc.

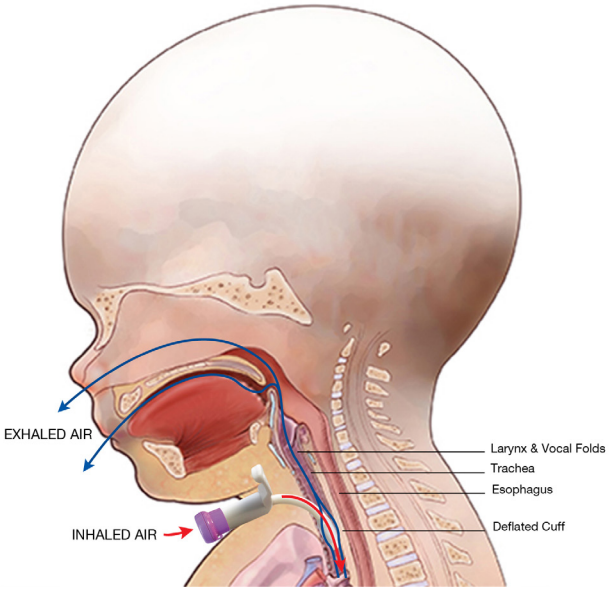
Laura B Brooks attended the University of Florida, finishing in 1997, and the University of Virginia, graduating in 1999. She worked at NYU Medical Center, became the supervisor of the pediatric SLP department, and then joined Children's Healthcare of Atlanta in 2009. She works with patients in the Intensive Care and acute care units; is Board Certified in Swallowing and Swallowing Disorders; and participates in research related to tracheostomies, speaking valves, and evidence-based care.

Another factor is the actual fit of the tracheostomy tube within the trachea—measuring the size of the tracheal lumen and providing a tracheostomy tube that allows for space in the trachea around the tracheostomy tube for translarygeal airflow. A consensus statement from ATS (Sherman et al., 2000) is that most cases should have a tracheostomy tube that extends at least 2 cm beyond the stoma and no closer than 1-2 cm to the carina. As to the diameter of the tracheostomy tube, it should be selected to avoid damage to the tracheal wall, to minimize work of breathing, and, when possible, to promote translaryngeal airflow (Sherman et al., 2000). Lastly, the pediatric patient population has the added complication of a growth rate that influences airway patency over time. Often, pediatric tracheostomy tubes are up-sized, instead of down-sized like we see in adults; therefore, airway patency becomes a critical factor to monitor.

Best care for these patients occurs with the multidisciplinary team, including referral to a speech-language pathologist (SLP). These consultations often call on the SLP's expertise in evaluating and treating speech, language, swallowing, communication, and cognition, among others. However, these broader areas of focus also require that the SLP assess the more nuanced areas impacted, investigating contributing factors that may affect the plan of care, such as airway patency. In the pediatric population, developmental factors, in combination with medical concerns, impact treatment considerations, but the research literature in the pediatric population is inadequate to provide sufficient evidence-based practices (Suiter, 2003). Review of recent literature suggests that approximately half of all pediatric patients who receive a tracheostomy are younger than one year of age (Barbato et al., 2012). For best management, understanding airway patency, its impact and how to achieve it, is critical for patients with tracheostomies.

What Is Airway Patency?

Simply put, airway patency is the ability of a person to breathe, with airflow passing to and from the respiratory system through the oral and nasal passages. Airway patency may be impacted by anatomical or physiologic changes that impede airflow or even by a foreign object, such as a tracheostomy tube. These factors become particularly relevant to speech-language pathologists when the mechanisms for maintaining airway patency are affecting the ability to speak or swallow. In the pediatric population, the ability to feed and speech-language development may be delayed. The relationships between upper airway function, intra-oral and intra-pharyngeal pressure, and



activation of the muscles involved in respiration all interact during speech (vocalizations) and swallowing. Because of this direct relationship, understanding airway patency is critical.

Airway patency is assessed by evaluating for the presence or absence of obstructive signs or symptoms that suggest the airway either is or may become obstructed. Signs and symptoms include such findings as stridor with breathing, secretions, snoring, difficulty with inhalation and/or exhalation, coughing, and changes in respiratory status, such as decreased oxygen saturations. Obstruction may occur due to injury with edema, direct trauma to the airway, neurologic impairment, inhalation or swallowing of a foreign object, allergic reaction, tumors, vocal fold changes, viral or bacterial infections, abscesses to the tongue or epiglottis, bronchitis or pneumonia, COPD, and many others. Some of these causes may lead to emergent or planned intervention, such as intubation or tracheostomy, to provide more direct access to breathing and to bypass the obstruction. With infants and children, several causes may lead to a tracheostomy. Three main categories of tracheostomy indications include airway obstruction, lung disease, and neuromuscular/neurological involvement. These categories include, but are not limited to, chronic obstruction within the airway, such as choanal atresia, subglottic stenosis, tracheomalacia, laryngomalacia, and bronchomalacia; vocal cord paralysis, leading to chronic aspiration or poor pulmonary toileting with an inability to clear secretions; severe CNS (Central Nervous System) impairment, such as seen with Arnold-Chiari malformation, Werdnig Hoffmann disease, and Congenital Hypoventilation Syndrome; craniofacial anomalies, such as seen with Pierre Robin sequence and Treacher Collins, Beckwith-Wiedemann, and CHARGE syndromes; and chronic lung disease, including bronchopulmonary dysplasia (Shaker & Mutnik, 2012).

Another consideration is that an infant or child may be intubated for months prior to transitioning to a tracheostomy tube, particularly in extremely premature infants. Prolonged intubation in the pediatric population can result in an acquired upper airway abnormality characterized by inflammation, scarring, and narrowing. Common acquired upper airway abnormalities associated with prolonged intubation include tracheal and subglottic stenosis, granulomas, and vocal cord paralysis. The potential for airway injury increases with a difficult airway and with multiple intubation attempts (Coyle, 2014).

When Is Airway Patency a Consideration with Tracheostomy?

The changes that occur to communication and swallowing following tracheostomy have been well-documented (Bartow & King, 2020; Freeman-Sanderson et al., 2018). Airway patency is an immediate consideration following tracheostomy as it has the potential to negatively impact various functions, such as cough, throat clear, voicing, and swallowing. When considering airway patency, the ability to pass air through the trachea is paramount. With the outer diameter of a tracheostomy tube causing a partial occlusion in most and potentially complete occlusion of the airway in others, knowing the state of patency becomes a critical piece of information.

Generally, cuffless tracheostomy tubes are the preferred tracheostomy tube type for children. However, patients with severe restrictive lung disease or neuromuscular disease require high pressure be delivered, and it is done more effectively with an inflated cuff (Hess & Altobelli, 2014). Previously, only cuffless tracheostomy tubes were available for pediatrics, but in the past decade, cuffed tracheostomy tubes have become more popular (Watters, 2017). The choice of cuffed versus cuffless tracheostomy tubes is usually institution or patient dependent. The cuffless tracheostomy tube has benefits not observed in cuffed tracheostomy tubes, such as reducing the incidence of acquired tracheal wall injury (Hess & Altobelli, 2014) and improving phonation (Watters, 2017).

The patient with a cuffless tracheostomy tube also may have less difficulty with the application of the Passy-Muir® Valve (PMV) as there is less change in the exhalation physiology (Watters, 2017). Typically, a patient inhales and exhales through the tracheostomy tube, which is either cuffed or cuffless. Even though the cuff must be completely deflated prior to PMV application, the deflated cuff material may still cause some resistance when exhaling (Beard & Monaco, 1993). A tight to the shaft (TTS) tracheostomy tube or cuffless tracheostomy tube may allow for more space in the tracheal lumen for exhalation out through the mouth and nose. When the PMV is placed, a child still inhales through the Valve and tracheostomy tube, but the Valve closes at the end of inspiration and redirects airflow out through the upper airway, mouth, and nose.

For children, the most common reasons for PMV success involve both physiologic and behavioral factors (Lieu at al., 1999). As such, cuffless tracheostomy tubes may help prepare the patient physiologically and behaviorally for the change in exhalation. Additionally, a cuffless tracheostomy tube has the potential to allow the patient to sense the secretions in their pharynx, resulting in improved swallow or cough response. One study, with critically ill patients with tracheostomies randomized to groups, found that deflating the tracheostomy tube cuff shortened weaning time, reduced respiratory infections, and improved swallowing (Hernandez et al., 2013).

As an SLP initiates a communication or swallowing evaluation with a patient following tracheostomy tube placement, one of the first steps of that evaluation is to assess airway patency. Knowing the status of a patient's airway patency provides information relevant to options for communication and swallowing, both for assessment and interventions. From a developmental or

communication standpoint, is the child able to use a PMV which allows access to phonation for crying, cooing, babbling, and other sounds in the infant or to the development of language in the young child? From a feeding and swallowing standpoint, how might the ability to throat clear and cough potentially assist with protecting the airway during swallowing? Is a Valve an option to assist with increasing intra-oral pressure; restoring subglottic pressure; improving sensation and hyolaryngeal excursion; and other functions impacting feeding and swallowing (for a more detailed review, see the article by Bartow & King, 2020)?

How to Assess Airway Patency?

When a child has a tracheostomy tube, several options exist for evaluating airway patency. The method used is dependent on whether they are on mechanical ventilation, off mechanical ventilation, and whether the child has a cuffed or cuffless tracheostomy tube. When on mechanical ventilation with a cuffed tracheostomy tube, Sudderth (2016) shared:

> Once the cuff is completely deflated, airway patency can be determined by assessing voicing on exhalation, listening for exhalation though the upper airway using a stethoscope, or by reading the peak inspiratory pressure (PIP) and/or exhaled volumes via the ventilator. The clinician can objectively document an adequate leak and upper airway patency when reading a 40-50 percent drop in PIP and/or decrease in exhaled tidal volume measured by the ventilator. These measurements would suggest that the tracheostomy tube is properly sized to allow for sufficient airflow around the tracheostomy and upwards to the upper airway. It also suggests that there is no significant obstruction above the tracheostomy tube. A no-leak speaking valve then can be placed into the ventilator circuit while mechanical ventilation continues.

If the child is not on mechanical ventilation, then the options include listening for voicing or breath sounds with cuff deflation (or with cuffless tracheostomy tube) or using finger occlusion. Finger occlusion involves the clinician deflating the tracheostomy tube cuff, if present, then occluding the tracheostomy tube hub with a gloved fingertip. The clinician watches the patient's respiration and occludes just after inhalation. Observing exhalation out through the mouth and nose indicates potential airway patency. If the patient achieves any voicing, a cough, or blows air out the mouth and nose, this indicates that airflow is passing around the tracheostomy tube. If there is no voice or airflow, then the patient may have some or complete occlusion.

Another option is to use transtracheal pressure measurements (TTP) (for full review and description see Brooks, 2018). TTP is an objective method for measuring airway patency with tracheostomy tubes. It is a process involving the use of a manometer to measure the pressure that is occurring within the airway. Research has shown that when the TTP measurement is at 6-10 cmH_2O, then the airway is patent and airflow past the tracheostomy tube occurs (Barraza et al., 2014; Utrarachkij et al., 2005). TTP may be conducted during finger occlusion or with the use of a speaking valve, both on and off mechanical ventilation.

If an airway is not patent, then back pressure (also, called breath stacking) may be observed. This occurs because what is inhaled is not exhaled sufficiently past the tracheostomy tube, causing pressure to build below the tracheostomy tube. A sign of back pressure that may be observed occurs when there is a woosh of air released at the site of the tracheostomy hub when the finger is removed. Back pressure not only indicates that the airway is not patent but also may provide more clinically relevant or even diagnostically important information as to what is happening with a patient. Back pressure is a negative sign indicating occlusion. This occlusion may be anatomical, physiological, or due to placement of a tracheostomy tube in situ. Determining the cause provides pertinent information affecting the next steps in the care plan.

It is when an airway is not patent that further diagnostic steps must be taken by the team. The first step for troubleshooting the issue is to look at the tracheostomy tube size. If a patient has minimal space due to the size, this puts the child at more risk for mucosal tissue injury in the trachea, with the potential for problems such as stenosis, granulation tissue, and tracheoesophageal fistulas, especially if the cuff is not effectively managed (King & Harrell, 2019). If the patient has a tracheostomy tube with a cuff, just the presence of the cuff may occlude the airway (Watters, 2017).

If the issue is not caused by the tracheostomy tube, then additional investigation into anatomical changes, such as swelling or vocal fold injury; physiological impacts, such as increased work of breathing and secretions; and behavioral considerations, such as anxiety and stress, must be considered. Evaluating each area systematically allows the team to determine information relevant to what the next steps may need to be for addressing the airway patency and improving the child's ability to exhale through the mouth and nose. Having a team approach provides a more comprehensive review of the patient's systems. Respiratory therapy (RT) may address secretion issues, tracheostomy tube issues, or other respiratory factors that may impact airway patency. If the potential cause is not readily identified, then referral to a laryngologist (ENT) may lead to an endoscopic evaluation to assess for vocal fold function, edema, or other structural abnormality or change to better assess the cause. Determining the cause allows the appropriate intervention and contributes to the SLP assessment and intervention plan for communication and swallowing, including the potential for using a speaking valve.

Why Evaluate Airway Patency?

Airway patency is critical for translaryngeal airflow, which directly impacts the ability to develop or access stages of communication. The most critical stages of speech and language development occur birth to three years of age. Zabih et al. (2017) conducted a systematic review of the literature and reported that previous research has shown that the absence of an effective and consistent communication modality has a negative impact on a child's medical, psychological, and social well-being. While the research has indicated that a tracheostomy tube may have a negative impact on speech-language development and use of a speaking valve has shown promising results for enhancing speech-language acquisition and development, the authors report that further research is needed to reach a scientifically based consensus as it relates to communication and speech development.

The functional significance of the respiratory-swallow coordination and interaction during the act of swallowing also is far from fully understood. To swallow involves a synergistic relationship between multiple complex functions that involve the ability to generate pressure, subglottic, intra-

oral, pharyngeal, and esophageal, to assist with propelling a bolus through the aerodigestive tract while simultaneously protesting the airway (Martin-Harris, 2008). The airway is protected by movement of structures, subglottic pressure, respiratory control, and use of a cough and throat clear. This interdependent relationship between swallowing and respiration may already be compromised following a medical event, such as stroke, brain injury, head and neck cancer, and other diagnoses which may lead to airway patency issues. The complication of a tracheostomy just compounds the issue and further impacts the relationship of respiration and swallowing.

Not only is this relationship key during the act of swallowing, but the provision of behavioral modifications and compensatory strategies often involve the ability to modify respiratory behavior, including alterations in the respiratory-swallow coordination. Airway patency is the first step in addressing both the relationship of respiration to swallowing and the ability to intervene by manipulating the respiratory system. Alterations in respiratory-swallowing patterns have been shown to be associated with increased aspiration and swallowing difficulty (Martin-Harris, 2008). For this coordination to be optimal, the airway must be patent. For these reasons, evaluating airway patency is a critical first step when initiating assessment of communication or feeding and swallowing with a child following tracheostomy.

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Advancing Precision Medicine in the Neonatal Intensive Care Unit with Big Data and Innovative Noninvasive Sensors

Lawrence Prince, MD, PhD

In the neonatal intensive care unit (NICU), data is power. Since the beginning of medicine, we've relied on noninvasive monitoring techniques—the stethoscope to assess heart sounds, the weight of a baby to measure growth and development—to guide our care. Yet imagine what we could do as neonatologists if we directed data to not only measure vital signs, but also to guide development, cure diseases, and promote healthy lives. This is the future of precision medicine in the NICU. Small, incremental victories are paving the way, often in the form of noninvasive sensors and data analysis.

Harnessing Big Data to Improve Care in the NICU

We already collect substantial data on hospitalized infants from continuous monitors, ventilators, and other devices, yet health care systems currently do not have an effective way to integrate all of this data to tell us if a patient is doing well or not. By using an artificial intelligence (AI) or big data approach, we can harness data and ask specific questions about how to best care for babies in critical care units or consider how to improve life for a particular patient using a precision medicine approach.

At Stanford Children's Health, physician-scientists are collaborating across specialty lines, and with Stanford University faculty, to develop innovative solutions to major challenges in the NICU. Our large neonatology care team taps into the knowledge we have developed in caring for older children and adults, and tackles clinical questions that need to be answered. We assemble multidisciplinary teams of neurologists, cardiologists, pulmonologists, endocrinologists, infectious disease specialists, whose unique perspectives develop strategies for disease processes or organ system challenges in infants. These collaborations routinely involve developmental biologists, molecular biologists, engineers, and computer scientists who are working in big data and AI to find the biologic medical signal in the data that correlates with our clinical questions. As we go through this process, we discover additional needs for developing technology, imaging techniques, or specific components such as small molecule metabolites or polymers.

Because we have a complete team of diverse experts at the table, there are few knowledge gaps and no limits on the questions we can ask. Everyone's perspective is vital. Engineers develop the means, e.g. the sensors, and neonatal professionals define the questions needing to be measured or solved.

Lawrence Prince is the Chief of Neonatal and Developmental Medicine at Stanford Children's Health.

One area where we've applied a multidisciplinary/big data approach is in understanding prematurity. The March of Dimes Prematurity Research Center at Stanford University is a transdisciplinary program bringing together over 130 scientists from neonatology, maternal-fetal medicine, OBGYN, genetics, microbiology, biology, biomedical informatics, computer science, data mining, data analytics, AI and other specialties to identify the causes of premature birth and consider multifaceted solutions and interventions. In 2018, Stanford researchers within the center developed a new, noninvasive blood test that can predict which women are at highest risk of going into preterm labor. The simple blood test uses modern genomic technology to reveal biomarkers that determine the risk of delivering preterm with 75% to 80% accuracy, and predicts the date of delivery as reliably as a prenatal ultrasound.[1]

Developing Non-Invasive Sensors to Guide Care

In the NICU, our goal is to foster normal human growth. Success requires measuring a child's physiological and developmental processes as noninvasively as possible. When we free premature babies from the tangle of wires that monitor their vital signs, we enhance their ability to grow naturally and gain the physiological benefits that come from bonding with their parents. To this end, we've started to develop noninvasive sensors to improve care at Stanford Children's Health. Currently, we're using novel tissue perfusion sensors and innovative applications for point-of-care ultrasounds.

Tissue Perfusion Sensors

Measuring blood pressure and oxygen saturation doesn't provide the whole story on tissue perfusion and cellular oxygenation. A microvascular approach is needed to determine if the heart is effectively delivering blood to the body's various tissues, and to guide our care in the NICU. At Stanford Children's Health, Valerie Chock, MD and colleagues have pioneered a noninvasive way to measure tissue perfusion with a sensor that incorporates near-infrared spectroscopy (NIRS) to detect oxygen levels in different regions of the body.

Researchers have applied the sensor, a small patch with a cable attached to the location doctors' want to measure, in various ways. Physician-scientists are using the tissue perfusion sensor to measure oxygenation in infants with congenital heart disease, cerebral injury, and kidney disease. Sensors are also being studied for their ability to measure blood flow in the gastrointestinal tract.

Dr. Chock and her colleagues are investigating the sensor's use as a continuous brain monitoring tool for estimating cerebral oxygenation in term and preterm infants at risk of cerebral hypoxia and ischemia.[2] Dr. Chock's team uses NIRS to detect the risk for cerebral injury and to improve hemodynamic monitoring in the NICU.[3] Another study from Dr. Chock and her colleagues investigated how using NIRS along with amplitude-integrated electroencephalography (aEEG) could improve our understanding of newborn neurodevelopmental physiology. The study found that using both modalities could improve detection of cerebral injury, especially in infants with hypoxic-ischemic encephalopathy (HIE). The researchers speculate the combined monitoring modalities could become the future standard for neonatal neuromonitoring.[4]

The tissue perfusion sensor has the potential to enhance care decisions, such as helping neonatologists determine when a transfusion is needed, or determining how blood flow relates to gut motility so we can discover better ways to feed premature infants, support their microbiomes, and achieve normal feeding in the future.

Point-of-care ultrasound use in the NICU

Only recently have ultrasounds become a part of the inquiry into a premature baby's health. In the NICU at Stanford Children's Health, we are performing point-of-care ultrasounds to serially monitor the overall growth of a baby. Point-of-care ultrasounds are also being used to monitor and diagnose common conditions related to prematurity including pulmonary disease, persistent pulmonary hypertension of the newborn (PPHN), patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), and other diseases.

At Stanford Medicine, physician-scientists researched the use of short-lag angular coherence (SLAC) doppler instead of conventional power doppler to eliminate clutter caused by neonate motion during a scan to image small vessels in the brain. With this method, researchers found visualization not only improved, but they also concluded SLAC was better at tracking blood flow in the brain over time. Investigators envision using SLAC to create a detailed map of a premature baby's brain to serve as a baseline for evaluating the functional impact of a transient ischemic attack (TIA).[5] Stanford researchers are exploring a variety of ways to put point-of-care ultrasound to use to better care of NICU patients.

Future Considerations of Noninvasive Sensor Use in the NICU

Advances in noninvasive sensor technology are growing globally. Sensors can potentially improve care by identifying serious infections sooner, supporting more accurate care decisions, and minimizing invasive testing and procedures. In the future, noninvasive monitors may allow measurement of multiple human developmental trajectories, ensuring optimal growth and facilitating earlier and safer discharges from the NICU. Current challenges include the need for smaller, lighter, more flexible, and wireless systems to provide important data while allowing babies to be babies.

Incorporating the use of noninvasive sensors in the NICU will also require ongoing education and training of staff and physicians along with updating current care guidelines. Hospital infrastructure must support not only the use of the sensors, but the ability to process, analyze, and present the data achieved in a comprehensive, useful manner. A hospital's culture needs to be one of innovation, with a willingness to implement novel ideas that drive future discoveries.

More research is needed to ensure noninvasive sensors address the important clinical challenges at hand. For example, novel sensors may one day allow us to monitor ongoing neurodevelopment in premature babies in real time. Such technology might allow us to measure future strategies aimed at improving brain growth, such as specific growth factors, nutritional interventions, metabolic therapies, or nurturing environmental changes. A future noninvasive sensor could possibly monitor EEG brain waves or incorporate imaging strategies to combine functional and morphogenic aspects of brain development.

Modern sensors could further improve our ability to diagnose serious infections. Using novel analyses of existing data to predict when babies have serious bacterial infections or sepsis has been years in making. We can currently mathematically measure vital signs to see when the human body isn't responding in a normal way. Stanford researchers are furthering this work to more accurately predict true infections. As sepsis continues to be a major cause of death in the NICU, rapid infection diagnosis using noninvasive sensors and data analysis can help us treat infants more quickly, save lives, and prevent unnecessary antibiotic use.

Conclusion

Multidisciplinary approaches driving innovations in device technology and data analysis are the future of precision medicine in the NICU. The ultimate long-view goal is to use noninvasive sensors to monitor discovery-based therapies that one day will cure currently untreatable diseases. Eventually, big data approaches might reveal patterns of health and resilience to disease, shifting our focus from managing disease to promoting health. Such data-driven advances in care could improve the health of premature children not just during infancy, but throughout their lifetime.

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Dart Not on Target

Leanna Barker, PharmD, George Smith, MD, Shabih Manzar, MD

The Dexamethasone: A Randomized Trial (DART)[1] study has been frequently referenced by neonatal practitioners when using dexamethasone in the neonatal population. However, postnatal use of steroids remains controversial.[2] Although some agreement is achieved with its use in the ventilated preterm infants, no consensus has been reached regarding its use in infants receiving non-invasive ventilation. Doyle et al[1] in their DART study concluded that a low-dose dexamethasone treatment after the first week of life facilitates extubation and shortens the duration of intubation among ventilator-dependent, very preterm/ extremely low birth weight infants; however, delayed use of dexamethasone per DART remains controversial.

We analyzed two cases recently where we noted sudden weight loss with the use of dexamethasone (Figures 1 and 2). A tapering dose was used per DART protocol (cumulative dose 0.89 mg/kg):

Day 1-3: 0.075 mg/kg per dose 12 hourly
Day 4-6: 0.05 mg/kg per dose 12 hourly
Day 7-8: 0.025 mg/kg per dose 12 hourly
Day 9-10: 0.01 mg/kg per dose 12 hourly for two days, then cease

As depicted in the Figures, an immediate weight loss was observed with the higher doses of dexamethasone in the first 3 days. Growth delay, including length and head circumference, has also been reported with the use of dexamethasone.[3-8]

In addition to the risk of weight loss and growth delay, the delayed use of postnatal steroids (PNS) after 33 weeks' post-menstrual age (PMA) was associated with greatest odds for death or neurodevelopmental impairment.[9] Another study by Harmon et al[10] showed higher odds of severe BPD among infants treated with PNS ≥ 50 days of life. Overall, the short-term respiratory benefits of delayed dexamethasone use do not translate to long-term benefits, nor do they outweigh the potential long-term adverse effects.

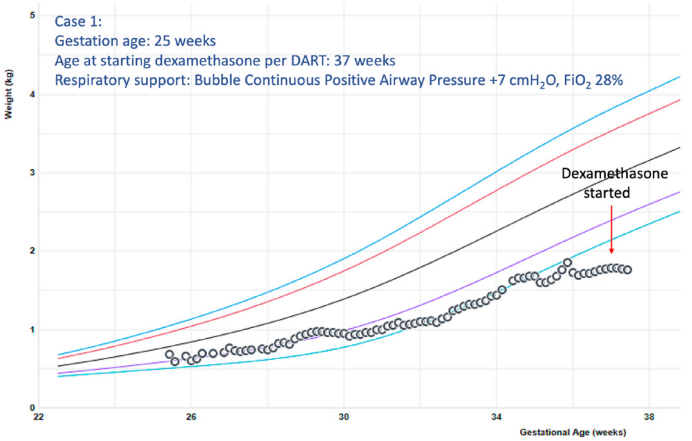

Figure 1

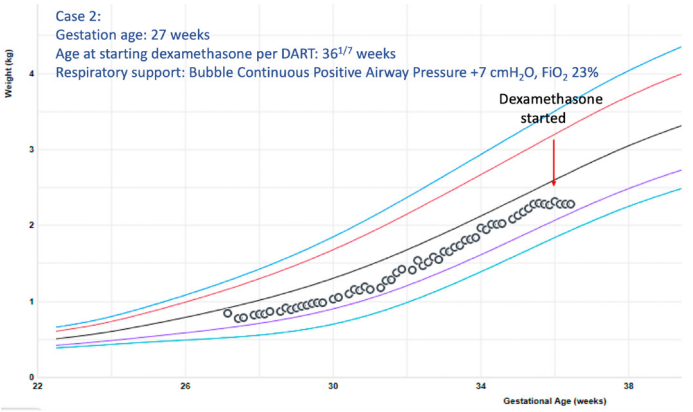

Figure 2

Based on our observation, we may conclude that the use of dexamethasone per DART should be carefully targeted. The appropriate patient for dexamethasone is the intubated infant on significant respiratory support in the early weeks of life, less than three weeks of life. Delayed use of dexamethasone per DART is not encouraged.

Leanna Barker is a Clinical Pharmacist at the Department of Pediatrics, Louisiana State University of Health Sciences (LSUHSC). George Smith is a Pediatric Resident at the Department of Pediatrics, LSUHSC-Shreveport. Shabih Manzar is an Attending MD from the Division of Neonatology, Department of Pediatrics, LSUHSC-Shreveport. Address correspondence to: Shabih Manzar, MD, Associate Professor, Department of Pediatrics, School of Medicine, Louisiana State University Health Sciences Center. 1501 Kings Highway, Shreveport, LA 71103. Telephone: 318-626-1623. Fax: 318-698-4305. Email: smanza@lsuhsc.edu.

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(AJOG), looked at 131 women of reproductive age (84 pregnant, 31 lactating and 16 non-pregnant), all of whom received one of the two new mRNA vaccines: Pfizer/BioNTech or Moderna. The vaccine-induced titers — or antibody levels — were equivalent in all three groups. Reassuringly, side effects after vaccination were rare and comparable across the study participants. "This news of excellent vaccine efficacy is very encouraging for pregnant and breastfeeding women, who were left out of the initial COVID-19 vaccine trials," said Andrea Edlow, a maternal-fetal medicine specialist at MGH, director of the Edlow Lab in the Vincent Center for Reproductive Biology and co-senior author of the new study. "Filling in the information gaps with real data is key — especially for our pregnant patients who are at greater risk for complications from COVID-19. This study also highlights how eager pregnant and lactating individuals are to participate in research." According to the Centers for Disease Control and Prevention, individuals who are pregnant are more likely to become severely ill with COVID-19, require hospitalization, intensive care or ventilation — and may be at increased risk for adverse pregnancy outcomes. The team also compared vaccination-induced antibody levels to those induced by natural infection with COVID-19 in pregnancy, and found significantly higher levels of antibodies from vaccination. Vaccine-generated antibodies were also present in all umbilical cord blood and breast milk samples taken from the study, showing the transfer of antibodies from mothers to newborns.

New Tool Helps Predict Preterm Birth, Neonatal Problems

Progesterone metabolites in plasma coupled with patient factors can help identify pregnant women at risk for preterm delivery and neonatal morbidity, researchers report. This research "breaks new ground," by demonstrating that 11-deoxycorticosterone (DOC) and 16-alpha-hydroxyprogesterone (16-alpha-OHP) in plasma can predict the extent of preterm delivery-associated neonatal morbidity and length of neonatal hospitalization when measured early in pregnancy, Dr Avinash Patil of the University of Arizona College of Medicine in Phoenix said. "Previously, much of the research in obstetrics focused purely on predicting gestational age at delivery as a surrogate (estimate) for neonatal outcomes," he said. "The findings of this research are particularly applicable to value-based healthcare models, which are increasingly prevalent for maternity care. The ability to screen a population of pregnancies and identify those at risk for poor neonatal outcomes can decrease healthcare costs while improving the health of newborns." An imbalance of progesterone metabolism has been linked to an increased risk of preterm delivery. In a prior study, Dr Patil and his colleagues found that DOC and 16-alpha-OHP, when measured during the late first trimester/early second trimester, can predict a woman's risk for spontaneous preterm delivery prior to 32 weeks. In the new study in PLOS ONE, they set out to determine if obstetric and demographic variables known during the pregnancy, when combined with these steroid-metabolite biomarkers obtained early in pregnancy, could predict the risk of preterm-delivery-associated neonatal morbidity in a low-risk population of pregnant women. The researchers quantified the two progesterone metabolites using mass spectroscopy from plasma of 58 pregnant women collected in the late first trimester or early second trimester. They combined the steroid-level data with patient demographic and obstetric history data in multivariable logistic regression models. Forty of the pregnant women
Continued on page 49…

Guided by Evidence-Based Care in the Use of Human Milk-Based Nutrition in the NICU: Learning from the Past

Sergio Golombek, MD, MPH, FAAP

Premature and extremely premature infants being cared for in hospital neonatal intensive care units (NICUs) are some of our most fragile and vulnerable patients. Their medical needs are great, and the stakes are high. We know now that their health, growth, and development during the critically important first weeks of life can have effects that will last a lifetime. Our charge to provide the best possible standard of care for these patients includes using evidence-based interventions whenever possible. Increasingly, studies have showed that human milk-based nutritional interventions reduce complications as well as achieve appropriate growth and development. However, it is very important to recognize that not all human-milk based products are interchangeable. Differences in collection, screening, and processing practices by various manufacturers can have a profound impact on the safety and efficacy of the resulting product. In the NICU, we must be guided by clinical evidence when deciding on products, as past experience has taught us that premature infants may not tolerate even the slightest margin of error (remember NICU history as related, for example, to oxygen toxicity and retinopathy of prematurity [ROP], overventilation and intraventricular hemorrhage [IVH], Phisohex soap and "bubbly" brain disease)! Equally important is the fact that premature infants are not just small children or adults, and what is good for an older patient may certainly be dangerous for a premature baby.

- As many as 18% to 29% of infants in the NICU may experience iatrogenic events.
- This rises to 57% for infants born at 24 to 26 weeks' gestation.

Errors of the Past

The NICU is arguably where the greatest effort is put into avoiding iatrogenic harm. Nevertheless, premature infants are exquisitely fragile, and, unfortunately, harm is sometimes unavoidable despite everyone's best efforts. An observational, prospective study by Ligi et al. that comprised all 388 patients admitted to the division of neonatology in an academic tertiary neonatal center in southern France between January 1 and September 1, 2005, revealed that 267 iatrogenic events were recorded in 116 patients. Of these, 34% were deemed to be preventable and 29% were severe. Two were fatal.[1] In a prospective, observational study of four NICUs in Israel, the rate of iatrogenic events was about 18%, with 8% of these events classified as life-threatening and 45% as harmful. Importantly, 83% were considered preventable. The rate of iatrogenic events was far greater—at 57%—among infants born at 24 to 27 weeks' gestational age.[2]

Complications have occurred as a direct result of misguided or inadequately studied interventions to improve outcomes. In a letter to the editor of the *Journal of Perinatology*, Miller provided a list of well-meaning medical interventions once delivered in the NICU that were ultimately demonstrated to produce more harm than good.[3]

Ramachandrappa and Jain identified rapid technological advances and new therapeutic modalities in the NICU as sources of iatrogenic harm—they wrote: "Some of them received critical evaluation and withstood the test of time; others managed to slip into use with less critical evaluation. Many of these therapeutic modalities are the major contributors to neoiatrogenesis. … [M]any interventions … although well intentioned, were never subjected to rigorous controlled trials." Examples they give include IV vitamin E resulting in multiorgan damage as well as hyperalimentation resulting in cholestasis, metabolic acidosis, and essential fatty acid deficiencies.[4]

The Adoption of Human Milk-Based Nutrition

An important advance in the management of premature infants in the NICU is the use of human milk-based nutrition. Over the past 20 years, there has been mounting evidence that use of human milk, particularly in the form of an *exclusive human milk-based diet* (EHMD), results in decreased morbidity and mortality as short-term NICU outcomes,[5-8] as well as improved neurodevelopmental outcomes during the first two years of life.[9-12] It is crucial to recognize, however, that *all* clinical research in this space has been conducted with milk obtained directly from patients' mothers, donated milk collected through the Human Milk Banking Association of North America (HMBANA), and/or human milk-based nutritional products made by Prolacta Bioscience (Duarte, CA).

- Only Prolacta human milk-based products, HMBANA milk, and mother's milk have been tested in studies demonstrating the clinical benefits of human milk-based nutrition in the NICU.

Sergio Golombek is a Professor of Pediatrics and Cl Public Health, SIBEN, The Iberoamerican Society of Neonatology.

Differences Among Human Milk Banks

As new players enter the human milk-based nutrition space, it is tempting to assume that the products they offer will be just as safe and effective as mother's milk, HMBANA milk, and Prolacta® products. After all, it is all breastmilk.

Nothing could be further from the truth!

At the present time, unfortunately, there are no federal-level quality and safety standards specific to human milk and human milk-based products in the US. As a result, some human milk manufacturers seem to be promoting unproven and untested manufacturing processes absent supporting clinical data on safety and efficacy. Lack of regulation poses a potential risk to NICUs and the fragile premature infants who rely on human milk nutrition for survival.

As with any human tissue, the benefits and safety of the final product depend on collection, screening, and processing practices. Blood transfusions are life-saving, but their benefits are compromised if they are a vector for transmission of blood-borne illness. The same is true for human milk. There is evidence that medications, drugs of abuse, and infectious pathogens can all be found to various degrees in human milk.[13] It is only via careful screening of donors and regular testing, including direct testing of milk itself, that we can be sure that human milk and human milk-based nutritional products are free from drugs, pathogens, or adulterants. While many human milk companies only test milk once pooled, Prolacta tests every individual milk donation received. According to Prolacta, its raw milk is directly tested using the nucleic acid amplification test (NAAT) to detect the presence of infectious disease-causing pathogens and bacteria in donated breastmilk, including human immunodeficiency virus type 1 and type 2 (HIV-1, HIV-2), human T-cell lymphotropic virus type I and type II (HTLV-I, HTLV-II), hepatitis virus B and C (HBV, HCV), and Zika virus. This is very important to ensure the safety of the final human milk product.

Benefits of an EHMD using Prolacta/HMBANA/mother's milk include:

- Reduced risk of complications (e.g., bronchopulmonary dysplasia, necrotizing enterocolitis, retinopathy of prematurity)[5-8]
- Adequate growth[6,16,17] when used as recommended
- Improved long-term neurodevelopmental outcomes[9-11]

Another factor that can have a profound impact on the safety and benefits of nutritional products made from human milk is the processing method. Currently, all human milk banks employ some sort of pathogen reduction or sterilization process, but not all of these processes are created equal. The goal is to eliminate pathogens while preserving the highest possible level of bioactive nutrients. Prolacta accomplishes this using a US Food and Drug Administration-regulated vat pasteurization process, similar to Holder pasteurization. Others rely on retort sterilization, a technique used in commercial food processing that lengthens the shelf life of the final product.

To discern the difference in bioactivity resulting from one pathogen reduction process to another, Lima et al. compared Holder pasteurization, retort sterilization, and no pasteurization in 36 breastmilk samples taken from 60 mothers.[14] While bioactivity was greatest with raw milk, Holder pasteurization retained far greater bioactivity than retort sterilization for both lysozyme activity (54% vs 0%) and secretory immunoglobulin A (sIgA) activity (87% vs 11%).[14]

The convenience of shelf-stable human milk products is attained at the expense of safety and bioactive proteins. While retort sterilization kills *almost* everything harmful, it does not eliminate bacterial enterotoxins produced by staphylococci or *Bacillus cereus* (*B. cereus*) that may be present in human milk and can be deadly to a premature infant.

Unique features of Prolacta screening and processing include:

- Direct testing of milk for drugs and adulterants
- NAAT testing for pathogens on every donation
- Vat pasteurization, to kill pathogens while preserving bioactive nutrients better than retort sterilization[14,15]

Meredith-Dennis et al. compared the composition of human milk samples acquired from three different milk banks in the United States: 1) Holder pasteurized "hospital grade" donor pooled milk from Mother's Milk Bank (San Jose, CA); 2) vat pasteurized pooled donor milk from Prolacta Bioscience®; and 3) retort sterilized pooled milk from Medolac Laboratories® (Lake Oswego, OR). Once again, retort sterilization came in last with respect to maintaining concentrations of bioactive compounds, including IgA, IgM, IgG, lactoferrin, lysozyme, α-lactalbumin, α-antitrypsin, casein, human milk oligosaccharides (HMOs), and HMOs containing fucose, sialic acid, and nonfucosylated neutral sugars ($P < 0.05$ for all comparisons of retort sterilization with Holder and vat pasteurization).[15]

In summary, applying commercial food processing methods to human milk yields products that may contain significantly less bioactivity, are not clinically proven, and are not as safe or effective in providing premature infants with the vital nutrition necessary to continue improving outcomes in the NICU.

Err on the Side of Caution

Vulnerable infant populations who rely on human milk-based products for vital nutrition deserve clinically proven products manufactured with the highest quality and safety standards available — studies that have been published in journals after being carefully reviewed.

It is not prudent to assume that human milk that has been collected, screened, and/or processed using differing tools and strategies will offer equivalent, or even near equivalent, safety and benefits. It is not evidence-based care if a tested human milk-based product (in terms of safety and efficacy) is substituted for an untested product produced by a different manufacturer.

Given the known differences in screening and processing of human milk-based nutritional products, adoption of products in the NICU that were not tested in large and/or multiple clinical studies is tantamount to conducting an uncontrolled experiment on our most vulnerable patients. As mentioned before, we have done this with other interventions, and the consequences were devastating. Let us learn from the past and reach for evidence-based solutions!

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Bedside Upper Gastrointestinal Series In The Neonatal Intensive Care Unit

Choeum Kang[1], Haesung Yoon[1], Hyun Joo Shin[1], Ho Sun Eun[2], Kook In Park[2] and Mi-Jung Lee[1]

Abstract

Background: In neonatal intensive care unit (NICU) patients with intubation status, fluoroscopic evaluation for the bowel is limited. This study was to evaluate the utility of bedside upper gastrointestinal (UGI) series with delayed radiographs (DR) for assessing duodenojejunal junction (DJJ) and small bowel passage in NICU patients with nonspecific bowel ultrasonography and contrast enema findings.

Methods: We reviewed clinical and imaging data for bedside UGI with DR of NICU patients from 2014 to 2019. Five abdominal radiographs were obtained at fixed time intervals of immediately after, 1 min, 5 min, 1 h, and 2 h following the administration of 5 cc/kg isotonic water-soluble contrast agent via the nasogastric tube.

Results: Twenty bedside UGI with DR were performed in 17 patients (weight range: 520-3620 g, age range: 0-4 months). Confidence identifying the DJJ was either good (n = 7) or equivocal (n = 8) at immediate or 1 min radiographs. The DJJ could not be evaluated in five from four delayed passage (including two meconium plug syndrome and one gastric volvulus) and one inadequate timing. There was only one case of intestinal malrotation, which was not detected on ultrasonography, but detected at the first UGI examination with good DJJ confidence.

Conclusions: Bedside UGI with DR can evaluate intestinal malrotation using immediate and 1 min delay and small bowel passage using 1 and 2 h delay images in NICU patients with nonspecific ultrasonographic and contrast enema findings. The majority with delayed contrast passages can have bowel pathology. Because of a small number of patients in this study, further studies with more infants are needed.

Background

Preterm neonates are defined as babies born alive earlier than 37 weeks of gestation. An estimated 15 million babies were born preterm in 2014, and this number is rising.[1] Complications due to preterm birth are the leading cause of death in children under 5 years of age, resulting in 1 million deaths in 2015.[2] Among preterm birth complications, neonatal bowel disorders include both congenital and acquired entities of the upper gastrointestinal (UGI) and lower gastrointestinal tracts.

The first diagnostic tool is ultrasonography for the evaluation of UGI obstruction and contrast enema for the cases with lower gastrointestinal lesion or no stool passage.[3,4] Bowel ultrasonography is good to detect the position of duodenojejunal junction (DJJ) to the point that 42% of patients with malrotation in a recent study did not require an UGI for confirmation.[5] However, the findings of bowel ultrasonography can be nonspecific or non-diagnostic in some cases and can be limited in cases with marked gaseous bowel distention. In addition, in preterm neonates with gasless abdomen and no stool passage even after bedside contrast enema, bowel passage evaluation is needed.

A fluoroscopic UGI and small bowel series is the next step for the evaluation of the neonatal UGI tract and bowel passage.[6] UGI examination is a cornerstone investigation for the delineation of proximal bowel anatomy and diagnosis of midgut malrotation.[7] Suspected malrotation can require emergent UGI study, because findings on radiographs and ultrasonography may appear normal.[6,8] However, preterm neonates often require bedside examinations because it can be dangerous to transport neonates from the neonatal intensive care unit (NICU) to other locations such as the fluoroscopy room. Intra-hospital transports of NICU patients increase the risk of clinical complications such as hypothermia as well as the need for respiratory support.[9] Therefore, with the increasing number of preterm neonates, the importance of bedside examinations has also increased.

The use of bedside UGI technique was suggested in 2014[10] and its efficacy for excluding malrotation in critically ill neonates for whom transportation from the NICU was risky was demonstrated. This bedside UGI can be helpful not only for the evaluation of DJJ location, but also for the assessment of bowel transit time using delayed abdomen radiographs. However, to date, no study has validated the bedside UGI technique in contexts other than within the original institution where it was developed. Moreover, no study has evaluated the usefulness of delayed radiographs after this bedside UGI technique in NICU patients. Therefore, the purpose of this study was to evaluate the utility of bedside UGI series including delayed radiographs for assessing the position of the

[1]Department of Radiology and Research Institute of Radiological Science, Severance Children's Hospital, Yonsei University College of Medicine, 50-1Yonsei-ro, Seodaemun-gu, Seoul 03722, South Korea. [2]Division of Neonatology, Department of Pediatrics, Severance Children's Hospital, Yonsei University College of Medicine, 50-1Yonsei-ro, Seodaemun-gu, Seoul 03722, South Korea.

DJJ, passage of stomach and small bowel loops, and clinical impact on critically ill neonates and infants in the NICU.

Methods

Patient data

Institutional Review Board of Severance Hospital approved this retrospective study (approval number, 4-2019-0366) and the requirement for obtaining informed consent was waived. However, informed consent for each procedure and examinations were obtained routinely from parents. We reviewed all bedside UGI examinations performed in our hospital NICU between 2014 and 2019. We generally conduct bedside UGI examinations with delayed abdomen radiographs in NICU patients who have persistent abdominal distention without obvious causes, including volvulus, in ultrasonography or have no stool passage even after contrast enema, and exhibit unstable clinical conditions to move to the fluoroscopy rooms. This study included all bedside UGI examinations and analyzed the indications and successes/failures on completion of the study.

We collected data through a review of electronic medical records from January 2014 to May 2019, including gender, gestational age at the time of birth, birth weight, age at the time of examination (weeks), indications of bedside UGI, and final diagnosis of abdominal findings. Final diagnoses were based on operative or pathologic findings, or clinical follow up results.

Bedside UGI technique

We performed bedside UGI technique with delayed abdomen radiographs as modified from the previous report.[10] The technique consisted of a baseline abdominal radiograph to evaluate bowel gas patterns and to locate the nasogastric tube. After adequate location of the nasogastric tube, 5 cc/kg of isotonic, water-soluble contrast medium (Iohexol 350 mg/mL, Omnipaque, GE Healthcare) was administrated via the nasogastric tube. Serial abdominal radiographs without position change were obtained at specific time intervals. The time intervals for examinations were immediately after administrating contrast medium and at 1 min, 5 min, 1 h, and 2 h after administrating contrast medium. If we were unable to evaluate the passage of contrast media due to delayed passage on 2 h follow up imaging, additional abdominal radiographs were also obtained at time intervals suitable to each patient's situation.

Image review

The serial radiographs were reviewed by a pediatric radiologist with 15 years of experience in pediatric radiology. Each abdominal radiograph was assessed for DJJ position and time required to identify DJJ, passage of contrast medium, and any complication such as leakage or pneumoperitoneum.

Normal DJJ position was defined as lying to the left of the left spinal pedicle, over the gastric antrum, and at the level of the duodenal bulb. We evaluated whether the DJJ was seen clearly or indistinctly. When the DJJ location was clearly identified on abdominal radiographs obtained at specific time intervals, it was considered to indicate good confidence. When the DJJ was not clearly identified, but the duodenum and jejunum were seen and the position of the DJJ could be extrapolated, it was considered equivocal. Cases in which the patient's position was rotated but normal DJJ position was presumed were considered equivocal.

Contrast passage and bowel transit time were objectively evaluated for the level of distal contrast at each specific time interval and subjectively assessed as normal range or passage delay. Additional findings such as volvulus or contrast leakage were also recorded. To evaluate clinical impact of bedside UGI studies, final diagnosis compared with imaging findings and management change including surgery were reviewed. Radiation dose from the radiographs were checked with tube voltage (kVp), tube current (mAs) and dose area product (DAP, mGy × cm^2).

We also reviewed for ultrasonographic studies conducted within 10 days prior to the bedside UGI study and checked findings about bowel pathology including malrotation by assessing the axis of superior mesenteric artery and vein, the course of duodenum posterior to the superior mesenteric artery and the presence of whirlpool sign.

Results

Demographics and radiation dose

All 20 bedside UGI examinations in 17 patients were included without any exclusions or examination failures occurring during the study period. We examined 7 boys and 10 girls. The median gestational age at the time of birth was 32 weeks (range, 24-40 weeks). The median birth weight was 1630 g (range, 520-3620 g). The median age at the time of UGI examination was 5.5 weeks, with a range of 0-42 weeks. One patient underwent UGI

Table 1 Confidence and evaluation of the duodenojejunal junction (DJJ) location

Confidence of DJJ location	DJJ location	Time to identify DJJ	Limitation	Final diagnosis
Good (*n* = 7)	Normal (*n* = 6)	Immediately after (*n* = 1) 1 min (*n* = 4) 5 min (*n* = 1)		Normal bowel (*n* = 6)[b]
	Malrotation (*n* = 1)	1 min (*n* = 1)		Malrotation (*n* = 1)[a]
Equivocal (*n* = 8)	Equivocal (*n* = 7)	Immediately after (*n* = 2) 1 min (*n* = 4) 1 h (*n* = 1)		Normal bowel (*n* = 5)[b] Malrotation (*n* = 1)[a] Meconium plug syndrome (*n* = 1)
	Rotated patient's position (*n* = 1)	1 h (*n* = 1)		Malrotation (*n* = 1)[a]
Could not evaluate (*n* = 5)			Delayed passage (*n* = 4)	Meconium plug syndrome (*n* = 2) Gastric volvulus (*n* = 1) Normal bowel (*n* = 1)
			Inadequate time (*n* = 1)	Meconium plug syndrome (*n* = 1)

[a]These three studies are from same patient
[b]These two studies are from the same patient

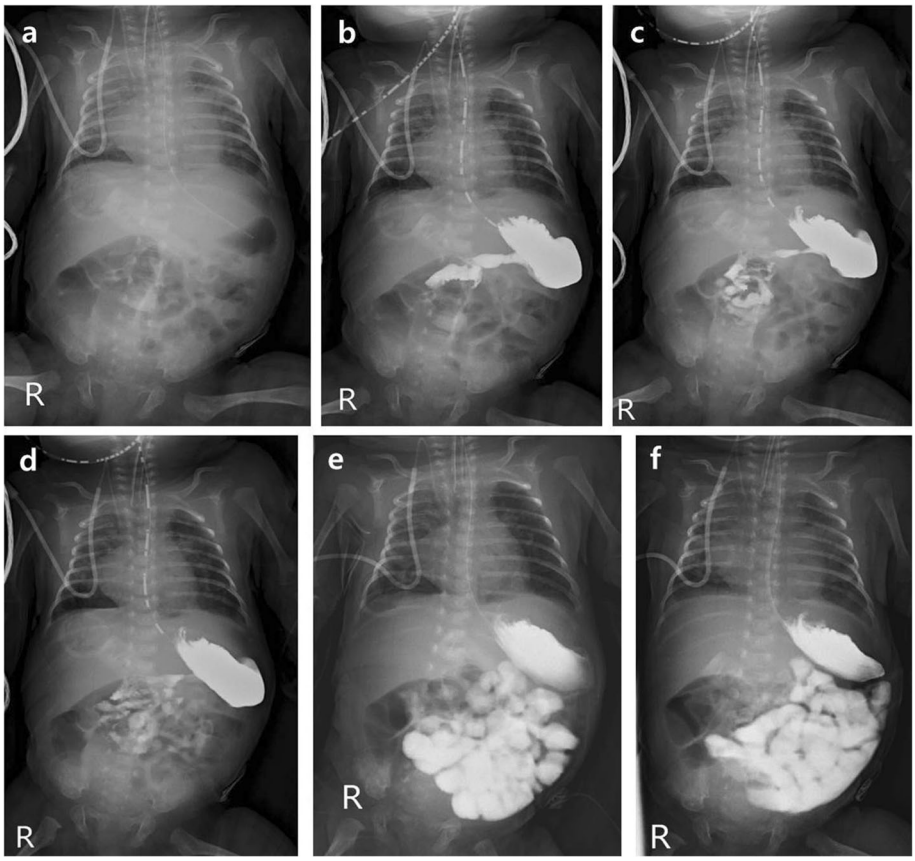

Fig. 1 A 4-week-old neonate with intestinal malrotation. Images from the bedside upper gastrointestinal series of a 4-week-old neonate who was born at the gestational age of 30 weeks. **a** A baseline abdominal radiograph, radiographs obtained **b** immediately after administration of contrast medium, **c** at 1 min, **d** at 5 min, **e** at 1 h, and **f** at 2 h. There were localized areas of gaseous bowel distention in the upper abdomen on the baseline image. Inferomedial location of duodenojejunal junction with mid-abdominal location of the jejunum suggesting malrotation are seen in the radiographs taken after **c** 1 min and **d** 5 min of delay. This was the first study out of the three repeated examinations in this patient. The patient's intestinal malrotation was surgically confirmed at the age of 10 months

examinations twice, at the ages of 14 and 20 weeks. Another patient underwent three examinations at 6, 15, and 42 weeks of age. All others underwent UGI studies only once. Indications for the 17 initial exams were bowel distension (n = 7), gasless abdomen (n = 3), vomiting or regurgitation (n = 3), and no stool passage (n = 2). Two examinations were conducted for UGI tract motility evaluation (n = 2). The indications for follow up UGI examinations were unchanged, with follow ups performed for bowel distension in all three studies.

Radiation dose parameters for each bedside UGI radiograph were 45-52 kVp (median, 50 kVp) and 1-2 mAs with the DAP of 3-8 mGy × cm^2 (median, 5.0 mGy × cm^2).

Ultrasonographic findings before bedside UGI study

All patients underwent bowel ultrasonography before bedside UGI study within 10 days interval. Most examinations (15/20, 75%) found no remarkable bowel pathology (n = 8) or only mild and nonspecific bowel wall edema (n = 7) on ultrasonography. There was no examination showed evidence of intestinal malrotation or volvulus on ultrasonography images.

Bedside UGI findings: DJJ evaluation

The bedside UGI study findings are summarized in Table 1 and all data are available in Supplementary Table 1. Of 20 examinations, seven (35%) demonstrated good DJJ confidence. For six cases, we noted normal location of the DJJ, while one case showed malrotation without volvulus (Fig. 1). The time required to identify the DJJ was about 1 min after administration of contrast medium in most patients (n = 5), and for the other two studies the times were immediately after administration of contrast medium (n = 1) and 5 min after administration of contrast medium (n = 1). There were no cases of contrast passage disturbance or medical or surgical bowel problems during follow up among patients with normal DJJ location. The patient with intestinal malrotation underwent Ladd's operation at the age of 40 weeks, 3 weeks after the third bedside UGI study, due to midgut volvulus.

In eight cases (8/20, 40%) the DJJ confidence was equivocal, including one study in a patient whose position was rotated. Among them, two studies were follow-up exams in a patient with known intestinal malrotation. There were no cases of contrast passage delay in this group, similar to the group with good DJJ confidence. The time to identify the DJJ was 1 min after administration of contrast medium in four cases (n = 4). In the other four studies, the DJJ location was identified immediately after (n = 2) or 1 h after (n = 2) administration of contrast medium.

Bedside UGI with delayed radiographs findings: contrast passage

Contrast passage was to ileum (14/20, 70%) or ascending colon (1/20, 5%) on 1 h delay images and to distal ileum (10/20, 50%) or colorectum (6/20, 30%) on 2 h delay images in most cases. Five cases showed delayed contrast passage on 1 h delay images,

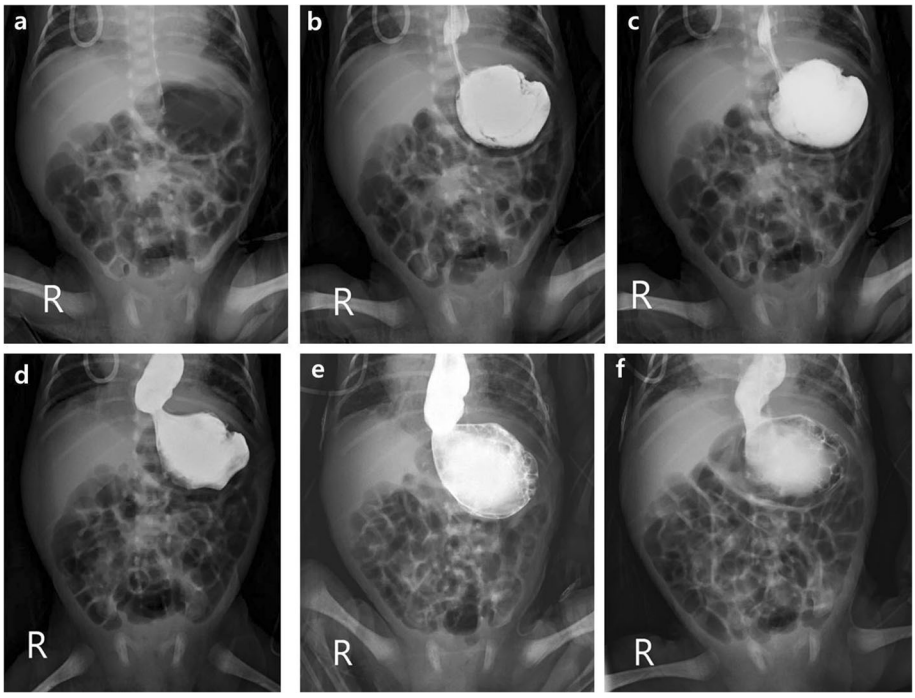

Fig. 2 A 3-week-old neonate with gastric volvulus. Images obtained from a 3-week-old neonate who was born at the gestational age of 30 weeks. **a** There is diffuse gaseous bowel distention, including the stomach, on baseline image. The contrast became localized only in the stomach with dilated distal esophagus **b** not only immediately, but also **c** 1 min and **d** 5 min delayed images. Distended distal esophagus and stomach without contrast passage was seen on **e** 1 h and **f** 2 h delayed images, with the proximity of the antrum and fundus suggestive of mesenteroaxial gastric volvulus. The findings were confirmed via surgery

and four of them showed delayed contrast passage even on 2 h delay images (passage to stomach in three cases and jejunum in one case). Finally, 3/4 of these cases of delayed passage had bowel pathology (one gastric volvulus and two meconium plug syndrome) (Fig. 2).

Bedside UGI findings and final diagnoses

The clinical follow up intervals ranged from 39 to 1978 days, with a median of 462 days. Finally, two patients each underwent surgery for gastric volvulus and midgut volvulus with malrotation, and these diagnoses were consistent with bedside UGI examinations. The rest of the patients were treated conservatively after confirming the DJJ location and contrast passage in bedside UGI studies. There were no false positive or false negative cases. No patients experienced contrast aspiration, leakage or bedside UGI study-related complications.

Discussion

Moving high-risk neonates and infants being treated in the NICU for imaging is burdensome. Even though abdominal ultrasonography is the first modality of choice to evaluate bowel pathology, it can be not easy in small patients with abdominal distention and often shows nonspecific findings without detectable cause. Moreover, some cases with or without bowel distention show no stool passage even after bedside contrast enema, and bowel transit time evaluation is needed. Therefore, additional imaging study that can be performed by the bedside is needed in these NICU patients. In this study, we assessed the usefulness of bedside UGI examinations including delayed abdomen radiographs. The DJJ location was usually identified immediate or 1 min after contrast administration with good or equivocal confidence for the diagnosis of intestinal malrotation. In cases with delayed contrast passage on 1 and 2 h delay images, 75% (3/4) of the patients had underlying bowel pathology. Therefore, bedside UGI examinations with fixed time interval are useful as screening and diagnostic tests for NICU patients who have only nonspecific ultrasonographic or contrast enema findings and are difficult to move.

Bedside UGI tests with delayed radiographs have several advantages. First of all, it is easy to examine patients without moving them. The low-dose abdominal radiographs routinely used in NICU patients may be conducted by taking several shots before and after the injection of contrast medium, so no special techniques are required. Tracing the duodenum and confirmation of intestinal malrotation by ultrasonography requires skill and experience on the part of the examiner, but the results of bedside UGI tests are not affected by the examiner's experience. Moreover, in cases with gaseous bowel distention which is one of the most common indications of bowel evaluation in neonates, detection of intestinal malrotation is more difficult with ultrasonography. Ultrasonography could not detect the one case with intestinal malrotation in our study, however, it is also known that up to 29% of malrotation can have normal axis of superior mesenteric artery and vein.[8] In addition, low-dose abdominal radiographs are part of the daily routine in NICU patients with abdominal distention, and it is estimated that conducting up to five more radiographs will not expose patients to more radiation than would a fluoroscopic UGI study.

Recording a conventional UGI series is considered to be the most important tool for the diagnosis of intestinal malrotation in neonates. For the diagnosis of malrotation in neonates and infants, conventional UGI series had the positive predictive value of 90% (47/52) with 4% (4/112) false negative rate in surgically confirmed cases.[7] There has been only one previous study of a bedside UGI series including 27 NICU patients,[10] and it showed a similar diagnostic performance of 78% (21/27) compared to our

study (15/20, 75%). There was only one case of malrotation that was recorded as a true positive, and there were no false negative cases in their study.[10] In the present study, we also observed only one case of intestinal malrotation during the study period, in which we performed repeated bedside UGI studies and finally confirmed malrotation surgically. There were no false negative or false positive cases in our preliminary study during the limited follow up period.

For the patient with malrotation observed in our study, we repeated bedside UGI examinations three times, and the time of DJJ location and diagnostic confidence were different at each of these examinations: 1 min at the first exam with definite malrotation, 1 h at the second exam with equivocal confidence due to rotated position, and immediately after at the third exam in the patient with equivocal DJJ location due to gaseous bowel distention.

This suggests that the optimal time for the confirmation of DJJ location is variable according to the patient's condition, and may change between observations even in the same patient. Consistently examining all patients at a single given time is likely to cause clinicians to miss the DJJ location. Therefore, several overlapping examinations with fixed time intervals, as used in this study, are mandatory. In addition, because the study is performed at bedside, not in the fluoroscopic room, confirmation of no rotation of patients and exact timing of radiographs is important to interpret bedside UGI study.

On the evaluation of contrast passage delay, there were two cases of meconium plug syndrome and one case of gastric volvulus, resulting 75% incidence of bowel pathology in passage delay cases. Midgut volvulus can occur in patients with intestinal malrotation and UGI series show the characteristic corkscrew-like appearance with duodenal redundancy.[11] In a previous study, the sensitivity of the UGI series was 96% (156/163) for the diagnosis of malrotation and 79% (30/38) for the diagnosis of midgut volvulus.[12] Gastric volvulus is uncommon and usually divided into two types of organoaxial and mesenteroaxial.[13] In our study, one patient demonstrated mesenteroaxial gastric volvulus as shown no contrast passage from stomach to duodenum during bedside UGI study. Meconium plug syndrome is a neonatal disease with transient large bowel obstruction relieved by the passage of the meconium plug.[14] In the presence of radiographic evidence of a dilated bowel, contrast enema is both diagnostic and therapeutic in most cases.[15] However, it is sometimes difficult to differentiate proximal and distal bowel obstruction in premature neonates with gaseous bowel distention. In our study, there were two cases with meconium plug syndrome who showed contrast passage delay on bedside UGI with delayed radiographs which was performed first rather than contrast enema.

There are some limitations in our study. First, we included only 17 patients and 20 studies, a number too small to be amenable to statistical analysis. Second, we only analyzed cases of bedside UGI series and did not compare bedside UGI series with conventional UGI series directly. However, there were no cases requiring additional study due to false negative results or unexpected emergency conditions during the study period. Third, there could be selection bias in this retrospective study, even though we did not have exclusion criteria for patient selection. Fourth, we evaluated only anteroposterior views without considerations of oblique or lateral views. If the DJJ cannot be clearly depicted on a straight anteroposterior view of the UGI series, lateral views could be helpful.[16] If the lateral view is absent, there are frequent false negative exams.[12] However, in intubated NICU patients, lateral positioning is not easy and may be dangerous. Trans-table lateral views are another option. Further evaluation is needed to establish the utility of this view. The other limitations of this study are that both the upper and lower gastrointestinal diseases were analyzed in combination and we could not directly compare bedside UGI finding with ultrasonographic findings because of only nonspecific findings on ultrasonography in our patients. Additional study is needed for these concerns.

Conclusions

Bedside UGI series with delayed radiographs including only five abdominal radiographs of fixed time interval (immediately after, 1 min, 5 min, 1 h, and 2 h) after administrating contrast medium can be useful to evaluate DJJ location, identify passage delay, and detect bowel pathology in NICU patients who have nonspecific findings on bowel ultrasonography and are at risk of adverse effects during transportation. Because this study is limited due to small number of patients, additional studies with more infants are warranted to confirm these findings.

Supplementary Information

The online version contains supplementary material available at https://doi. org/10.1186/s12887-021-02554-x.

Abbreviations

UGI: Upper gastrointestinal; NICU: Neonatal intensive care unit; DJJ: Duodenojejunal junction

Authors' contributions

All authors have read and approved the manuscript. - CK: Collected the data, analyzed and interpreted the data and drafted the manuscript. HY: Conceptualized the study, designed the study, collected the data and revised the manuscript. HJS: Collected the data, interpreted the data and approved the manuscript. HSE: Conceptualized the study, collected the data, and interpreted the data. KIP: Conceptualized the study, collected the data, and interpreted the data. ML: Conceptualized the study, designed the study, interpreted the data, revised and approved the manuscript.

Availability of data and materials

All data generated or analyzed during the current study are available in the Supplementary Table 1.

Ethics approval and consent to participate

Institutional review board of Severance Hospital approved this retrospective study (IRB number, 4-2019-0366) and the requirement for obtaining informed consent was waived.

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delivered preterm (<37 weeks) and 18 delivered at term (greater than or equal to 37 weeks). Ten women had elevated Hassan scores of 2 or higher, with the remaining 48 had scores of zero to one. Women delivering babies with an elevated Hassan score of two to four were more likely to have a higher BMI and deliver at a lower gestational age than peers delivering babies with a low Hassan score. Neonates with an elevated Hassan score were born at a lower gestational age and birthweight, were more likely to receive antenatal corticosteroids, have a lower five-minute Apgar score, and require resuscitative measures at birth compared to babies with a low Hassan score. The final neonatal morbidity model, which incorporated antenatal corticosteroid exposure and fetal sex, was able to predict high morbidity (a Hassan scale score of 2 or higher) with an area under the ROC curve (AUROC) of 0.975, with an optimal sensitivity of 90% and specificity of 96%. The final model characteristics included a positive predictive value (PPV) of 0.82 and negative predictive value (NPV) of 0.98. With the addition of the two biomarkers to the final model, the positive likelihood ratio for neonatal morbidity as measured with a Hassan Score of two to four was 21.6 (95% confidence interval, 5.48 to 85.21) for women with a positive test result. Newborns of women who screened positive with the model had significantly longer median length of hospital stays compared with newborns of women who screened negative (53 days vs. 4.5 days; P=0.0017). The researchers caution that this "discovery work and findings need to be validated in an independent cohort before we can fully implicate the changes in these biomarkers with preterm birth and neonatal morbidity." "The test is not yet clinic ready," Dr Patil said. "Steps that remain include validation of the results and meeting federal guidelines for development of new tests. The biomarkers in the study are very promising, so we are pushing forward to accomplish these milestones and make a new test reality.

Labor Induction at 39 Weeks May Improve Neonatal Outcomes

Labor induction at 39 weeks instead of 41 weeks may have a positive impact on neonatal outcomes, Aaron B. Caughey, MD, PhD, said at the 2020 virtual meeting of the American College of Obstetricians and Gynecologists. For much of the 20th century, term gestation has been defined as 37 weeks and beyond, said Caughey, of Oregon Health & Science University, Portland.
He noted several studies showing a U-shaped distribution in neonatal outcomes during the period from 37 weeks to 41 weeks for some outcomes, including Apgar scores. However, respiratory outcomes in a study from 2008 showed an increase, with meconium stained amniotic fluid increasing from 2.27% at 37 weeks to 10.33% at 41 weeks, and meconium aspiration increasing from 0.07% at 37 weeks to 0.27% at 41 weeks. The study "that really got everyone's attention" in terms of neonatal outcomes was published in 2009 in the New England Journal of Medicine. The cohort study included 24,077 elective cesarean deliveries between 37 and 42 weeks and reviewed a range of neonatal outcomes based on gestational age. The rate of any adverse outcome decreased from 37 weeks to 39 weeks, "but then started going back up again," Caughey said. He reviewed data from another study that factored in stillbirth and the risk of expectant management based on gestational age. A composite risk of perinatal death with expectant management was 15.4 deaths per 10,000 cases at 37 weeks and 39 weeks, but increased to 19.9 at 42 weeks. "The morbidity appears to have a U-shaped distribution and the mortality seems to favor delivery at 39
Continued on page 54…

Does High Dose Intravenous Acetaminophen Affect Liver Function For PDA Closure In Premature Neonate?

Reza Bahrami[1,2], Aida Ezzatabadi[3], Nima Mehdizadegan[1,2*] , Hamid Mohammadi[1,2], Hamid Amoozgar[1,2] and Mohammadreza Edraki[1,2]

Abstract

Objectives: The aim of this study was to collect consistent data on the efficacy and safety and evaluation hepatotoxicity of intravenous acetaminophen for the treatment of PDA in preterm infants.

Methods: This is an observational longitudinal prospective study on 46 preterm infants with PDA who treated with high dose of acetaminophen and evaluated with echocardiography and serum liver enzymes at Hafez and Zeinabiyeh hospitals from January 2016 to December 2019.

Result: Forty-six preterm infants with PDA treated with intravenous acetaminophen. Rate of closure of PDA was 82.6. There was no significant difference after treatment regarding AST, ALT, Albumin, total and direct bilirubin (*P* value > 0.05) and no adverse side effects were observed in association with intravenous acetaminophen.

Conclusion: High dose of acetaminophen is not more effective than that with standard doses although without hepatotoxic side effect for PDA closure.

Keywords: Acetaminophen, Hepatotoxicity, Liver enzymes, Patent ductus arteriosus, Premature infants

Introduction

A common complication in preterm neonates is patent ductus arteriosus (PDA). PDA is a congenital heart defect that communicate aorta into the pulmonary artery. Patency of PDA is necessary for fetal circulation. In healthy term neonates spontaneous PDA closure happen normally 24-72 h after birth because of increase pressure of oxygen in artery.

Incidence of PDA in preterm neonates between 30 and 37 week gestational age is 10%, those delivered in 25-28 week of GA is 80 and 90% is the percentage of infants born before 24 week GA that after a week would reduce to 2%, 65 and 87%.[3,4]

PDA intervention is controversial, and there is limitation of evidence to guide treatment. There is 3 strategies for closure of PDA in prelatures: Prophylactic management, treatment of clinically detected asymptomatic PDA, and treatment when the PDA is symptomatic neonates. Management of ductal closure include conservative treatments (i.e. fluid restriction, diuretics, etc. and waiting for spontaneous closure), pharmacological management and surgical ligation.[1,4-6]

FDA approved intravenous (IV) indomethacin and ibuprofen (cyclooxygenase inhibitors) as first drug use for treatment of PDA. These drug reduce the levels of prostaglandin that promote ductus arteriosus muscular wall constriction lead to fibrosis as anatomical ductal closure. Prenominated NSAIDs were successful in closure of PDA.[7]

NSAID adverse effect include renal function impairment, GI bleeding, necrotizing enterocolitis, intestinal perforation, thrombocytopenia, pulmonary hypertension and hyperbilirubinemia and etc.[1,3]

In recent years increasing acetaminophen administration for PDA treatment because this drug is has same efficacy as NSAIDs with fewer side effects because acetaminophen is prostaglandin synthesis inhibitor with affect at peroxidase site of prostaglandin H synthetase (POX) that differs from COX inhibitor.[1,3]

In neonates who have contraindication for treatment with indomethacin and ibuprofen or the NSAIDs have failed in closure of PDA administration of acetaminophen suggested as a choice before surgical ligation.[3]

Evaluating of advantages and disadvantages of pharmacological treatment by assessment of following outcomes: PDA closure failure (according to clinical evaluation or echocardiography criteria) as primary outcome; require surgical ligation of PDA, death, and selected any untoward medical occurrence, as secondary outcomes., not certainly having a causal association with treatment.[5]

Prospective trials may support more perception of acetaminophen effectiveness and safety as a further or even as a first-line option for closure of PDA in neonates.[8] Some hepatic side effects have been happened after usage of iv acetaminophen, which may determine a transient raise in liver enzymes or more serious acute liver toxicity.[9,10]

Acetaminophen itself not directly cause of hepatotoxicity in neonates but can be caused by N-acetyl-p-benzoquinoneimine

[1]Neonatal Research Center, Shiraz University of Medical Sciences, Shiraz, Iran. [2]Department of Pediatrics, Division of Pediatric Cardiology, Nemazee Hospital, Shiraz University of Medical Sciences, Shiraz 7193711351, Iran. [3]Medical School, Shiraz University of Medical Sciences, Medical School, Shiraz, Iran.

(NAPQI) produced by hepatic cytochrome P450 (CYP) as metabolite production-dependent mixed function oxidase enzyme. The action of NAPQI formation, sulphate elimination, and glucuronide production rate are not known in preterm neonates exactly.[11,12]

The existence of a large therapeutic serum concentration range for acetaminophen suggested by clinical evidence that demonstrate a low or absent hepatic toxicity in neonates.[3,7,13,14]

In this study we use high dose acetaminophen in infants with a clinically significant PDA to determine efficacy and hepatic side effects of high dose IV acetaminophen.

Methods

This is an observational longitudinal prospective study.

The study involved 46 preterm infants (gestational age < 37 weeks, mean birth weight 1099.3 g) with hemodynamically significant patent ductus arteriosus (HsPDA) born at our hospitals (Hafez and Zeinabiyeh) hospitals with the approval of the local ethics committee from January 2016 to December 2019. All patients were admitted in NICU with impression of prematurity.

Exclusion criteria

Preterm neonates with complex congenital heart disease, those were PDA as life saving for them, the cases who ibuprofen or indomethacin administrated before treatment with acetaminophen, and if the parents did not accept to enroll in this study.

Treatment eligibility criteria and drug administration protocol

Infants with a gestational age < 37 weeks and who Had clinical signs of significant PDA within the first week of life, diagnosed by pediatric cardiologist were enrolled in the study after obtaining written consent from their parents.

Echocardiography for diagnosis of PDA was done by pediatric cardiologist. We considered PDA as a hemodynamically significant if the patients had at least one of these finding after 3 days or later: Respiratory or cardiovascular compromise (dependency to invasive ventilation or CPAP without RDS or extubation failure), large shunt (LA/AO ratio > 1.5 or sign of LA and LV dilation), PDA larger than 2.5 mm after 1 week, diastolic reversal flow in abdominal aorta after 3 days old (without aortic valve insufficiency), more than 40 mmHg difference between systole and diastole.

Treatment with high dose of intravenous route acetaminophen was started at a dose 20 mg/kg every 6 h for 4 d, with echocardiographic evaluation performed at the end of the treatment. The usual dose of acetaminophen in our center was 10 mg/kg per dose and most references indicates maximum 15 mg/kg/dose q6h for acetaminophen.

Treatment success was defined as complete ductal closure on echocardiography. Pre- and post-treatment levels of liver enzymes (alanine transaminase (ALT), aspartate aminotransferase (AST), albumin, total and direct bilirubin) were measured for evaluation liver toxicity.

Data analysis was done with SPSS version 19 and p value < 0.05 consider as significant.

Result

Forty-six preterm infants were included in this study (January 2016 to December 2019). The median gestational age was 30.1 weeks (minimum-maximum: 25.5-36) and the median birth weight was 1099.3 g (800-3300) (28% below 1000 g and 59% between 1000 to 2000 g) were PDA positive born at our institution enrolled in this study for "first-line" i.v acetaminophen treatment (dose 20 mg/kg every 6 h for 4 d). PDA echocardiographic parameters before starting any i.v acetaminophen treatment are given in Table 1 In this study 23 patients (54%) were intubated and 10 patients was on CPAP. Dependency to ventilator or CPAP were the most common indications for PDA treatment. Only 6 patients had heart failure including clinical sign (poor capillary filling, respiratory distress or gallop rhythm) or echocardiographic features ejection fraction below 50% with dilated LV). Mean ejection fraction in all cases was 61.2 ± 7.6. The most common finding in echocardiography was tricuspid regurgitation (88%). Mitral regurgitation was seen in 23.9% of patients that 2 of them had moderate mitral regurgitation (most probably related to birth time hypoxia). LA/AO ratio was larger than 1.5 in 27 cases.

Medical treatment of the PDA was failed in 8 patients out of 46 infants and 1 patient because of sepsis, expired during course of treatment. The expired neonate had no sign of liver failure (Hepatomegaly, raising of liver function test or decrease of albumin level. The echocardiography of 46 patients with PDA on treatment cardiac ultrasound resulted in successful closure of PDA among 38 patients (82.6%).

Pre- and post-treatment levels of liver enzymes and bilirubin levels of all infants for the purpose of assessing the treatment's safety are summarized in Table 2.

There was no significant difference after treatment regarding AST, ALT, Albumin, total and direct bilirubin (P value > 0.05). Pre- and post-treatment levels of liver enzymes and bilirubin levels were normal in all patients, and no adverse side effects were observed in association with iv acetaminophen. The liver size and clinical examination of the 46 infants during and after treatment were normal. No sign and symptom of hepatotoxicity such as Jaundice, yellowish sclera and hepatomegaly were

Table 1 Baseline characteristics and echocardiographic data of preterm infants

		Count	Percent	Mean Bitrh weigh(gram)	Gestational age(weeks)
PDA size categories	Small:< 2 mm	14	30.4	1395	30.54
	Medium between 2 to 4 mm	19	41.3	1528.4	30.08
	Large:> 4 mm	9	19.5	1409	29.7
	Total	42	91.3		
Missing System		4	8.7		

seen during and after treatment with high dose acetaminophen. Bleeding tendency, GI bleeding and oliguria did not detect. 39 cases cured in first course of acetaminophen administration with clinically improved signs and symptoms of PDA. PDA closure improves dynamic compliance and increases tidal volume in preterm neonates receiving mechanical ventilation and a significant decrease in ventilator setting in our patients with PDA closure than those with failure of PDA closure. Seven infants failed in closure of PDA treated with second course combination acetaminophen and ibuprofen.

Discussion

Recent results reported on the use of acetaminophen in the treatment of PDA are highly promising, but adequately powered. The aim of this study is to collect consistent data on the efficacy and safety of high dose intravenous acetaminophen for the treatment of PDA in preterm infants. Drugs like cyclooxygenase (COX) inhibitors, e.g., indomethacin and ibuprofen, were used for closure of PDA. Acetaminophen is an alternative therapeutic approach for ductal closure through inhibition of prostaglandin synthetase activity. Although its efficacy in PDA closure has been approved.[7] Acetaminophen seems to inhibit peroxidase segment of the enzyme prostaglandin synthetase, unlike NSAIDs that inhibit cyclooxygenase pathway of this enzyme. NSAIDs are associated with significant adverse effects, including peripheral vasoconstriction, gastrointestinal bleeding and perforation, renal failure, oliguria and impaired platelet aggregation or inhibition of bilirubin glucuronidation in the liver and hyperbilirubinemia. These adverse effects emphasize the possible benefits of alternative treatment with acetaminophen for PDA management.[8]

We used acetaminophen as a first line in the treatment of PDA for 46 patients successfully without any significant complication. Our study showed that acetaminophen is effective in promoting ductal closure of PDA in preterm infants with 82.6% closure rate that was comparable with other treatment options in other studies. El mashad et al. 2017 showed The rate of closure in acetaminophen therapy in 100 neonates (80%) was more or less similar to that after ibuprofen (77%) and indomethacin (81%) therapy.[7] Hammerman et al. reported that they used acetaminophen in five cases because of different contraindications and unresponsiveness to the treatment. At all cases, the ducts were closed and positive responses were observed to the acetaminophen treatment.[15] Oncel et al. have reported eight cases who were unresponsive to ibuprofen or ibuprofen was contraindicated and received acetaminophen with successful PDA closure.[16]

Even higher rate of PDA closure (> 95%) was reported by some other investigators. In the study of Dash et al. enteral acetaminophen showed a PDA closure rate of 100% and no hepatotoxicity was detected. This surprising high result about acetaminophen efficacy deviates from other studies' results, but it must be considered that this RCT evaluated patients showing a mean GA of 31.6 weeks, higher than neonates in other trials. With better response to pharmacological treatment[17] PDA is known to be less responsive to cyclooxygenase inhibition in young preterm neonates due to higher expression of prostaglandin receptors in their PDA walls. H¨arkin et al. demonstrated a faster PDA closure rate in acetaminophen group (95%) than in placebo group. The authors used a different drug dosage, administering 20 mg/kg of acetaminophen at 24 h of life, followed by 7,5 mg/kg every 6 h for 4 days and the ductus closed at a mean of 177 h of postnatal life in treated patients versus 338 h in controls. However, GA influenced ductal closure; in fact, in extremely preterm infants (< 27 weeks' GA), acetaminophen did not show a significant effect; among these, 4 preterms (50%) required PDA ligation.[18] Le et al.[1] agree with the idea that acetaminophen seems to be a good alternative in PDA treatment and should be considered, in case of ibuprofen contraindication, before ligation. The author also recommends performing other trials because two studies published on 2013 found low iv acetaminophen success rate in small groups of patients (n = 29 and n = 3) Roofthooft et al.[19] had disappointing results with PDA closure after iv acetaminophen treatment with a low success rate of only 17%. This could be due to a late start of acetaminophen administration in their study (median of 14 days). But El Kuffash et al.[20] evaluated late treatment with iv acetaminophen beyond the 2nd week of life which became effective in PDA closure, avoiding PDA ligation.

In this study we try to use higher dose of acetaminophen and although we have no further complication related to this dose it did not lead to higher rate or PDA closure in compare to similar studies with lesser dose. The liver size and clinical examination of the 46 infants during and after treatment were normal.This result was in agreement with Jacqz-Aigrain et al.[14] who reported that neonates tend to suffer less from the hepatotoxic effects of acetaminophen than do older children. Hammerman et al. reported that acetaminophen could offer important therapeutic advantages over NSAI D (e.g., indomethacin and ibuprofen) as acetaminophen has no peripheral vasoconstrictive effect, so it can be given to infants with clinical contraindications to NSAI Ds;[5] But it seems higher dose of acetaminophen dose not promote this safe benefit and the optimum dose to achieve this effect is 10 to 15 mg per kg weight.

Table 2 Comparison between value before and after treatment (paired t test)

		Mean Serum level	Number	Std. Deviation	*P*-value
Albumin	Before	3.04	23	0.47	0.672
	After	3.09	23	0.60	
Total bilirubin	Before	5.43	40	3.03	0.258
	After	4.82	40	4.72	
Direct bilirubin	Before	0.46	29	0.16	0.123
	After	0.58	29	0.40	
AST	Before	32.78	31	23.91	0.205
	After	48.55	31	84.26	
ALT	Before	14.85	33	16.21	0.111
	After	19.36	33	18.48	

In our study bleeding tendency and GI complication did not detect. GI bleeding never seen that went with the results of other investigators. A safer profile in terms of gastrointestinal bleeding and hyperbilirubinemia after acetaminophen administration instead of ibuprofen has been described by Evans[21] and Terrin et al.[22] In contrast to our results. Dash et al.[17] reported striking high intestinal bleeding rate in the acetaminophen group (26.3%) The high intestinal bleeding rate in their study may be related to high osmolality of acetaminophen used in their study.

Limitation of this study

Due to significant cost and need of multiple sampling at specific time to achieve a reliable blood level of acetaminophen we did not perform acetaminophen blood level measurement for our patients. This study focus on short term hepatotoxicity effect of acetaminophen but it is worth to mentioned that acetaminophen has neurocognitive and fertility effect that need long term follow up and is beyond the scope of this article but it should be evaluated in a long term study. Also, the extend of hepatotoxicity could be evaluate by some less familiar testes such as acylcarnitines that were not performed in this study mostly due to need of more sampling in premature cases.

Conclusion

The goal of the studies on PDA management would be to perform an individualized therapy, choosing the for each of the patient characteristics, which could be the most effective as much as possible, personalized, and with the lowest side effects. Acetaminophen is as effective as indomethacin and ibuprofen in closure of PDA in preterm neonates with less side effects than both in compare to result of other studies. But higher dose than 10 to 15 mg/ kg/dose did not lead to higher rate of PDA closure and not recommended in addition of safe side effect profile with 20 mg/kg/dose and also it is safe in case of liver function based on liver function test in this study.

Abbreviations

PDA: Patent ductus arteriosus; LFT: Liver function test; LA: Left atrium; LV: Left ventricle; I.V: Intravenous; COX inhibitors: Cyclooxygenase inhibitors

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Authors' contributions

GhA: design and analysis and manuscript preparation. FA: Sample collection and data preparation, manuscript preparation. HM: Design, analysis, statistics and manuscript preparation. M.R.E: Data collection and Drafting, analysis. AAA: patient referring, data collection and Drafting. NM: critical revision and manuscript preparation. HA: drafting. MB: critical revision. KK: sample collection and data preparation. FP: critical revision, patient referring. AN: critical revision, patient referring. BG: patient referring, data collection and Drafting. All authors read and approved the final manuscript.

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Availability of data and materials

We state that the data used and/or analyzed during the current study are available from the corresponding author on reasonable request. Data sharing is applicable to this article and datasets were generated and analyzed during the current study and data sharing is allowed.

Ethics approval and consent to participate

All procedures performed in this study were in accordance with the ethical standards of the "Research Ethics Committee of Shiraz University of Medical Sciences" and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was submitted to and approved by the "Research Ethics Committee of Shiraz University of Medical Sciences" with Ethics code IR.SUMS.MED.REC.1395.68. The study was explained for the patients or guardians and informed consent forms were signed by them.

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weeks," he said. When it comes to induction of labor, medically indicated vs. nonmedically indicated does matter, Caughey said. Factors not considered a medical indication include impending macrosomia, increased risk for developing preeclampsia or intrauterine growth retardation, and a favorable cervix, he noted. "For indicated induction of labor, the risks and benefits of induction of labor vs. expectant management have been considered and weighed in by the field of experts that care for pregnant women," he said. With nonmedically indicated induction, experts "either decided that risks and benefits don't favor induction of labor, or we haven't come down hard on what the protocol might be. "It is important to consider the risks and benefits," said Caughey. The factors you want to include are neonatal outcomes, maternal preferences, and doctor preferences. However, "we want to be thoughtful about this intervention," because of the association of higher costs and increased risk of cesarean with induction of labor. As for timing of induction of labor, certain conditions favoring early-term induction include preeclampsia and gestational hypertension, chronic hypertension, diabetes, intrauterine growth restriction, nonreassuring fetal testing, cholestasis, placenta previa or accreta, and twins. As for late-term induction of labor, "at 41 weeks it is pretty clear that neonatal outcomes would be improved by delivery," he said. Historically, clinicians have raised concerns about the increased risk of cesarean delivery following induction of labor, but this risk has not been borne out in recent studies. Caughey said. However, in the findings from the ARRIVE trial, a large study of 6,106 women who were randomized to induction or labor or expectant management at 39 weeks, "they found a reduction in their risk of cesarean delivery compared to expectant management (18.6% vs. 22.2%). Rates of preeclampsia also were lower among induced women, while rate of chorioamnionitis, postpartum hemorrhage, and intensive care were similar between the groups. The researchers did not find significant differences in perinatal outcomes.

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