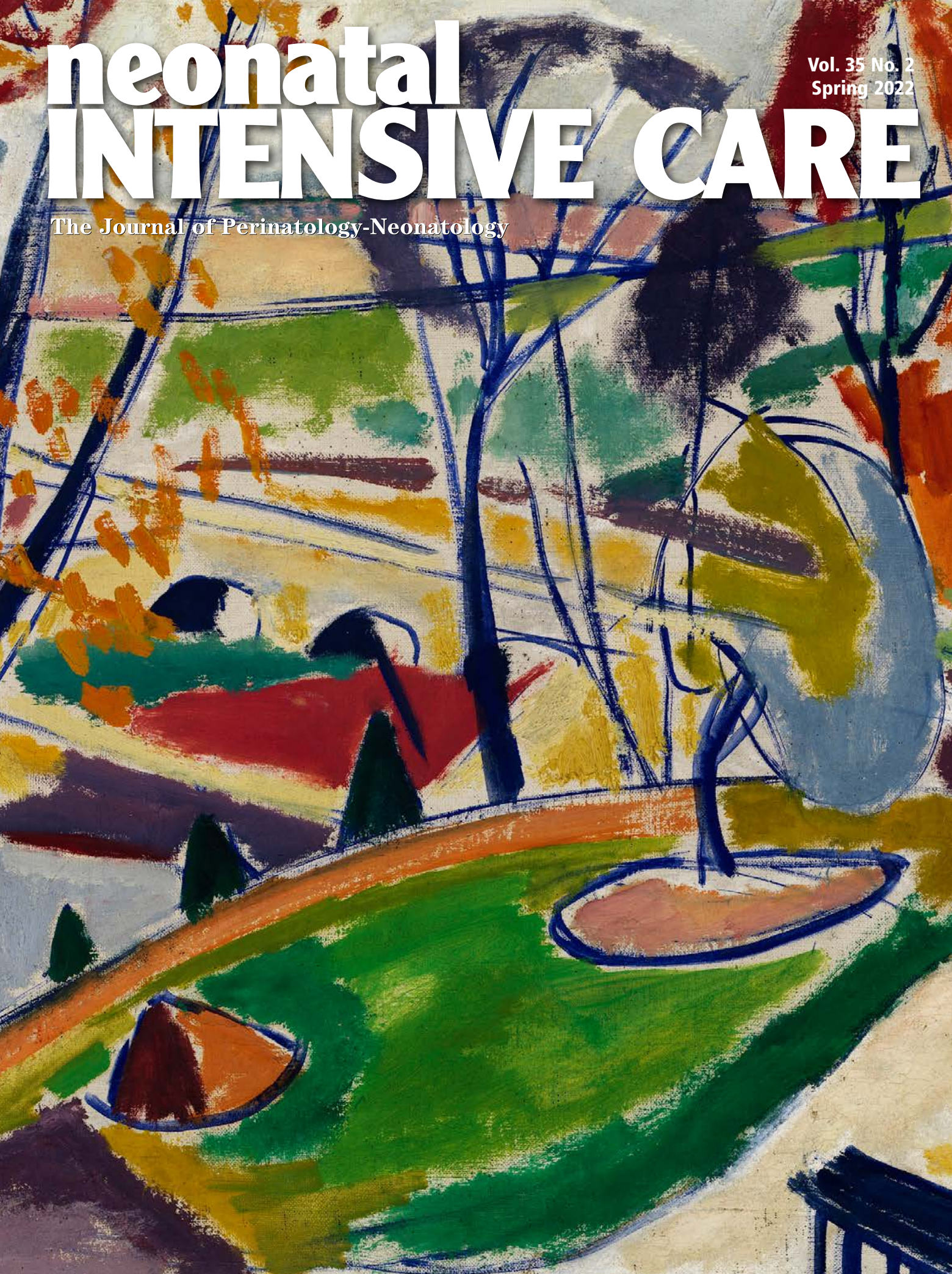


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University of Saskatchewan
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Los Angeles, CA

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Baby-Friendly' Steps Help Women Meet Prenatal Breastfeeding Goals

A first-ever study of the effect of evidence-based maternity care practices on prenatal breastfeeding intentions in women from low-income U.S. households shows that the use of “baby-friendly steps” during birth hospitalization made it possible for almost half to breastfeed exclusively for 1 month. Analyses of national data from a longitudinal study of 1,080 women enrolled in the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) revealed that 47% were able to meet their prenatal intention to breastfeed without formula or other milk for at least 30 days.

The odds of meeting prenatal breastfeeding intentions more than quadrupled when babies received only breast milk (risk ratio, 4.4; 95% confidence interval, 3.4-5.7), the study showed. Breastfeeding within 1 hour of birth was also associated with greater likelihood of breastfeeding success (RR, 1.3; 95% CI, 1.0-1.6). The study, led by Heather C. Hamner, PhD, MS, MPH, of the National Center for Chronic Disease Prevention and Health Promotion, Atlanta, was reported online in *Pediatrics*. “This study confirms the relationship between experiencing maternity care practices supportive of breastfeeding and meeting one’s breastfeeding intentions, and adds evidence specifically among low-income women, who are known to be at higher risk of not breastfeeding,” the study authors wrote. Women

from low-income households often face additional barriers to meeting their breastfeeding goals, including lack of access to professional lactation services, Hamner said in an interview. “We want physicians to know how important maternity care practices supportive of breastfeeding are to helping all women achieve their breastfeeding goals. Physicians can be champions for implementation of evidence-based maternity care practices in the hospitals and practices in which they work.” Hamner emphasized that physicians need to discuss the importance of breastfeeding with patients and their families, brief them on what to expect in the maternity care setting, and ensure women are connected to lactation resources. The American Academy of Pediatrics is working to increase physician capacity to support breastfeeding through the Physician Engagement and Training Focused on Breastfeeding project. For the study, Hamner and colleagues analyzed data from the longitudinal WIC Infant and Toddler Feeding Practices Study-2 (ITFPS-2), which assessed the impact of 6 steps from a 10-step maternity care protocol known as The Ten Steps To Successful Breastfeeding. These steps are part of the worldwide Baby-Friendly Hospital Initiative (BFHI), which has been shown to improve rates of breastfeeding initiation, duration, and exclusivity.

Enzyme Deficiency Linked to Preeclampsia

Both preeclamptic mice and human placentas from women with preeclampsia show a deficiency of S-nitrosogluthathione reductase (GSNOR), suggesting that the deficiency underlies the condition, researchers have found. Notably, in mice, ascorbic acid ameliorated most of the symptoms. “It was surprising that a mutation in a single gene, GSNOR, can cause many of the complications associated with preeclampsia,” Shathiyah Kulandavelu, PhD, of the University of Miami, said. “Preeclampsia is a multisystemic/multifactorial disease, and based on the heterogeneity of the clinical presentation, there may be different subtypes,” she said. “Therefore, identifying women showing dysregulation in nitrosylation and/or altered GSNOR activity levels may be an ideal target subpopulation for treatment with vitamin C or another antioxidant, permitting for a precision medicine approach for future clinical trials.” The disorder is characterized by “an increase in nitrosylated proteins and reactive oxygen species, suggesting a pathophysiologic

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Phone: 310-443-4109

Fax: 310-443-4110

E-mail: s.gold4@verizon.net

Web: www.nicmag.ca

Publisher/Editor in Chief

Steve Goldstein

Managing Editor

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role for dysregulation in nitrosylation and nitrosative stress,” Dr Kulandavelu and colleagues noted in their study, published in the *Journal of the American Heart Association*. The team showed that mice lacking S-nitrosoglutathione reductase, a denitrosylase that regulates protein S-nitrosylation, have a preeclampsia phenotype, including hypertension, proteinuria, renal pathology, cardiac concentric hypertrophy, decreased placental vascularization, and fetal growth retardation. In such mice, reactive oxygen species, nitric oxide, and peroxynitrite levels are elevated and, notably, mass spectrometry showed elevated placental S-nitrosylated amino acid residues. Further investigation showed that ascorbate reverses the phenotype, except for fetal weight, and reduces the difference in the S-nitrosoproteome. The team then studied human preeclamptic placentas and found decreased GSNOR activity and increased nitrosative stress, similar to the mouse model. “Deficiency of GSNOR creates dysregulation of placental S-nitrosylation and preeclampsia in mice, which can be rescued by ascorbate. Coupled with similar findings in human placentas, these findings offer ... insights and therapeutic implications for preeclampsia,” the authors wrote. Dr Kulandavelu said the team’s next research steps will include studying the placentas collected from preeclamptic mothers to identify biomarkers that could inform treatment and better mechanistic understanding of what may be driving the increased mortality and complications in both the mother and newborn. “Furthermore,” she said, “emerging data suggest that preeclamptic mothers and babies born to preeclamptic mothers are predisposed to future cardiovascular and renal disease. Therefore, the next step will be to follow these mothers and newborns later in life to examine whether they show early signs of cardiovascular and renal disease.”

Lara Kovell, MD, director of the Pregnancy and Heart Disease Clinic at the University of Massachusetts, Worcester, said in an email, “This is an exciting study that helps to shed light on the pathology of preeclampsia” Regarding specific findings, she noted, “Antioxidant treatment rescued preeclampsia phenotypes in the mouse model. However, prior human studies on antioxidants have not ended up helping to prevent preeclampsia. The authors suggest that is because of multiple preeclamptic phenotypes, with likely more than one potential cause. Eventually, precision medicine should help to determine who would benefit the most from these antioxidant treatments. “Another concern is that in the mouse model, fetal weight did not improve in the GSNOR knockout mice treated with ascorbate,” she said. “So, while the maternal condition improved, the infant outcomes were not uniformly improved.”

Obesity, Diabetes in Women Linked to Their Birth Weight

In a study of just over 4000 middle-aged women in China, researchers found: A U-shaped relationship between low, normal, or high birth weight and risk of adult obesity, with the lowest risk at a birth weight of 3000 g (the midpoint of the normal birth weight range of 2500 g to < 3500 g); risk of type 2 diabetes in normal-weight women was highest in those with a low birth weight and decreased as birth weight increased. Among these middle-aged women, those with a high birth weight had a high obesity rate but a low prevalence of type 2 diabetes, whereas those with a low birth weight had a high obesity rate and a high prevalence of type 2 diabetes. Women with overweight or obesity had a higher prevalence of type 2 diabetes, independent of their birth weight. Women with a lower birth weight and overweight or obesity had the highest prevalence of type 2 diabetes. The results confirmed that overall low birth weight is associated with increased risk of having type 2 diabetes in middle-aged women.

The results also showed that overweight or obesity in middle age upped the risk of diabetes, independent of birth weight.

Pediatrics Group Stresses Benefits of Vitamin K Shots for Infants

After the American Academy of Pediatrics (AAP) began recommending vitamin K shots for newborns in 1961, infant bleeding as a result of vitamin K deficiency plummeted. The life-threatening disorder is so rare that some parents now question the need for injections to safeguard against it. The situation amounts to “a failure of our success,” Ivan Hand, MD, a co-author of a new AAP statement on vitamin K, said. Much like diseases that can be prevented with vaccines, vitamin K deficiency bleeding isn’t top of mind for parents. “It’s not something they’re aware of or afraid of,” he said. In 2019, however, the AAP listed public education about the importance of the shots in its 10 most important priorities. The policy update urges clinicians to bone up on the benefits and perceived risks of vitamin K deficiency, which is essential for clotting, and to “strongly advocate” for the shot in discussions with parents who may get competing messages from their social circles, the internet, and other healthcare professionals. Hand, director of neonatology at NYC Health + Hospitals Kings County in Brooklyn, said clinicians walk a line between educating and alienating parents who favor natural birth processes. “We’re hoping that by talking to the families and answering their questions and explaining the risks, parents will accept vitamin K as a necessary treatment for their babies,” he said.

Vitamin K does not easily pass through the placenta and is not plentiful in breast milk, the preferred nutrition source for newborns. It takes months for babies to build their stores through food and gut bacteria. Infants who do not receive vitamin K at birth are 81 times more likely to develop late-onset vitamin K deficiency bleeding, which occurs a week to 6 months after birth, according to the Centers for Disease Control and Prevention. One in five babies with the disorder dies and about half have bleeding in the skull that can lead to brain damage.

LGBTQ Parents Fare Worse Giving Birth

Members of the LGBTQ community who give birth appear to have a greater risk of hypertensive disorders of pregnancy and postpartum hemorrhage, according to new research presented at the annual meeting sponsored by the Society for Maternal-Fetal Medicine.

“Our study found that birthing patients in likely sexual and gender minority partnerships experienced disparities in clinical outcomes,” Stephanie Leonard, PhD, an epidemiology and biostatistics instructor at the Stanford (Calif.) University division of maternal-fetal medicine and obstetrics, told attendees at the meeting. The disparities are likely because of various social determinants and possibly higher use of assisted reproductive technology (ART). The findings establish “how these are significant disparities that have been largely overlooked and set the groundwork for doing further research on maybe ways that we can improve the inclusivity of obstetric care.” Jenny Mei, MD, a maternal-fetal medicine fellow at the University of California, Los Angeles, who attended the presentation but was not involved in the research, said the findings were “overall unfortunate but not surprising given the existing studies looking at LGBTQ patients and their poorer health outcomes, largely due to lack of access to health care and discrimination in the health care setting.” Leonard described the societal, interpersonal, and individual factors that can contribute to health disparities among gender and sexual minority patients.

“At the societal level, there are expectations of what it means to be pregnant, to give birth, and to be a parent. At the community level, there’s the clinical care environment, and at the interpersonal level, there’s an obstetrician’s relationship with the patient,” Leonard said. “At the individual level, most notably is minority stress, the biological effects of the chronic experience of discrimination.” It has historically been difficult to collect data on this patient population, but a change in the design of the California birth certificate made it possible to gather more data than previously possible. The updated California birth certificate, issued in 2016, allows the parent not giving birth to check off whether they are the child’s mother, father, parent, or “not specified” instead of defaulting to “father.” In addition, the parent giving birth can select mother, father, parent or not specified instead of being “mother” by default. The researchers classified sexual and gender minority (SGM) partnerships as those in which the parent giving birth was identified as the father and those where both parents were identified as mothers. Non-SGM minority partnerships were those in which the birthing parent was identified as the mother and the non-birthing parent was identified as the father.

Assisted Reproduction Tied to Increased Risk for Vascular, Pregnancy Complications

Women who conceive with assisted reproductive technology (infertility treatment) may be at increased risk for vascular and pregnancy-related complications, according to new research published today in a special Go Red for Women issue of the Journal of the American Heart Association, an open access, peer-reviewed journal of the American Heart Association. Assisted reproductive technology, also known as ART, is the umbrella term for infertility treatments in which eggs or embryos are handled to improve the odds of pregnancy. These treatments may involve administering medication to control timing of ovulation,

as well as procedures such as in vitro fertilization (IVF) or intracytoplasmic sperm injection, during which a woman’s eggs are surgically retrieved and fertilized in a laboratory before being implanted back into her uterus. According to 2019 statistics from the U.S. Centers for Disease Control and Prevention, the use of assisted reproductive technology has more than doubled during the past decade. More than 2% of infants born in the U.S. every year are conceived with assisted reproductive technology. Since 1978, ART has contributed to the birth of more than 5 million infants worldwide.

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Perinatal Deaths From COVID Show ‘Extensive’ Placental Damage

Recent evidence has shown women who contract COVID-19 during pregnancy are at increased risk for pregnancy loss and neonatal death. Now, an analysis of pathology data from dozens of perinatal deaths shows how. Unlike numerous pathogens that kill the fetus by infecting it directly, SARS-CoV-2 causes “widespread and severe” destruction of the placenta that deprives the fetus of oxygen, a team of 44 researchers in 12 countries concluded after examining 64 stillbirths and four neonatal deaths in which the placentas were infected with the virus. They noted that such damage occurs in a small percentage of pregnant women with COVID, and that all the women in the study had not been vaccinated against the disease. The findings

were published online today in the *Archives of Pathology & Laboratory Medicine*. Nearly all placentas had each of three features that pathologists have dubbed *SARS-CoV-2 placentitis*: large deposits of fibrin, a clotting protein that obstructs the flow of blood; death of cells in the trophoblast; and an unusual form of inflammation called *chronic histiocytic intervillitis*. Some had other abnormalities that could have exacerbated the condition. The researchers called the extent of damage “striking,” affecting 77.7% of the placenta on average. The virus did not appear to harm fetal tissue, but placental damage “was

extensive and highly destructive,” they write. Notably, none of the women in the analysis was known to have severe COVID.

Endometriosis Not Linked With Preterm Birth, New Study Finds

Researchers evaluating whether endometriosis is linked with preterm birth found no such association in a multicenter cohort study of more than 1300 women. These new findings, which were published online in *JAMA Network Open*, suggest that changing monitoring strategies to prevent preterm birth for women with the disease may not be necessary. The research team, led by Louis Marcellin, MD, PhD, with the Department of Obstetrics and Gynecology at Université de Paris, in France, also found that disease phenotype or whether the preterm birth was induced or spontaneous did not appear to alter the result. Those results differ from previous research. Data on the phenotypes and their link with preterm birth have been scarce, but previous studies have shown the risk for preterm birth is more pronounced in women who have deep endometriosis than in women with ovarian endometriosis. Marcellin said, “Little is known about the impact of endometriosis on obstetric outcomes. In contrast to previous studies, we reported no differences in the risk for preterm delivery between women with endometriosis (34 of 470 [7.2%]) and those without endometriosis (53 of 881 [6.0%]), even when adjusted for multiple factors.” The authors accounted for mother’s age, body mass index before pregnancy, birth country, number of times the woman had given birth, previous cesarean delivery, and history of preterm birth. After adjusting for potential confounders, endometriosis was not associated with preterm birth (adjusted odds ratio, 1.07; 95% CI, 0.64 – 1.77). The researchers found no differences among preterm births based on a mother’s endometriosis phenotype. Those phenotypes include Isolated superficial peritoneal endometriosis, ovarian endometrioma, and deep endometriosis. “Monitoring pregnancy beyond the normal protocols or changing management strategies may not be warranted in cases of endometriosis,” Marcellin said.

Pregnancy Outcomes Improving After Treatment for High-Grade Cervical Neoplasia

The risk for pregnancy-related complications following treatment for grade-3 cervical intraepithelial neoplasia (CIN 3) has declined over time, thanks to advances in treatment, a new study indicates. However, women treated for CIN 3 should still be managed as “high risk” to reduce risk of preterm birth, infant sepsis, and other adverse outcomes, researchers write in *Annals of Internal Medicine*. Treatment for CIN 3 removes or destroys part of the cervix and might subsequently influence pregnancy outcomes. However, over the years, treatment for CIN 3 has advanced, with more conservative treatment methods used today. The researchers used data from five national Swedish registries to investigate pregnancy outcomes in women diagnosed with CIN 3 between 1973 and 2018. They identified 78,450 births after a maternal CIN 3 diagnosis and matched them to 784,500 births to women without a CIN 3 diagnosis. Even after accounting for family factors, a history of treatment for CIN 3 was significantly associated with adverse pregnancy outcomes, including preterm birth, especially extremely preterm (odds ratio, 3.00) or spontaneous preterm (OR, 2.12); infection-related outcomes, including chorioamnionitis (OR, 3.23) and infant sepsis (OR, 1.72); and early neonatal death (OR, 1.83). A sibling-comparison analysis that included 23,199 babies born to women diagnosed with CIN 3 and 28,135 born to their sisters without a CIN 3 diagnosis rendered largely similar results. Of note, say the researchers, the risk for all pregnancy complications in women

treated for CIN 3 declined over the 46-year study period time and the risk for infant death disappeared. A possible explanation for this is less-invasive treatment methods for CIN 3. “Our results indicate that caution should be taken when applying a screen-and-treat approach to women of reproductive age, given that over treatment of the cervix may have a detrimental effect on future pregnancies,” write Dr Wei He with Karolinska Institutet in Stockholm and colleagues. “In the context of a screen-and-treat strategy in countries where diagnostic resources are limited, patients are often treated after a positive result on a screening test, without additional diagnostic confirmation. As such, a large proportion of women with low-grade lesions or with a healthy cervix may be treated unnecessarily, which may consequently lead to adverse outcomes in future pregnancies,” they caution.

Vaginal Progesterone for Preterm Birth Has Mixed Results

The potential effectiveness of using vaginal progesterone to prevent preterm birth in two different populations was the focus of a pair of studies with mixed results at the annual meeting sponsored by the Society for Maternal-Fetal Medicine. One study found no benefit from vaginal progesterone in those with first trimester bleeding, while the other, in a head-to-head comparison with 17-alpha-hydroxyprogesterone caproate (17-OHPC), found vaginal progesterone performs similarly to 17-OHPC in singleton pregnancies with a history of preterm birth. While the first study does not suggest any changes in clinical practice, the second one suggests that vaginal progesterone is an alternative to 17-OHPC, as the American College of Obstetricians and Gynecologists currently recommends. SMFM currently only includes 17-OHPC in its guidelines. “In otherwise low-risk pregnancies with first trimester bleeding, progesterone should not be prescribed for the prevention of miscarriage or prematurity,” Haim A Abenham, MD, MPH, of the Jewish General Hospital at McGill University, Montreal, told attendees in his presentation. “Publishing the negative result is so important because this helps the overall body of literature reduce the amount of publication bias that exists in the literature,” Michael Richley, MD, an ob.gyn. and maternal-fetal medicine fellow at the University of California, Los Angeles, said in an interview. Dr Richley was not involved in the research but attended the presentation. Most preterm birth occurs in pregnancies with no identifiable risk factors, but first-trimester bleeding may indicate subchorionic hemorrhage from placental detachment, which can increase the risk of preterm birth. Other risk factors where progesterone has previously shown effectiveness in reducing preterm birth risk include short cervix and a history of prior preterm birth. The first study (PREEMPT) was a double-blind, randomized controlled trial conducted at six Canadian hospitals with 533 women. The participants all experienced bleeding within the first 14 weeks of pregnancy and a documented subchorionic hemorrhage. The trial excluded those who already required progesterone, had contraindications to progesterone or had an alternate cause of bleeding. The intervention group included 264 women randomly assigned to use 200 mg of micronized progesterone administered with a vaginal suppository at bedtime, while the placebo group included 269 women who used a vaginal suppository with no medication, both administered until 34 weeks of pregnancy. The groups were not significantly different in age, race, or former pregnancies, live births, and miscarriages. They were also similar in clinical characteristics of bleeding and subchorionic hemorrhage.



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Data Suggests *B. infantis* EVC001 Improves Preterm HMO Utilization

A study published in January in *Frontiers in Pediatrics* shows *B. infantis* EVC001 is well-tolerated and improves human milk oligosaccharide utilization in preterm infants in the neonatal intensive care unit. Not all infants carry specialized gut microbes such as *Bifidobacterium infantis* (*B. infantis*), meaning they cannot fully digest human milk oligosaccharides (HMOs), an important constituent of human milk. In fact, according to one analysis of samples taken from across the United States, more than 90% of infants studied were not seeded with *B. infantis*. Research has shown that *B. infantis* EVC001 converts the full array of HMOs in human milk into compounds usable by the infant, making it an ideal candidate to stabilize gut function and improve nutrition in preterm infants. A prospective, open-label study was conducted at one of the most technologically advanced NICUs in the nation to evaluate the tolerability of *B. infantis* EVC001 and its effects on the fecal microbiota in preterm infants in the NICU. “This study clearly establishes the tolerability of activated *B. infantis* EVC001 in preterm infants,” said Dr Sarah Bajorek, DO, neonatologist and co-lead author of the study. “There is so much upside to activated *B. infantis* EVC001 effectively populating the infant intestine, as it can potentially outcompete pathogenic bacteria and improve the health of infants.” The study followed 30 preterm infants divided into two matched groups. Fifteen control infants received no EVC001 and 15 infants received once-daily feedings of *B. infantis* EVC001 (8.0×10^9 CFU) in MCT oil. Control infants were discharged before enrollment of EVC001 group to reduce cross-colonization. Clinical information regarding medications, growth, nutrition, gastrointestinal events, diagnoses, and procedures was collected throughout admission. Infant stool samples were collected at baseline, Study Days 14 and 28, and 34-, 36-, and 38-weeks of gestation to assess the taxonomic composition of the fecal microbiota, functional microbiota analysis, *B. infantis*, and excretion of human milk oligosaccharides (HMOs). Researchers found no adverse events or tolerability issues related to EVC001. Moreover, control infants had no detectable levels of *B. infantis*, while EVC001 infants achieved high levels of *B. infantis* by Study Day 14, correlating with fewer fecal HMOs, indicating better HMO utilization in the gut. To conclude, *B. infantis* EVC001 was shown to be safe, well-tolerated, and efficient in colonizing the preterm infant gut, able to increase the abundance of bifidobacteria that metabolizes HMOs, resulting in significantly improved utilization of human milk. “This study further builds strain-specific evidence regarding the safety and tolerability of activated *B. infantis* EVC001,” said Rebecca Duar, PhD, co-lead author of the study and Principal Scientist at Evolve BioSystems. “This study is a positive step in setting the stage for future research into the potential health benefits of the single-strain probiotic *B. infantis* EVC001 in the hospitalized infant population.”

After Preterm Birth, Family Care May Boost Dads’ Mental Health Too

After the birth of a preterm baby, new fathers appear to derive as much benefit from a family-integrated-care model in the neonatal ward as do new mothers, with less stress and improvements in mental health, according to a prospective study conducted in the Netherlands. “Integrating the family as a relevant and irreplaceable part of the health care team and creating an environment welcoming continuous parental presence and active participation in neonatal care, or family integrated care (FICare), has been shown to be beneficial for mothers and their

newborns,” the study team explains in *JAMA Network Open*. But during the newborn’s stay, fathers often feel anxious and excluded from the baby’s care and decision-making and few studies and interventions have focused on their mental health and participation in neonatal care, they point out. To investigate, Dr Anne van Kempen of the Department of Pediatrics and Neonatology at OLVG, in Amsterdam, and colleagues enrolled 263 fathers of preterm newborns staying in the hospital for more than one week; 126 were enrolled in a FICare model consisting of single family rooms with couplet-care for the mother and newborn and 137 were enrolled in standard neonatal care (SNC) in open bay units. Mental health and parent-participation surveys were completed by 89 fathers in FICare (71%; mean age, 35 years) and 93 fathers in SNC (68%; mean age, 36 years). At discharge, FICare fathers perceived less stress (adjusted beta, -10.02; 95% CI, -15.91 to -4.13) and potentially participated more in caring for their newborns (adjusted odds ratio, 3.4; 95% CI, 0.86 to 5.988) compared with fathers in standard neonatal care, the researchers report. This FICare model allows fathers to “participate more, which is associated with fewer depressive symptoms and better parent-newborn bonding,” they note in their paper. Regardless of the neonatal unit’s architectural design, fathers should be supported to actively participate in all aspects of care of preterm newborns, the researchers say. “Fathers should be enabled and supported to participate actively in all aspects of newborn care, and NICU care culture should be tailored to participation and the needs of fathers regardless of architectural design of the neonatal unit,” they add.

Alternative Birthing Practices Tied to Neonatal Infection Risk

Increasingly popular alternative peripartum practices such as water immersion and nonseverance of the umbilical cord may increase the risk of infections in newborns, a new clinical report from the American Academy of Pediatrics found. Another perinatal measure potentially raising infection risk was placentophagy, according to a review led by Dawn Nolt, MD, MPH, a professor of pediatric infectious diseases at Oregon Health & Science University, Portland. “Awareness of emerging alternative peripartum and neonatal practices helps pediatricians provide counseling to families before birth and to appropriately evaluate and treat neonates who have been exposed to these practices,” Dr. Nolt and colleagues wrote online in *Pediatrics*. Amid growing inquiries made from women seeking a positive and meaningful birth experience through alternative approaches as well as reports of possibly related illness in newborns, Dr. Nolt’s group reviewed observational studies, case series, and medical society guidance on the risks associated with seven alternative birthing practices. Based on their summation, it was not possible to quantify the actual risk associated with any one practice. “But of the seven we reviewed, as an infectious disease pediatrician I would say the most discernible immediate risk is likely attached to nonseverance of the cord,” Dr Nolt said in an interview. “Left attached, the tissue can potentially necrotize and transfer bacteria directly to the child.”

Abdominopelvic Surgery Risks in Pregnancy Vary by Gestational Age, Indication

Abdominopelvic surgery for non-obstetric reasons is often necessary during pregnancy and the risk of harm to the fetus varies by gestational age, indication and acuity, according to a large meta-analysis. The analysis included 114 observational studies with more than 67,000 pregnant women undergoing
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Should Cervical Ripening Become Routine in Primigravid Low-Risk Patients?

BM Petrikovsky, MD, PhD

Introduction

Induction of labor is the most common medical procedure in pregnancy. The success rate of induction depends on the condition of the cervix before induction. Induction of labor in the case of an unfavorable cervix leads to an increased rate of cesarean delivery.¹ Methods used for ripening of the cervix include mechanical devices and medications (prostaglandins) (PGs). PGs are used in a variety of forms, dosages, and application routes.^{2,3}

Our PubMed research using the keywords: cervical ripening, Bishop score, labor induction, and misoprostol, failed to find any peer-review publications on routine medical ripening of the cervix in primigravidas without the intention of inducing labor. However, the results of cervical ripening using herbs (primrose oil, etc.) have been reported recently.⁴ The goal of our pilot study was to assess the safety and efficacy of outpatient cervical ripening using misoprostol in nulliparous patients with a low Bishop score. A Bishop score of 6 or less was considered unfavorable, while a cervix with a Bishop score of 8 and more was considered favorable.

Materials and Methods

10 primigravid patients with poor Bishop scores (6 or less) were administered 50 mg of misoprostol sublingually at 39 plus weeks of pregnancy in the office setting. Bishop scores were taken twice a week until delivery.

Results

In 7 out of 10 patients who reviewed misoprostol, the Bishop score became favorable, in 3 it remains the same. Three out of 10 patients experienced self-limited episodes of uterine contractility, 2 went into labor within 3 days of using misoprostol. All patients delivered within 2 weeks of treatment without induction: 8- vaginally, 2 by a cesarean section. Cesarean section was done for fetal distress (1 case) and prolonged second stage of labor (1 case). All neonates were born in satisfactory condition with an Apgar score between 7 and 10.

Discussion

The use of sublingual misoprostol for cervical ripening prior to induction was recently investigated.⁵ The sublingual has a low-uterine hyperstimulation rate.⁵ The sublingual route of

misoprostol administration does not restrict patient's mobility after administration, which allows for office use. The majority of articles on misoprostol deal with its use for labor induction rather than cervical ripening. In many cases, however, induction may not be indicated. Research on cervical ripening is currently limited to alternative/ herbal remedies. Kalati, et al.⁴ reported the results of the effect of primrose oil on cervical ripening. The study was performed as a triple blind placebo controlled randomized clinical trial on nulliparous low-risk women with a Bishop score of less than 4.

In the study group, evening primrose oil capsules were administered, twice daily, for 7 days, and in the control group, the placebo was administered in a similar fashion. The women of the two groups were followed up to delivery. In this study, primrose oil did not improve the Bishop score.

One of the limitations of the study is the late onset of primrose oil administration.

We, therefore, postulated that intervention on the stage of labor may be too late and ripening of the cervix before the onset of labor may represent a better approach.

This current report represents a pilot study only without control group or careful statistical analysis. Our preliminary results demonstrated a marked improvement in cervical ripening judged by Bishop score in 70% of patients. A prospective randomized study is in the works with the following agenda:

- 1) Is late pregnancy medical cervical ripening affects labor course and cesarean section rate
- 2) What is the optimal dose of misoprostol
- 3) What is the optimal gestational age for the initiation of treatment

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Dr Petrikovsky is a professor of Obstetrics and Gynecology and an Editorial Board Member. This project is partially sponsored by Fetal Research Fund, Inc. This research is in progress.

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non-obstetric abdominopelvic surgery, including appendectomy (52 studies), adnexal (34 studies), cholecystectomy (eight) and mixed surgery types (20). Overall pooled proportions of fetal loss, preterm birth and maternal mortality were 2.8%, 9.7% and 0.04%, respectively. "Rates of fetal loss and preterm birth were higher for pelvic inflammatory conditions (e.g. appendectomy, adnexal torsion) than for abdominal or non-urgent conditions (e.g. cholecystectomy, adnexal mass," the study team reports in *Annals of Surgery*. "Surgery in the second and third trimester was associated with lower rates of fetal loss (0.1%) and higher rates of preterm birth (13.5%) than surgery in the first and second trimester (fetal loss 2.9%, preterm birth 5.6%)," they say. "This is the most comprehensive systematic review and meta-analysis of adverse fetal and maternal outcomes following non-obstetric abdominopelvic surgery to date," note Dr Maria Cusimano of the University of Toronto, Canada, and colleagues. "Our pooled estimates identify clinical scenarios with the highest risk of adverse fetal outcomes following surgery; while we are unable to provide specific management recommendations due to the nature and quality of studies identified, these data may help multidisciplinary teams tailor mitigation strategies," they write. These strategies may include use of tocolytics and/or corticosteroids perioperatively; consideration of pre-emptive elective surgery (e.g. for adnexal masses at substantial risk of torsion); and deferral of surgery to the second trimester when safely possible, the researchers say.

At-Home Cervical Ripening Safely Shortens Inpatient Labor

Women who undergo balloon cervical ripening at home spend less time in the labor and delivery unit and have fewer cesarean deliveries than those who have the induction procedure in a hospital, researchers have found. The findings, from a meta-analysis of eight previously conducted randomized clinical trials involving 740 women, should spur hospitals to "create and adhere to evidence-based guidelines" for outpatient balloon use, according to the researchers. "Outpatient balloon cervical ripening is a safe alternative for low-risk patients and has the potential for significant benefits to patients, and labor and delivery units," the authors reported. The rate of labor induction in the United States rose to 29.4% in 2019, the year following publication of the ARRIVE trial of low-risk nulliparous pregnant women, which found that induction at 39 weeks resulted in fewer cesarean deliveries with no difference in neonatal outcomes compared with expectant management, defined as continuing pregnancy until at least 40 weeks 5 days unless induction was medically indicated. Most women require preparation with a balloon-tipped catheter that slowly inflates to stretch and thin out the cervix, a process that can take many hours. The devices have been shown to be safe, effective, and inexpensive, but the data on outpatient use are limited, according to the researchers. The new study is the "most comprehensive" examination of randomized clinical trials comparing outpatient and inpatient balloon cervical ripening, they say. The trials included singleton gestations of at least 37 weeks of primarily low-risk patients. Body mass index was slightly lower in the outpatient group, with no differences in maternal age, gestational age at induction, or parity. Six studies with 571 patients reported on the primary outcome, defined as time from labor unit admission to delivery. The outpatient group had a mean 16.3 hours compared with 23.8 hours for the inpatient group, a difference of 7.24 hours. However, data from

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Transcutaneous Monitoring in the NICU: Overcoming Challenges and Driving Consistent Implementation in an Academic Medical Center's Level IV NICU

Ann Donnelly MS, RRT-NPS, Jennifer Erkinger MS, RRT-NPS, AE-C, C-NPT

Summary

Neonatal care providers have long understood the intrinsic advantages to monitoring carbon dioxide (CO₂) transcutaneously; among other benefits, avoiding unnecessary blood draws can have significant implications for preterm infants with regard to pain and stimulation, infection potential, and even blood loss. Unfortunately, early transcutaneous monitoring (TCM) introduced in the early 1990s presented challenges including frequent calibration, difficult maintenance, and a high operating temperature that adversely affected skin integrity in these fragile patients. However, the experience with modern transcutaneous CO₂ equipment (Sentec Digital Monitor, Sentec, Therwil, Switzerland) at Hershey Medical Center's Level IV NICU demonstrates that the technology has evolved to accommodate the needs of neonatal care providers and patients; and that with the right education and implementation, transcutaneous monitoring can be an effective tool for ventilator management and reducing blood draws in the NICU.

Introduction

Carbon dioxide (CO₂) levels are integral values in the NICU as they relate to cerebral blood flow and titrated respiratory care. High, low, and fluctuating levels of CO₂ have been associated with intraventricular hemorrhage (IVH)¹ which has been shown to occur in as many as 42% of neonates weighing less than 1500 grams.² Hypocapnia has also been associated with periventricular leukomalacia (PVL),² permanent white matter damage that is most associated with poor neurodevelopmental outcomes.

While ventilation is key to maintaining CO₂ values appropriate for managing IVH and PVL risk (and supporting the underdeveloped lungs of premature infants), mechanical ventilation has been linked to the development of chronic lung disease (bronchopulmonary dysplasia [BPD]), which occurs in 40-50% of neonates born below a gestational age of 28 weeks.³ In recent years, to combat the high incidence of BPD, emphasis has been placed on lung protective strategies and gentle ventilation in the NICU. Execution of a lung protecting strategy means ensuring that the respiratory support is sufficient to keep the lung inflated (to avoid derecruitment and atelectasis) but gentle enough to avoid overdistension (and

associated volutrauma) while also preventing brain injury. Carbon dioxide levels help guide this titration.

Complexities with Blood Gases and Capnography

Historically, CO₂ levels have been available through blood draws—either arterial blood gases (ABGs) or capillary heel sticks (CBGs). While this methodology is considered the gold standard, heel sticks specifically introduce risks associated with pain, infection, and blood loss. The study of long-term impact of neonatal pain is a rapidly growing field with early results suggesting connections between cumulative pain in the NICU

and brain formation changes, which are then linked to poorer behavioral and cognitive outcomes even at school age.^{4,5} Outcomes like these have driven the vast majority of NICUs to employ strategies like clustered care and touch times to lessen the amount (or at least the frequency) of stimulation and pain for their patients. Iatrogenic blood loss has also been a focus of recent research,⁶ with an emphasis on reducing neonatal anemia as well as transfusion rates.

Intermittent blood gases are additionally limited in the management of neonatal care because the values only represent a moment in time and cannot provide instantaneous results. Often the blood draw itself causes the patient to react to the pain with crying and stress—likely resulting in their CO₂ levels being different from when the sample was drawn.

Capnography (end tidal CO₂), while continuous, provides little clinical utility in the NICU as the technology is largely inaccurate with small tidal volumes and uncuffed endotracheal tubes, adds deadspace to the ventilator circuit, and is not compatible with high frequency or noninvasive ventilation methods prioritized for neonatal patients. The limitations of both blood gases and capnography make transcutaneous monitoring (TCM) of CO₂ a desirable option for patient management in the NICU.

Our Facility's Experience Early TCM Experience

Transcutaneous monitoring was first implemented at Hershey Medical Center's NICU prior to 2009 with limited success. Early challenges were multifaceted: changes in care and technology were difficult to implement across a wide group; concerns about skin integrity or burns remained from team members who had used older iterations of the technology; clinicians at all levels struggled to trust the transcutaneous CO₂ (TcPCO₂) values and had different opinions about patient

Ann Donnelly and Jennifer Erkinger are with Milton S Hershey Medical Center, Penn State Health. This article is republished from *RT: For Decision Makers in Respiratory Care*. Read the original article here <http://digitaledition.rtmagazine.com/rtmagazi/diged/20220102/index.html>

selection and implementation; and the maintenance of the devices seemed confusing and overwhelming. Thus, use of the technology was paused.

Implementation Strategy

Because there were still several physicians who believed in the benefits of the technology, our team decided to make a final effort to standardize use and thoroughly evaluate the clinical utility of the technology and equipment. We developed standardized training in conjunction with the manufacturer (Sentec Digital Monitor, Sentec, Therwil, Switzerland), began collecting and analyzing our own correlation data, and organized a proactive approach to device maintenance including roles and responsibilities.

Results

The standardized education program successfully drove competency about the technology, how to use it and maintain the devices, and how the parameters supported our care goals. The correlation data built trust in the transcutaneous values and furthermore allowed our team to identify best practices and develop a deeper understanding of device functionality and optimal use. Clear roles and responsibilities relative to the equipment and the parameter have drastically reduced previous troubleshooting and maintenance issues, and our team is better prepared to handle any issues when they do occur.

Current Clinical Use

Once broad competency was achieved, we quickly expanded the number of transcutaneous monitors from 3 to 9 and then to 16, representing nearly 30% of our licensed NICU beds. Blood gases that were previously performed every 4 hours were reduced to every 12 hours once a stable trend was achieved for TcPCO₂. Blood gases now are obtained once a day, to once or twice per week, or not done at all in the absence of a clinical concern or discrepant TcPCO₂ value or trend. TcPCO₂ readings and their correlation with blood gases are communicated during rounds, and we have consistently expanded patient selection for transcutaneous monitoring from only patients on high frequency ventilation to any intubated patient, including high frequency oscillatory ventilated patients in the pediatric intensive care unit (PICU). TCM has also been used to monitor patients receiving bubble CPAP to evaluate changes in ventilation status post-extubation.

Enduring Challenges

As with other technologies, extremely low birth weight (ELBW) infants are difficult to manage. Adhesion of the attachment rings is challenging in high humidity environments and with ELBW infants with immature skin. For those babies born <750 grams, finding the appropriate anatomical surface for sensor placement can also be a struggle. Importantly, we have seen the benefit of having continuous TcPCO₂ information for these micropreemies and have not had any skin integrity issues related to adhesion or heat from the transcutaneous sensor in this vulnerable population.

Perfusion at the monitoring site and correlation of the TCM are intimately related—therefore any neonate or infant with systemic poor perfusion, low blood pressures, or even a large patent ductus arteriosus (PDA) can present correlation challenges. In these cases, we continue to monitor these patients but rely more on TcPCO₂ trends rather than actual values.

Additional Benefits

- Noninvasive, continuous trending values support decision making related to ventilatory management decisions.
- When surveyed, >95% of our providers agree that the use of transcutaneous monitoring reduced the frequency of ordering invasive blood tests, which has implications for outcomes as well as cost.
- Reduction in blood draws was also perceived to have a positive impact on parental satisfaction due to decreased painful stimuli.

Keys to Successful Implementation of the TCM Program

- Develop a training program that addresses all members of the neonatal team: nurses, respiratory therapists, neonatal nurse practitioners, and neonatologists.
- Drive a high level of competency about the relationship between perfusion, device calibration, site selection, and correlation.
- Build broad trust in the technology by generating quality correlation data at the bedside with a review of proper blood sampling technique, and attention to detail with logging TcPCO₂ values at the moment the blood draw is performed.
- Establish “super users” and a proactive maintenance strategy to ensure monitors are always ready for use and to minimize time spent troubleshooting.
- Educate the entire team regarding the potential impact of fewer blood draws in relation to blood loss, pain, and infection, as well as the lung protective value of titrated ventilatory care.

Conclusion

With time, effort, and the right education, transcutaneous monitoring can offer neonatal intensive care teams continuous, clinically useful CO₂ values that support real-time ventilatory decision-making while reducing the pain, stimulation, and blood loss associated with frequent blood draws.⁷

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A Single Center Comparison of Introducing an Inhaled Nitric Oxide Initiation and Weaning Protocol into the Neonatal Intensive Care Unit

Abbey M Hudgins, Jennifer A Desiredi, Nathan A Rodrigues and Arzu Ari

Abstract

Background: Inhaled Nitric Oxide (iNO) is a selective pulmonary vasodilator used in the Neonatal Intensive Care Unit (NICU) to treat hypoxic respiratory failure associated with pulmonary hypertension. Reducing practice variation through the use of a standardized protocol when weaning iNO may improve overall patient outcomes and decrease overutilization of iNO. The purpose of this study was to determine the impact of an iNO initiation and weaning protocol on patient outcome variables, including the average number of days exposed to iNO therapy, the average number of days on ventilatory support (both invasive and noninvasive), and the length of stay in the NICU. The average number of days for Milrinone and Sildenafil use were added to determine the effects of phosphodiesterase inhibitors with weaning.

Methods: An iNO initiation and weaning protocol was adapted into a level IV NICU using the plan-do-study-act method. The study sample consisted of a total of 41 subjects, 20 for the control group and 21 for the treatment group. The subjects included patients of both biological sexes, all ethnicities, and an age range of 23 weeks gestation or older. Retrospective data was collected from January 2016 to December 2016 to act as a control group and from January 2018 to December 2018, post protocol implementation, to act as the treatment group. Comparisons were made between the two groups using *t*-test analysis with negative binomial regression.

Results: The treatment year was statistically significant for iNO days with a decrease in median iNO usage from 23.25 to 11.14 days ($p = 0.047$). During this treatment year, there was also a statistically significant increase in Sildenafil usage from a median duration of 6.35 to 37 days ($p = 0.004$). There was no statistical significance for the length of stay ($p = 0.987$), ventilatory support days ($p = 0.789$), or Milrinone use ($p = 0.774$) post protocol implementation.

Conclusions: Findings from this study suggest that applying a respiratory therapy-driven iNO weaning protocol can reduce overutilization of iNO in the neonatal critical care setting.

Hudgins, Rodrigues, Ari: Department of Respiratory Care, Texas State University, Round Rock, Texas. Desiredi: St. David's Medical Center, Austin, Texas. We (the authors) have no conflicts of interest to disclose. This manuscript has not been submitted, nor is it under consideration, for publication elsewhere. We received no financial support.

Keywords: Inhaled nitric oxide, weaning protocol, pulmonary hypertension, neonatal intensive care, NICU, Sildenafil, phosphodiesterase inhibitors, ECMO

Introduction

Roberts and Kinsella first discovered the potential benefits of Nitric Oxide (NO) as an inhaled gas in 1992.¹ In 1999, after several randomized clinical trials, the Food and Drug Administration approved the use of inhaled Nitric Oxide (iNO) for term and near-term infants with hypoxic respiratory failure associated with persistent pulmonary hypertension.¹ Since then, iNO has become the gold standard in the medical management of neonates with respiratory failure.

iNO is a potent pulmonary vasodilator that selectively targets the pulmonary vessels allowing sustained vasodilation.² By dilating the pulmonary vessels, there is redistribution of pulmonary blood flow away from lung regions with low ventilation/perfusion ratios to well-ventilated areas of the lung.² This leads to improved oxygenation and decreased pulmonary hypertension. However, iNO can act as a pulmonary irritant, possibly causing damage to the epithelial cells in the lungs.³ iNO is often over-utilized or unnecessarily applied in the Neonatal Intensive Care Unit (NICU) due to practice variations and lack of respiratory therapy (RT)-driven protocols.⁴

Inhaled Nitric Oxide has been studied extensively in terms of its effects on the lungs, appropriate target population, and morbidity in the neonatal population. However, there is limited information regarding appropriate iNO weaning strategies, including the addition of phosphodiesterase inhibitors, such as Milrinone and Sildenafil, when weaning from iNO becomes difficult.⁴⁻⁵ An electronic literature search and review of articles specific to iNO weaning from 1995-2015 was conducted by Ware and Golombek to determine the best strategy for weaning iNO.⁶ This literature search and review determined that there is lack of conclusive evidence specific to iNO initiation and weaning protocols, and there is no consensus on a national standard for weaning iNO.⁶ In recent years, there have been additional studies regarding the use of iNO initiation and weaning protocols that have demonstrated promising results for minimizing usage, but we still lack a nationally accepted standard for initiation and weaning of iNO.⁷⁻⁸

The purpose of this study was to determine the impact of an iNO initiation and weaning protocol on patient outcome variables, including the average number of days exposed to iNO therapy,

the average number of days on ventilatory support (both invasive and noninvasive), and the length of stay in the NICU. Additionally, the average number of days patients received Milrinone and Sildenafil were included to determine if there was a correlation in usage when weaning iNO.

Risk and Benefit

The primary risk associated with this study is weaning the iNO too quickly causing a rebound effect. The rebound effect for iNO includes a reduced oxygenation and rebound pulmonary hypertension.² This risk is more often associated with the sudden withdraw of iNO therapy as opposed to gradual weaning. To minimize this risk, there will be consistent follow up with the practitioners.

Potential benefits of this study include improved patient outcomes, decreased exposure to iNO, and decreased overutilization of iNO. Due to a lack of consensus for best practices when weaning iNO, this study could add to the published literature for appropriate weaning methods and needed standard criteria.

Methods

Study Setting and Subjects

This study took place in a Level IV, sixty-five bed NICU in the southern United States. The study sample consisted of a total of 41 subjects, 20 for the control group and 21 for the experimental group. The subjects included patients of both biological sexes, all ethnicities, and an age range of 23 weeks gestation or older. The exclusion criteria included those patients who expired during their hospital stay or those transferred to another facility for a higher level of care. The patients received iNO through an invasive or non-invasive ventilator setup.

Study Design

The iNO weaning protocol was adapted into our NICU with permission from unpublished work in progress, Dr. Victor Levy.⁹ Additions were made to the protocol which included the use of Milrinone and Sildenafil if weaning from iNO became difficult or there was no response to iNO therapy. The protocol was implemented into the NICU using the plan-do-study-act method. This included comprehensive training with all practitioners, continuing education, standardized order sets, daily interdisciplinary rounds, and consistent follow-up for compliance.

Retrospective data was collected from January 1, 2016, to December 31, 2016, to act as a control group because the protocol was not yet implemented. Data was not collected during the calendar year of 2017 because during this time, the protocol was being developed, and education of the patient care team regarding the use of the protocol was conducted. Data utilizing the protocol was collected to use as a treatment group from January 1, 2018, to December 31, 2018, following the protocol implementation.

Primary indications of iNO included term or near term (≥ 34 weeks gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension or PPHN.⁶ Secondary indications of iNO include patients with severe hypoxia and infants less than 34 weeks gestation with severe hypoxia secondary to pulmonary hypertension.⁶

The physician would place an order for iNO therapy with a set dosage. The Electronic Medical Record (EMR) would automatically attach the iNO weaning protocol to the order set as a reminder to the practitioners. The typical initial dosage is 20ppm, and doses greater than 20ppm are not recommended for the neonatal population.⁶ Once the order for iNO therapy was placed, the therapist initiating the iNO would document the date of initiation, the dosage of iNO, date patient admitted to NICU, gestational age, birth weight, primary diagnosis, and date of discontinuation from iNO and ventilatory support on an Excel spreadsheet. Ventilatory support (VS) days is defined as the use of both invasive and non-invasive ventilation. Once all data was collected, the neonatologist assisting with this study cross-referenced the data with a medical chart review to confirm the diagnosis and the accurate number of days. All patients received iNO therapy with the iNO_{maxIR} delivery system (Mallinckrodt Pharmaceuticals; Dallas, Texas, United States of America). Each day, interdisciplinary rounds were conducted within the unit, and the weaning protocol was discussed for each patient receiving iNO.

Once all data was collected, pre and post protocol initiation outcome variables were compared to determine the effect of the iNO protocol on the average number of days exposed to iNO therapy, average number of days on ventilatory support, and average length of stay in the NICU. Subsequently, a noted pattern of increased Sildenafil use in 2018 led to the addition of Milrinone and Sildenafil as outcome variables in this study. Number of days for the phosphodiesterase inhibitors were collected by the neonatologist through a medical chart review.

Data Collection, Protection, and Storage

All collected data were entered into an Excel spreadsheet located on a secured hospital computer that is username and password protected. The hospital follows all HIPPA regulations for the safety of patient information. Each study participant received an index number to achieve de-identification. The master key with the index numbers and identifiable information are on a secured hospital computer, only accessible to the participating neonatologist and nurse researcher. All collected data will be kept for three years and then destroyed. No identifiable information was used in this study.

Ethics

This study was approved by all participating Institutional Review Boards. No compensation was made to study participants.

Analysis

Comparisons were made between the control group and treatment group using *t*-test analysis with negative binomial regression.

Results

A total of 20 control year (2016) observations and 21 treatment year (2018) observations were available for this study. Table 1 displays patient characteristics for the control group and treatment group, including gestational age, birthweight, biological sex, and disease processes.

Table 2 displays descriptive statistics, *t*-tests, and Cohen's *d* effect sizes for study variables using *t*-test analysis.

According to the *t*-tests, the number of Sildenafil days was the only outcome that exhibited a statistically significant difference

Table 1. Patient Characteristics by Year

Patient Characteristics	Control (n=20)	Treatment (n=21)
Gestational Age (weeks)	34 ± 6	34 ± 6
Birthweight (grams)	2455 ± 1291	2484 ± 1233
Male biological sex (percent)	43	50
Pulmonary Hypoplasia (percent)	26	23
Chronic Lung Disease (percent)	30	32

between the two years. However, the outcome variables (iNO days, ventilator days, length of stay (days), Sildenafil days, and Milrinone days) are positively skewed integers and should be regarded as count variables rather than continuous variables. Therefore, negative binomial regression was utilized for hypothesis testing to accommodate the nature of these outcome variables. Specifically, each outcome variable was regressed on a dichotomous indicator variable that distinguished the treatment protocol/2018 (1) from the control protocol/2016 (0). Gestational age in weeks was included as a covariate. Results are shown in Table 3. The effect of gestational age was statistically significant for iNO days, ventilator days, and LOS. For example, each additional week of gestation is predicted to result in a decrease of .07 log iNO days. The effect of treatment condition/year was statistically significant for both iNO days ($p=0.047$) and Sildenafil days ($p=0.004$). The model for iNO days suggests that the log count of iNO days is .92 units lower in the year in which the weaning protocol was implemented, controlling for gestational age. Holding gestational age constant at the overall mean of 33.9 weeks, the regression model for iNO days thus predicts 23.51 iNO days for patients receiving standard treatment and 9.34 iNO days for patients on the weaning protocol. The log number of Sildenafil days is predicted to be 2.01 units higher in the treatment year while controlling for gestational age. Again, holding gestational age constant at the overall mean of 33.9 weeks, the regression model for Sildenafil days predicts 4.94 Sildenafil days for patients receiving standard treatment and 36.77 sildenafil days for patients on the weaning protocol. A p value <0.05 was considered statistically significant.

Discussion

Results from this study suggest that a RT-driven iNO weaning protocol can reduce unnecessary iNO usage. In this study, there were statistically significance outcomes pertaining to a decrease in the average number of iNO days and an increase in Sildenafil use in the treatment year compared to the control year. There was a 60% decrease in iNO usage once the protocol was implemented, which is clinically significant for several reasons, including decreased iNO exposure, decreased drug

overutilization, and the provision of standardization of care. These findings fall in line with recent studies regarding the need for protocol-based initiatives to decrease iNO overutilization.^{5,7-8} Cost savings was not an outcome variable in this research due to the study site having a monetary contract with the iNO vendor regardless of the amount of iNO usage.

With decreased iNO usage in the treatment year, there was also a significant increase in Sildenafil usage (mean of 6.35 days during the control year compared to 37.0 days during the treatment year). We hypothesize that adding Sildenafil to the protocol as a weaning mechanism for iNO caused a substantial increase in usage after protocol initiation. The protocol was discussed daily during interdisciplinary rounds, which reminded the practitioners to take a closer look at those patients who were having difficulty weaning, thus increasing Sildenafil use. Sildenafil administration could have influenced iNO days, but further research is needed to examine the true impact of Sildenafil on iNO usage.

This study did not find statistical significance for the outcome variables length of stay and ventilatory support days after protocol initiation. We believe this is due to prematurity and the pathophysiology of the disease process that caused the need for iNO therapy in the first place. There are multiple factors, other than iNO needs, that affect the length of stay and the need for ventilatory support, including apnea, feeding issues, temperature stability, and severity of lung disease.

Limitations for this study included small sample size and a single-center evaluation. Therefore, we recommend that further research, including large sample size and multi-center evaluation, should be conducted utilizing the iNO initiation and weaning protocol.

Conclusion

A RT-driven initiation and weaning protocol led to an overall reduction in iNO usage in the neonatal intensive care unit. There is a need for a national standard when using iNO to successfully decrease drug overutilization and standardize patient care.

Corresponding Author

Abbey M Hudgins, Texas State University, Department of Respiratory Care, 200 Bobcat Way, Willow Hall #214, Round Rock, TX, 78665, Office: 512.246.2684, Fax: 512.716.2805, E-mail: ah1297@txstate.edu

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Table 2. Descriptive Statistics by Year with t-tests and Effect Sizes.

	2016 ¹ (n = 20)			2018 ² (n = 21)			Mean Difference	t^3	p	d
	Mean	SD	Skew	Mean	SD	Skew				
Gestation (weeks)	33.45	6.57	-0.43	34.33	6.70	-0.87	-0.88	-0.43	0.67	--
iNO Days	23.25	41.15	2.70	11.14	15.38	2.57	12.11	1.26	0.22	0.43
VS Days	51.35	58.95	1.14	52.62	55.94	1.23	-1.27	-0.07	0.94	--
LOS (days)	92.50	83.09	0.99	85.48	75.48	0.77	7.02	0.28	0.78	--
Sildenafil Days	6.35	21.09	3.95	37.00	57.91	1.66	-30.65	-2.23	0.03	-0.77
Milrinone Days	3.55	8.11	2.67	4.67	7.89	2.84	-1.12	-0.45	0.66	--

Note. D = Cohen's d effect size. Negligible effect sizes are not reported in the table. VS = Ventilatory support. ¹Control year/no weaning protocol. ²Treatment year/weaning protocol in effect. ³ t -statistic for t -test with 39 degrees of freedom.

Table 3. Negative Binomial Regressions of Outcomes on Condition/Year While Controlling for Gestational Age

Outcome	Effect	Coefficient	S.E.	Coefficient/S.E.	p
INO Days	Treatment ¹	-0.92	0.46	-1.99	0.047
	Gestation	-0.07	0.03	-2.12	0.034
	Intercept	5.36	0.93	5.76	0.000
	Dispersion	1.15	0.26	4.39	0.000
VS Days	Treatment ¹	0.11	0.41	0.27	0.789
	Gestation	-0.10	0.03	-3.80	0.000
	Intercept	6.94	0.66	10.51	0.000
	Dispersion	0.98	0.21	4.74	0.000
LOS (days)	Treatment ¹	-0.01	0.33	-0.02	0.987
	Gestation	-0.08	0.02	-3.92	0.000
	Intercept	7.01	0.52	13.46	0.000
	Dispersion	0.72	0.18	3.98	0.000
Sildenafil Days	Treatment ¹	2.01	0.69	2.91	0.004
	Gestation	-0.08	0.05	-1.47	0.142
	Intercept	4.21	1.89	2.23	0.026
	Dispersion	10.63	3.31	3.21	0.001
Milrinone Days	Treatment ¹	0.17	0.59	0.29	0.774
	Gestation	-0.01	0.04	-0.32	0.752
	Intercept	1.79	1.69	1.06	0.288
	Dispersion	5.44	1.70	3.20	0.001

Note. S.E. = Standard error. VS= Ventilatory support. ¹Treatment is the dichotomous treatment indicator variable where 0 = 2016/control condition and 1 = 2018/weaning protocol condition.

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Problem-Solving Passy-Muir® Valve Use with Infants

Laura Brooks, MS, CCC-SLP, BCS-S

Questions frequently arise regarding the use of the Passy-Muir Valve (PMV®) with the pediatric population. Unfortunately, there is a paucity of research in this area and clinicians frequently must rely on lessons learned and shared by seasoned clinicians. Another method is participating in continuing education that is specific to the area of pediatric tracheostomy. Following is a series of questions presented to Laura Brooks, a speech-language pathologist at Children's Hospital of Atlanta, which begin to address considerations for problem-solving use of the Passy-Muir Valve, including an emphasis on a multidisciplinary approach with this patient population. Laura is well-versed in working with this patient population and has published research related to the care of pediatric patients with tracheostomies.

Considerations for the Initiation of PMV Use

Where do we begin?

Well, in order to problem-solve PMV use with pediatric patients, the clinician should have a good understanding of the fundamentals of tracheostomies, ventilators, and the anatomy and physiology of respiration in the pediatric population. The clinician may accomplish competency by taking continuing education courses, reading the latest research regarding PMV use with adults and pediatrics patients, establishing specific competencies for working with patients following tracheostomies and mechanical ventilation, and forming a multidisciplinary tracheostomy team for tracheostomy management. The team should establish a best practice guideline for the facility. This team may include respiratory therapy (RT), ENT, pulmonology, neonatologist, ICU attending (CICU, PICU), nursing, speech-language pathologists (SLP), and other stakeholders in the care of these patients.

Clinicians should be aware of the resources that are available to them. From online continuing education to published research, clinicians have options. I also would like to share information on a textbook that may help the clinician understand the basics with regard to patients who are tracheostomy and ventilator dependent. The highly regarded

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.

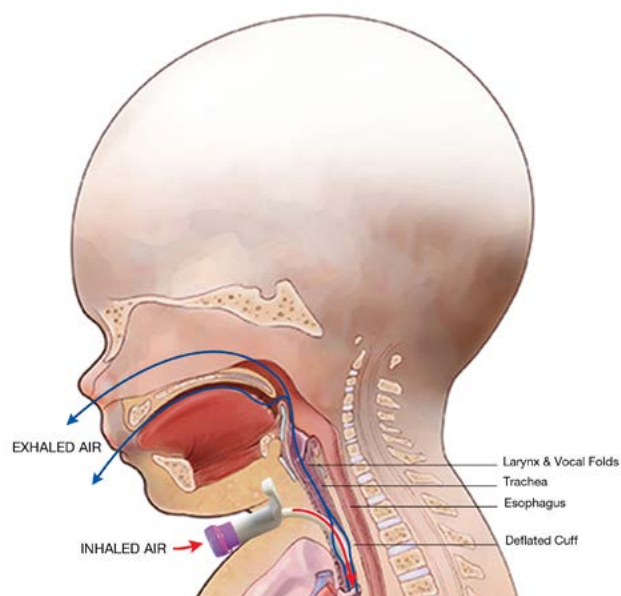


Photo credit

tracheostomy textbook, *Communication and Swallowing Management of Tracheostomized and Ventilator Dependent Adults*, by Marta Kazandjian, MA, CCC-SLP, BCS-S, CPT-EFS and Karen Dikeman, MA, CCC-SLP, is now in a third edition and titled *Communication and Swallowing Management of Tracheostomized and Ventilator Dependent Individuals*. The change in title occurred because pediatrics has been added to this comprehensive review of management of the patient with tracheostomy and ventilator. I had the honor of writing the chapter, "Management of Tracheostomized and Ventilator Dependent Pediatric Patients," which provides a detailed resource for both new and experienced clinicians working with infants and children who have a tracheostomy and/or ventilator dependence. The chapter presents an overview of prenatal and postnatal airway development, medical diagnoses affecting breathing and swallowing, and differences in the pediatric patient population as it relates to tracheostomy and ventilator dependence.

OK, so we have read and studied all about PMV with pediatric patients who are tracheostomy and ventilator dependent, but in practice, we sometimes run into barriers for PMV application. How should we address those barriers?

PMV application changes the dynamic of the patient's

breathing. With PMV application, the patient requires cuff deflation, and the patient exhales exclusively out of the mouth and nose. This change in breathing, particularly for a ventilator dependent patient, may cause some physicians and clinicians to be reluctant with trialing a PMV with a patient. The more you can educate yourself and your team on the benefits achieved with PMV use, the fewer barriers you will find. It is important to establish a team of physicians and clinicians, and to establish best practice guidelines for your facility, in order to ensure that everyone is on the same page in terms of candidacy and safety for PMV use with your patients.

What is the youngest age of a patient who can use a PMV?

There is no specific age criteria. Older children have larger airways and may tolerate PMV application better; however, infants successfully wear the PMV (Brooks et al., 2020). Younger infants have smaller airways, so some may need more time to grow if they do not do well with an initial PMV trial.

What do you say when a healthcare professional or a parent asks, “why are we doing this” or “this is a baby; babies do not talk. Why does the baby need a speaking valve”?

These are common questions, particularly when considering a PMV trial with an infant who is medically complex. I rarely call it a “speaking valve” for that reason. It IS a speaking valve, but to me it is just as equally important that the patient can normalize exhalation and have the benefits of secretion management. My answer to these questions tends to be specific to the person who is asking.

For parents, the most important reason for a PMV trial is to hear their babies coo, cry, and vocalize. Parents and babies develop bonding through touch and these sounds.

For a doctor, that may not be enough reason to do the PMV trial with a medically complex baby.

For example, I asked a PICU attending recently if I could do a PMV trial on one of his medically complex infants, and he said, “Can you explain the benefits at this point in his medical course?” My response to this question was to share that my purpose would be “to restore exhalation out of his mouth and nose which will help him sense his secretions in order to swallow or cough in response. This can reduce the need for suctioning [nose, mouth, trachea]. In addition, it will allow for vocalization; we can hear him cry to alert us that he has a need [diaper change, hunger].” He said, “OK, but he had a rough morning, can we do it tomorrow?” Actually, after reviewing the patient’s chart, I ended up deferring the trial for a few weeks because his CO₂ was high, and I wanted him to be successful with the PMV trial. Once he was more stable, we did the trial. He did well; we advanced PMV wear time, trained the caregivers, and he was discharged wearing the PMV with strict caregiver supervision.

Tracheostomy Tubes and Cuff Management

Why would a patient need a cuffed tracheostomy tube?

The cuff is inflated on the tracheostomy tube in order to avoid

a “leak” into the upper airway and to maximize ventilator support. A leak is the space between the tracheostomy tube and the trachea. If the cuff is deflated or the patient has a cuffless tracheostomy tube, the patient has space around the tracheostomy tube, allowing air to “escape” up into the upper airway. Patients with *high* ventilator settings need *all* the ventilator support to go directly into the lungs; therefore, physicians often do not want any air “escaping” into the upper airway for the patients with high ventilator settings.

However, a leak is important for PMV use as the air escaping through the patient’s vocal cords, pharynx, nose and mouth helps with our SLP goals of talking and eating. As soon as the patient’s ventilator settings are *appropriate* (PEEP 10 or less, PIP < 40 cm H₂O, and FiO₂ ≤ .50), I start the discussion with the team regarding cuff deflation, PMV trial, and PO trial (“per os” or eating by mouth).

What are some benefits of cuff deflation?

The same as the benefits of PMV use, only PMV placement magnifies the benefits. The benefits include increased upper airway sensation (nose, mouth, pharynx, larynx); better secretion management (cough or swallow secretions when they are sensed); improved ability to taste and smell; improved swallowing function; and increased ventilation from the upper airway (mouth and nose).

What do you do when a team member says that the patient is not a candidate for a PMV trial because of a cuff?

I explain that for every PMV trial, the FIRST step is to deflate the cuff COMPLETELY when the PMV is placed in-line (in the ventilator circuit) or on the tracheostomy hub for non-vent dependent children. With the PMV on, the patient can no longer exhale out of the tracheostomy tube, and the patient needs the air to move AROUND the tracheostomy tube (between the tracheostomy tube and the trachea out through the larynx, pharynx, mouth, and nose. If the patient’s cuff is inflated and the PMV is placed, that is extremely dangerous as the patient can inhale but not exhale.

When do you advocate for cuff deflation? Do you advocate for cuff deflation without a PMV?

As soon as the patient is on the following settings: FiO₂ ≤ .50, PEEP 10 or less, and PIP < 40 cm H₂O, I am advocating for a PMV trial. If the physician allows, then the cuff deflation will occur at the start of the PMV trial. If the physician does not want a PMV trial, I will ask for a cuff deflation trial.

The manometer measures TTP and tells the clinician about “airway patency,” whether the airway is patent and open. The manometer is placed between the PMV and the patient and will give the clinician many different values. It has a pressure value for every movement or every pressure, such as inhalation, exhalation, coughing, and different vocalizations. Every movement that the patient makes may be reflected in the pressure value on the manometer. The value that is the most important to know shows if the patient can adequately exhale out of the upper airway with the PMV applied. This value is the number at the END of exhalation, which will be the patient’s end-expiratory pressure or transtracheal pressure. If the patient cannot exhale adequately, the TTP will increase, and we will quickly remove the PMV. But it is critical that the TTP is measured with *resting breaths*, the patient

calmly breathing, so the clinician knows that the manometer is indicating the true TTP.

Ventilator Dependence and Impact on PMV Use

Switching gears now from upper airway issues to lower airway issues. What do you do when a team member says that the patient is not a candidate for a PMV trial because of being ventilator dependent?

That actually happens quite often, and I review that the PMV was invented for patients with or without ventilator dependence. David Muir was the inventor and was ventilator dependent; he made this valve to go into his ventilator circuit. There are so many benefits to early intervention with PMV application with patients who are ventilator dependent. Using the Valve and restores exhalation through the patient's upper airway and does not return exhalation to the ventilator. These benefits were highlighted earlier but include the ability to sense secretions in order to cough or swallow, sense the bolus during swallowing, vocalize, cry, talk, smell, taste, bear down for bowel movements, and to use the glottis to help engage the core for transfers. For these reasons, early intervention and application of the PMV benefits patients who are ventilator dependent and their caregivers greatly.

Do you change the ventilator settings with PMV trials?

I do not. I believe that for adult patients, the ventilator settings may need to be changed for a variety of reasons. But it is important to understand the literature and the population that is studied in the literature. The clinician also must be familiar with the ventilator modes and settings used during ventilation. For example, adults who are on pressure control ventilation may require a different assessment than an adult on volume control ventilation. It also is important that we do not apply adult studies directly to pediatric patients and assume that it is the same. An adult who requires mechanical ventilation at the age of 65 is very different from a premature infant with bronchopulmonary dysplasia or chronic lung disease. These two types of patients cannot be compared.

We use Transtracheal Pressure measurements (TTP) to assist in our assessment. A manometer is placed between the PMV and the patient and will give the clinician many different values. The manometer measures TTP and tells the clinician about "airway patency," whether the airway is patent and open. It has a pressure value for every movement or every pressure, such as inhalation, exhalation, coughing, and different vocalizations. Every movement that the patient makes may be reflected in the pressure value on the manometer. The value that is the most important to know shows if the patient can adequately exhale out of the upper airway with the PMV applied. This value is the number at the END of exhalation, which will be the patient's end-expiratory pressure or transtracheal pressure. If the patient cannot exhale adequately, the TTP will increase, and we will quickly remove the PMV. But it is critical that the TTP is measured with *resting breaths*, the patient calmly breathing, so the clinician knows that the manometer is indicating the true TTP.

When used with mechanical ventilation, our TTP measurements show that with a patent airway, the transtracheal pressure value is very close to the PEEP setting that is set on the ventilator. Our pulmonologists want that value to remain the same or be

very close to the same. The physician does not want the PEEP decreased due to the risk that the patient will not receive the support that the lungs need. With a PMV trial, we must show that the patient is still receiving the ventilator support that the physician wants and the patient needs.

For most of our patients, the ventilator does not alarm when the PMV is inline. If it did, the RT would be present to identify what the alarm is and to silence the alarm, when appropriate. For our facility, if the ventilator continued to alarm during a PMV trial, which rarely occurs, the physician would need to write an order for settings that could be changed for alarm management during the trial; however, then it is imperative that appropriate adjustments are monitored for patient safety. The clinicians must be aware of all changes and baseline parameters to mitigate any risk of forgetting to adjust the settings back after the PMV trial.

Do you ever take the patient off the ventilator for a PMV trials?

Never. If the patient is ventilator dependent, I would always do PMV trials in-line so that the patient receives the vent support they need during the trial.

Do you always partner with an RT for an initial PMV trial?

Always. RTs are always present, at least for the initial placement of PMV for patients with ventilator dependence. For patients with only a tracheostomy, the RT is either present or on the unit and alerted that I am doing a PMV trial.

Roles of the Team Members

Do all clinicians have experience with using the PMV?

Not all do. It is nice to have that team approach with consistency and a knowledge base for PMV trials, especially when working with our medically complex and fragile infants and children. If the RT educator is not present, I will do a PMV trial with the patient's assigned RT. In this scenario, if the RT does not have much experience with PMV use, I, as the SLP, take more of a lead on the placement, asking them to deflate the cuff, suction the tracheostomy tube, and other relevant steps. Then, the role of the RT primarily focuses on any ventilator needs or if the patient presents with any stress signs during the trial. The roles of the RTs and SLPs during assessment vary facility to facility. It is important to consider establishing a team of trained healthcare professionals to meet the needs of your patients.

The more the SLP can learn about mechanical ventilation the better equipped the clinician will be to work with the RT and "speak the same language." For example, SLPs and RTs have different training, and each discipline brings different viewpoints to a PMV trial. Success occurs when the SLP has a good understanding of anatomy and physiology of the upper and lower airway, changes that occur with physiology and respiration during a PMV trial, and effects of the various ventilator settings on the patient's breathing. Each discipline benefits from understanding the skills that each team member brings to the assessment and treatment. Establishing a policy and procedure assists with designating the role of each team member.

Conclusion

While we still have much to learn as it relates to working with the pediatric population, especially the medically complex and fragile infants with tracheostomies, clinicians who are using

the PMV with this population continue to inform our practice with their clinical experience and research. The more that we address the needs early in the patient's care, the better chance the patient has to feed, manage secretions, and communicate. Understanding the physiology and pathophysiology of respiration and swallowing are critical to providing best practices. Being informed of how normal infant anatomy and potential upper airway obstruction impact airway patency are key to successful Valve placement. Providing access to the upper airway will enhance overall care and progress of the patient. If a facility has established a team, policies and procedures, and a best practice guideline, then managing this special patient population will be possible when using a PMV during mechanical ventilation, PO, and communication.

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three of the studies showed the inpatient group experienced 5.19 hours on average less between balloon expulsion and delivery, potentially due to more frequent adjustments and evaluation for expulsion. The researchers observed no differences in adverse maternal or neonatal outcomes, and no stillbirths were reported among 378 patients who had the outpatient procedure. Cesarean delivery occurred less often in the outpatient group (21%) vs the inpatient group (27%) (risk ratio, 0.76; 95% CI, 0.59 – 0.98).

COVID-19 Vaccination During Pregnancy Not Linked to Complications at Birth: US Study

COVID-19 vaccination during pregnancy was not associated with preterm delivery or underweight newborns, in a study published by the US Centers for Disease Control and Prevention (CDC). Rates of preterm birth were 4.9% among more than 10,000 women who received at least one dose of a COVID-19 vaccine, compared to 7.0% for roughly 36,000 unvaccinated women, researchers said. The difference was not deemed to be statistically significant. In addition, COVID-19 vaccination did not increase the risk of delivering a baby who weighed less than usual for the number of weeks of pregnancy, the researchers found. Results from the study support the CDC's recommendation on the safety of COVID-19 vaccination during pregnancy. "Evidence of the benefits of COVID-19 vaccination during pregnancy continues to accrue, including the detection of antibodies in cord blood," the researchers wrote, noting that pregnant women with COVID-19 have increased risks for intensive care unit admission, need for mechanical ventilation and death. The women in the study had become pregnant between May and October of 2020, before vaccines were available. Nearly all who were vaccinated got the shots in their second or third trimester of pregnancy. Some 96% of them had received at least one dose of an mRNA vaccine from either Pfizer Inc (PFE.N) and BioNTech (22UAY.DE), or Moderna Inc (MRNA.O). The remaining women received the single-shot vaccine from Johnson & Johnson (JNJ.N).

Mediterranean Diet, Mindfulness Each Reduce Small-for-Gestational Age Births

Low birth weight affects up to 10% of pregnancies and stems from fetal growth restriction. Until today, no treatment that could improve this condition is available. A study published in JAMA led by researchers from BCNatal (Hospital Clínic-IDIBAPS and Hospital Sant Joan de Déu in Barcelona) with the support of the "la Caixa" Foundation, has demonstrated for the first time that fetal growth can be improved by maternal lifestyle changes. The study specifically demonstrates a reduction of low birth weight babies up to 29% and 36% by intervening on the mother's diet and lowering her stress level. The study was coordinated by Eduard Gratacós, director of BCNatal and the Fetal and prenatal medicine group at IDIBAPS and CIBERER, Francesca Crovetto (Hospital Sant Joan de Déu) and Fátima Crispi (Hospital Clínic), from the Maternal-Fetal Medicine Services of BCNatal and researchers from the same groups. It was conducted in collaboration with the teams of Ramon Estruch, from the Internal Medicine Service at Hospital Clínic, head of the Cardiovascular risk, nutrition and aging group at IDIBAPS and researcher at CIBEROBN; Eduard Vieta, head of the Psychiatry and Psychology Service at Hospital Clínic, from the Bipolar and depressive disorders group at IDIBAPS and scientific director of CIBERSAM, as well as professionals from the esMindfulness Institute, directed by Andrés Martín-Asuero. The project also

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Redefining Milk Management in the Neonatal Intensive Care Environment

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

Hospitals increasingly seek milk management systems that include barcode scanning technology and electronic health record (EHR) integration. Software that was previously considered “nice to have” is now “must-have” technology in neonatal intensive care units (NICUs) nationwide. Along with centralized milk preparation and registered dietitians’ utilization, barcode scanning is a critical component of state-of-the-art NICU feeding (Matous et al., 2019). Major healthcare organizations like the Academy of Nutrition and Dietetics, the Agency for Health Research and Quality, and the Healthcare Information and Management Systems Society also recommend scanning human milk as an essential patient safety practice (Steele & Collins, 2018; Dougherty, 2010; HIMMS).

Viewing infant feedings as “just food” has become an antiquated attitude as we grow to understand the importance of neonatal nutrition and the safety risks that stem from milk and formula mismanagement. Human milk is a bioactive and complex substance with life-saving qualities, such as immunological, neurodevelopmental, and gastrointestinal protection; meanwhile, it is also a substance that can transmit disease and cause illness if not properly handled (Cossey, 2016). As a result, several states have legislation treating milk as a human tissue (Campbell, 2016), and neonatal nutrition experts affirm this stance (Kim, 2018). Likewise, infant formula and additives are subject to contamination, misadministration, and recipe errors that pose a significant risk to patients (Steele & Bixby, 2021). Like other aspects of neonatal care, nutrition regimens are more complex than ever, so safety, accuracy, and precision are paramount.

As nutrition and feeding management processes demand more scrutiny, we face immense nursing workforce challenges, including staffing shortages and burnout. Nurses must deliver top-notch care despite limited physical and emotional

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



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bandwidth. In addition, nurses are tasked with integrating families into their infants’ care in a meaningful way.

With this context in mind, we urge hospital leaders to consider thinking outside the “four walls” of the NICU regarding milk and formula management. Implementing a feeding management system that supports safety, efficiency, and family-centered care provides hospitals with an impactful force multiplier.

Safety & Efficiency – What We Already Know

Most hospitals’ primary motivation for implementing a milk and formula management system is to increase safety in their unit. In addition, various professional organizations have recognized the importance of safe, accurate human milk handling (both maternal and donor milk) and have published guidelines accordingly. These organizations include the Academy of Nutrition and Dietetics, the American Society for Parenteral and Enteral Nutrition, the National Association of Neonatal Nurses, and the Human Milk Banking Association of North America (Steele, 2018).

The research underscores that scanning milk and formula throughout the feeding process is a worthwhile endeavor: every time feeding products are manipulated (including but not limited to collection, storage, fortification, or feeding), they’re at risk for safety errors like contamination, inaccurate preparation, and misadministration (Cossey et al., 2016). Steele & Bixby (2014) determined 282 potential safety failure points exist throughout the milk and formula handling process in hospital environments.

Given these potential errors at every step of the process, it's necessary to verify ingredients and manage safety at multiple points—not just before administering a feed. Unfortunately, hospitals with bedside scanning through barcode medication administration technology (rather than a comprehensive feeding management system) still experience misadministration errors. Many organizations rely on staff self-reporting or identifying another staff member's near misses or errors through cumbersome reporting software or manual processes. However, depending on self-reporting does not quantify the true extent of safety errors that occur since this only captures errors that staff notice.

In their most recent publication, Steele & Bixby (2021) illuminated that the safety benefits of scanning apply to human milk and the formula and nutritional additives. For example, they found that 480 errors (an average of 3.7 per week) were prevented over 2.5 years in a Level IV NICU thanks to incorporating formulas and fortifiers into their scanning process; without this safeguard, patients in these instances would have received the incorrect product, possibly resulting in feeding intolerance, allergic reaction, overnutrition, or undernutrition.

Not only does scanning milk prevent misadministration errors, but it also helps hospital staff enhance recipe accuracy and prevent contamination. For example, feeding management software with built-in recipe calculators and EHR integration can help staff precisely prepare per nutrition orders, while inventory viewing features and scanning barcodes help staff prevent feeding expired milk (in which contaminants can multiply to harmful levels).

Efficiency is another proven benefit of milk scanning systems (Steele & Bixby, 2021). The actions that support safety—like barcode scanning and EHR integration—simultaneously lighten staff's load. In addition, automating tasks like generating labels, charting feeding data, and eliminating two-nurse verification saves valuable time. Amid staffing shortages, nurses are expected to provide top-notch care despite having less bandwidth and energy than ever before. Efficiency is, therefore, more critical now than ever for staff retention and quality of work life.

Redefining Milk Management

The safety and efficiency features described above are undoubtedly meaningful benefits that milk/formula scanning systems offer hospitals. But what if we could ask for even *more* from these technologies?

As NICUs continue to embrace family-centered care, we must consider how every aspect of neonatal care can support that mission—and feeding management is no exception. We know that parents can be a vital part of a child's nutrition care plan, as the mother's own milk is the first-choice feed for many patients, and expressing milk can require an extensive commitment on the mother's part.

While mothers of NICU babies experience barriers to establishing and maintaining a milk supply (Lussier et al., 2019), receiving ongoing support and education can help overcome these barriers (Rossman et al., 2018). Supporting dyads in lactation is a crucial role for NICU clinicians. The National Association of Neonatal Nurses (NANN) takes the position that “it is essential to ensure that infants receive human milk through



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hospital discharge and that mothers have the opportunity to reach their personal breastfeeding goals” (Spatz & Edwards, 2015). A parent-facing component of a feeding management system can aid in just that.

Family Engagement: The Missing Component

Family-centered care has become an integral part of many NICUs' missions. Clinicians realize the importance of ensuring caregivers are engaged, educated, and emotionally supported during their child's hospitalization to yield a better experience. In addition, family-centered care interventions can improve weight gain and parents' satisfaction, knowledge, and skills, while decreasing readmission rates and parents' stress/anxiety (Ding et al., 2019; Scheutz Haemmerli et al., 2020).

Technology can help us extend engagement beyond the hospital's walls. While we know that face-to-face time is invaluable for parents and their hospitalized infant(s), the reality is that parents cannot always be at the bedside. This is particularly true for parents with barriers related to transportation, traveling distance, limited work flexibility, and additional family responsibilities.

We recommend the features listed below as simple yet effective tools for engaging parents in the feeding process. These features can seamlessly exist as part of a hospital's milk and formula management system. However, it is worth noting that these features should be optional and not preclude the use of the system within the hospital itself, as parents should have the autonomy to participate at their comfort level.

Enhanced Transparency into Inventory

Providing human milk is one of the few processes in the NICU journey in which parents truly have ownership. Qualitative research has shown that while NICU mothers can feel resentment and disconnection from pumping, it is also a “link” to their hospitalized child and can feel like an ongoing act of love to pump (Hurst et al., 2013). Understandably, parents must stay informed about how much milk their child has available in the unit and when to bring in more.

Inviting parents to view expressed breast milk inventory at home and the hospital via an app empowers them with more visibility into the process. This transparency may reduce anxiety, promote trust, and facilitate communication, as parents have 24/7 access to this information. This feature can also reduce unit

calls, freeing up staff bandwidth. In addition, parents and the care team can be on the same page regarding the feeding plan when both parties better understand how much maternal milk is available, thus reducing potential frustration.

Virtual Pumping Logs

An array of experts recommend that healthcare teams encourage mothers to log pumping sessions, then actively monitor those logs for proactive lactation counseling (Blatz et al., 2017; Lucas et al., 2014; Spatz & Edwards, 2015). Per NANN, “pumping information can be used to make research-based decisions regarding the mother’s pumping patterns” to inform the dyad’s care plan (Spatz & Edwards, 2015).

App-accessible pumping logs should have an easy-to-use interface in which a parent can enter pumping date and time; volume pumped and fresh versus frozen state. This information can then serve as data used in reports and graphs, through which both parents and clinicians can monitor milk production and pumping frequency over time. Studies have found that pumping patterns in the earliest days postpartum have a long-term impact on milk production among mothers of preterm infants (Hill & Aldag, 2005; Maastrup et al., 2014), indicating that timely lactation support is critical for a preterm dyad’s breastfeeding success. Clinicians who can monitor pumping trends in this time-sensitive window can make clinically impactful decisions about parents needing encouragement and intervention.

Breastfeeding Education

A core part of supporting lactation is providing mothers with evidence-based education. Education ultimately helps support a sense of self-efficacy, in which parents are more likely to feel prepared to take care of their newborns despite the stress and anxiety that comes with hospitalization. Lee et al. (2012) concluded that NICU parents need information to be delivered at the right time and in an individually tailored manner to minimize stress and feeling overwhelmed.

Feeding management systems with a parent-facing app can provide a hub for reliable education. We recommend the ability for healthcare providers to send photos, videos, and educational resources through this application so that the healthcare team can provide mothers with the correct information at the right time. NICU educational platforms like OnlineEducation can serve as another user-friendly way for information transmission. Receiving materials via computer, mobile, or tablet is a better fit for most modern parents than paper formats.

Communication with In-Hospital Lactation Resources

It’s well-established that breastfeeding rates increase when parents have greater access to hospital lactation consultants (Hallowell et al., 2014). However, lactation consultants may be thinly spread across multiple units and not encounter mothers on the NICU floor when help is needed. The need for lactation support is great: Lucas et al. (2014) found in their review that NICU mothers who perceived positive support and feedback from the healthcare team developed greater motivation, knowledge, and perseverance for pumping and transitioning to breastfeeding. They also found that even though a majority of mothers reported receiving some positive support, most still desired more help.

While technology cannot be a complete substitute for hands-on positioning and guidance from a lactation professional,

incorporating lactation-related messaging into a parent-facing app can be a force-multiplier for lactation staff.

Going Live with Better Milk Management

Comprehensive feeding management systems that leverage barcode scanning and EHR integration support hospital staff in feeding their patients more safely and efficiently. It’s an exciting opportunity for NICUs when these systems also support family-centered care; features like virtual pumping logs, breastfeeding education, and communication with lactation resources support lactation among NICU mothers.

For hospital leadership seeking to install a feeding management system, carefully considering what features you’ll have access to is vital. It’s also important to consider what project management and ongoing support will entail, as these components support safety, efficiency, and engagement long-term.

AngelEye Health has found that a key strategy for successfully supporting hospitals with new technologies is to embed NICU clinicians (rather than laypersons) every step of the way. When a vendor has a dedicated clinical team to provide training, onboarding, and software implementation, hospital partners can speak peer-to-peer, leading to an optimal experience. In addition, vendors utilizing clinical experts can uniquely facilitate staff buy-in and smoother transition to new processes in the unit.

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

After a feeding management system is live, ongoing support and data review facilitate smooth adoption and continued safety. We recommend seeking a vendor that offers data review sessions at regular intervals so that hospitals can track metrics like user adoption, “near miss” reports, and inventory usage. In exploring human milk errors in their NICU, researchers Luton et al. (2015) found that a “culture” of an ongoing commitment to quality improvement was paramount for safe feeding processes. Having data and spending time to review it on an ongoing basis with your vendor helps hospitals inform quality improvement projects that align with their priorities.

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A Unit Designed for the Neuroprotective Needs of Tiny Texans

Part Two: Our Journey to the Ideal Small Baby NICU

Sandra Carroll, OTR, CLC, C-ELBW, CNT

Introduction

Our job as neonatal intensive care unit (NICU) clinicians is both rewarding and challenging, and these challenges grow as we are tasked with caring for smaller and younger babies. Today, we have the capabilities to save the lives of extremely low birth weight (ELBW) infants as young as 22 weeks in the womb weighing less than 500 grams.

While every NICU baby requires specialized care specific to his or her condition, we have come to realize that the tiniest, most underdeveloped infants thrive best in an environment that protects both mind and body. Because they are developing right in front of our eyes, when they should be sheltered within their mothers' wombs, we must recreate that quiet, gentle and safe environment within the busy, and often noisy, NICU care setting.

In the first article of this two-part series, I presented information on the Engage, Grow, Thrive Small Baby Care Specialist program, which defines the elements of an ideal small baby NICU. This includes neuroprotective care, family-centered care and a team approach to clinical interventions.

This second article in the series focuses on the work I have led to establish a small baby unit at Baylor University Medical Center in Dallas, Texas, which we refer to as "The Tiniest Texans." I describe our journey to develop a team, clinical protocols and a space that is tailored specifically to the needs of our smallest, most fragile patients.

Reinvesting in Patient Care

Baylor, Scott & White Health's flagship hospital, Baylor University Medical Center in Dallas, Texas, has a designated

Sandra Carroll, OTR, CLC, C-ELBW, CNT, has nearly 30 years of experience in the neonatal intensive care unit (NICU). She is a Registered Occupational Therapist (OTR), Certified Neonatal Therapist (CNT), a Certified Lactation Counselor (CLC), Certified in the care of Extremely Low Birth Weight infants (C-ELBW), and is a NICU Trauma Informed Professional. With a deep interest and passion for providing care for infants with specialized needs, Carroll has been instrumental in contributing to the international growth of the highly specialized field of Neonatal Therapy. Carroll currently serves as NICU Supervisor of Therapy Services for Baylor University Medical Center in Dallas, Texas, where she helped establish the facility's Small Baby Unit (SBU) - "The Tiniest Texans". Sandra and Dräger worked in collaboration to develop this article as part of Dräger's continuing efforts to advance neonatal care through the sharing of insights, knowledge and best practices within the neonatal community.



Level IV NICU offering advanced life support services for premature and seriously ill newborns. The NICU team cares for babies ranging from full-term newborns with complex conditions to "micro-preemies," which are babies born at less than 28 weeks or weighing less than 1,000 g. This includes not only babies born at the medical center, but also those born at smaller community hospitals in the area with Level 1 and 2 NICUs who are transferred to our unit for specialized care.

In 2108, our NICU team at Baylor University Medical Center found itself with surplus funds to reinvest in care. We thought about how we could give back to the NICU and what we could do to help the babies in an impactful way. While we considered spending the money on new equipment for the unit, we determined that the funds would be better invested in staff education and training.

I had read about other hospitals, including CHOC and Cincinnati Children's Hospital Medical Center, that had established SBUs based on the Engage, Grow, Thrive Small Baby Care Specialist program, and the amazing results they had achieved in the clinical outcomes of pre-term babies. We decided to use the surplus funds to pay for every one of our NICU nurses to take the program. From there, we secured our hospital leaderships' support to establish our own SBU.

This marked the beginning of our Tiniest Texans Program, which is dedicated to the care of micro-preemies.

Developing Team Structure and Culture

Based on the Engage, Grow, Thrive program, we assembled a



multidisciplinary team dedicated to our SBU that includes sub-teams for nutrition, respiratory, pharmacy, neurodevelopmental and palliative care.

As a certified neonatal therapist, I lead the neurodevelopmental team. When I first joined Baylor, Scott & White in 1998, there were no certified neonatal therapists in the NICU but now we have many throughout our system. It has become a standard of care for our healthcare organization. In this role we serve as occupational therapists, physical therapists, and speech-language pathologists with specific expertise and advanced practice in the NICU.

All SBU team members are dedicated to the unit and have specialized training in caring for the smallest, most fragile pre-term babies. We are committed to ongoing education, with many earning certification for ELBW infants. We are also committed to continuous improvement, meeting regularly to perform problem cycles and come up with solutions.

Staff satisfaction is high as we all want to be members of this team and are honored to apply our skills to the care of these patients and their families. We take pride in belonging to a group that is looking at NICU care from a different perspective.

When we enter the SBU, we do so with a certain mindset. Walking into this space we acknowledge how these babies' brains are fragile and their parents are in complete distress. Entering this trauma filled environment requires calm and quiet energy. It is like taking on a completely different persona when we pass through the doors, one of intentional quiet and slow movements, similar to a library or spa.

We also hold each other accountable for our actions. This means being responsible and professional enough to tell another team member things such as, "maybe we could do this slower next time" or "what do you think about turning the lights off before we do this." We put aside our egos to do what is best for our tiny patients.

Standardizing Our Practice

In the past, we found NICU clinicians were sometimes practicing based on style versus standardized protocols. One

nurse might perform an intervention one way, while another did it a slightly different way. We realized that in order to understand what works best for patient outcomes, we had to standardize what we do.

In alignment with the Engage, Grow, Thrive program, the members of our SBU team were tasked with reviewing literature relevant to their practice area and coming back to the group with the specific guidelines for the babies in our care based on credible, clinical evidence.

Designing our Small Baby Space

Recognition of the importance of family-centered care on successful pre-term baby outcomes has driven significant changes in NICU design. Over the past 10 years, there has been a shift from "open bay NICUs" where all of the babies are housed together in one space, regardless of their size or condition, to single family rooms where the smallest and youngest babies and their mothers can be alone together.

We want families to be with their babies as much as possible during their time in the NICU. The outcomes are best when the parents are confident and competent in taking care of their baby no matter what age, rather than simply "visiting" their baby in the unit.

While some health systems and hospitals have the funds to build new NICUs designed around this principle, with individual rooms for family/baby units, most have to redesign what they already have in place. That was the case with our SBU. We would need \$85M to build a completely new unit.

While we did not have the funds necessary to build a new SBU, we were gifted money that enabled us to retrofit the space until we can get sufficient funding to build a new one.

First, we were gifted \$1M to purchase Dräger Babyleo® IncuWarmers and other equipment. Next, we received a portion of a \$35M gift to all Women's & Children's services, including the Labor and Delivery unit, as well as Antepartum unit and the outpatient Maternal Fetal Medicine department.

With our NICU having been built more than 30 years ago, space was a major constraint. We decided on a "unit within a unit" approach where the SBU would be housed within the larger NICU. We were challenged with finding a way to provide neuroprotective, family centered care, accommodating all of the required equipment, technology and supplies, from ventilators to computer stations to Kangaroo Care chairs and breast pumps at the baby's bedside.

We also wanted to avoid placing the babies in high traffic areas, such as entry and exit doors, because they needed a quiet, calm and low-light level environment that we could control. Other considerations were around where sinks and trash cans were placed in relation to the babies, as well as computer workstations where staff members tended to gather.

In our SBU space, instead of having two babies, side-by-side as we have in the general NICU, we leave open space between each baby. This accommodates not only medical equipment for each patient and his/her family, but also seating for Kangaroo Care and room for a breast pump so that mom can pump at her baby's side.

Between each of these family unit designed spaces is a cart that stores the most frequently used items for care. To facilitate medical records documentation, we have switched from stationary workspaces to computers on wheels (COWs) so the clinician can quietly chart at the baby's bedside and then move the equipment away.

Selecting Supporting Equipment

Throughout our SBU are signs that read, "Shhh, you are entering the Tiniest Texans, please be quiet, light and sound matters here." We have backed these words with equipment designed for neuro-supportive care.

All of us in the NICU have been taught that pre-term babies thrive in an environment where sound is below 45 decibels with low, cycled light, but historically the best way we could achieve this was to be quiet and turn the lights down. The problem with maintaining this environment is human behavior. For instance, a caregiver walks into the unit and turns up the lights not understanding the impact on the babies. Or others speak loudly in the unit without realizing the impact it has on the tiniest brains and bodies.

In 2018, while attending a medical conference, I discovered a solution that would meet our needs for neuroprotective and family-centered care in the SBU: The Dräger Babyleo® IncuWarmer. The hybrid incubator creates an individual environment for each baby in the SBU, with controlled heat and humidity and an integrated sound and light monitoring system that aligns with recommended NICU guidelines and best practices.

Babyleo supports family-centered care in a variety of ways. With variable height adjustment and knee pockets parents can easily get close to their baby, even when sitting in a wheelchair. This helps facilitate Kangaroo Care. When the baby is skin-to-skin with the mom or another caregiver, Babyleo documents this Kangaroo time to ensure the incubator settings remain the same for the baby's return.

Another way parents are encouraged to participate in their babies' care with Babyleo is through light and sound. Parents and caregivers can choose between eight different mood light colors to gently light the floor area beneath the incubator to create a pleasant, personalized atmosphere. It is also the first device to include an audio function which allows, for example, mothers to play music or recorded voice files for their babies via an MP3 player plugged into the side of the device.

Studies of music therapy with pre-term infants have shown improvement in physiological outcomes (e.g., oxygen saturation, heart rate, respiratory rate, blood pressure) as well as behavioral state (e.g., crying, facial expression, body movement) and pain scores.¹

We have found the Babyleo to be an effective and flexible solution for our NICU. It can support the needs of the tiniest Texans, as well as bigger babies who may not require a heat source but need a therapeutic environment with controlled light and sound and maybe some positive sound stimulation.

The incubator is also designed to prevent jarring movements when clinicians adjust the mattress or incubator height or transport the baby within it. This is important because

uncontrolled movements can increase intracranial pressure and increase risk of intraventricular hemorrhage (IVH) in preemies, especially very low birthweight babies weighing less than 1,500 g.²

One specific application in which Babyleo has been particularly valuable is during eye exams, which can be very traumatic to pre-term babies. We are able to ergonomically position Babyleo so the eye doctor and baby are comfortable, and the neonatal therapist can be at the bedside to contain the baby and provide a less disruptive environment for the procedure. Among the babies who have had eye exams in this way within the Babyleo, very few have experienced drops in heart rates, which is common during eye exams.

The Advent Health for Children in Orlando, Fla., which has also been using Babyleo in its NICU, has improved its Press Ganey Patient Experience Scores from 4.4% to over 92%, putting the unit well into the 10 top percentile.

Conclusion

While we would like every baby to remain in his/her mother's womb full-term, almost 1 of every 10 infants born in the US are premature (born before 37 completed weeks of pregnancy).³ As babies are born at earlier and earlier gestational age, NICU practitioners are face ever-growing challenges in not only keeping these babies alive, but also protecting them from damaging influences that could impact their development and well-being far down the road.

The SBU approach takes into account all of the factors that influence care for the tiniest infants—from medical interventions based on clinical evidence, to the critical role of the mother and family in supporting physical and neurological development. Over the past decade, NICUs with SBUs have witnessed incredible results, with pre-term babies suffering fewer complications, growing faster and leaving the NICU sooner, and living healthier lives as they progress through childhood and grow to adulthood.

While our SBU at Baylor University Medical Center is relatively new, we are already seeing the positive impact it has on our Tiniest Texans. We will continue to document our successes and look forward to reporting data on how this program benefits our babies' development.

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***Bifidobacterium infantis* EVC001 Administration is Associated with a Significant Reduction in Incidence of Necrotizing Enterocolitis in Very Low Birth Weight Infants**

Brian Scottoline, MD, PhD and Joe Tobias, MD

The development of necrotizing enterocolitis (NEC), a devastating inflammatory bowel disease that disproportionately affects preterm infants, has been strongly linked to dysbiosis of the preterm gastrointestinal tract. Changing the composition of the intestinal microbiota through enteral probiotic administration may promote a microbial community that attenuates, or even prevents, dysbiotic NEC. In the United States, NEC has an incidence of 5-10% among very low birth weight (VLBW) infants and carries an overall mortality of 23.5%, although mortality reaches as high as 50% among extremely low birth weight (ELBW) patients who require surgery.¹

Bifidobacterium longum subspecies *infantis* (*B. infantis*) is a mutualist colonizer of the infant gut that converts human milk oligosaccharides (HMOs) into beneficial substrates, including short-chain fatty acids such as lactate and acetate.² Results from prior research have demonstrated that *B. infantis* EVC001 is well-tolerated, colonizes the intestinal microbiota in infants fed human milk, lowers the abundance of NEC-associated pathogenic bacteria and fecal antibiotic resistance genes, and decreases enteric inflammation.³⁻⁶ Notwithstanding these previous findings, *B. infantis* EVC001 as a single strain had yet to be associated with a reduction in NEC in preterm infants.

Our unit at Oregon Health and Science University (OHSU), a level IV neonatal intensive care unit (NICU) that routinely cares for critically ill preterm newborns, had a high incidence of NEC despite evidence-based practices to prevent the disease. Aware of the research supporting dysbiosis as a contributor to NEC,^{7,8} and the evidence that administering probiotics to VLBW infants might reduce NEC incidence, we decided to begin probiotic administration to VLBW infants. The choice to use *B. infantis* EVC001 was based on biological plausibility, given that it is a natural colonizer of the gut of human milk-fed infants.⁹ Additionally, EVC001 is produced with stringent purity standards, and has Generally Recognized as Safe status. After noting a change in NEC incidence in the unit, we formally evaluated the effect of *B. infantis* EVC001 administration to VLBW infants on the incidence of NEC and NEC-related mortality. Using a single strain probiotic made determination of effects, whether beneficial or detrimental, more straightforward.

Brian Scottoline, MD, PhD is a board-certified neonatologist at Oregon Health and Science University. Joe Tobias, MD is a resident physician in the department of surgery at Oregon Health and Science University.

This study was a non-concurrent retrospective chart review of two cohorts of VLBW infants <32 weeks or <1500 grams: 301 VLBW infants admitted to the NICU from January 2014 to June 2018 who did not receive EVC001 compared to 182 VLBW infants from June 2018 onward who received more than one dose of the probiotic. Infants in the EVC001-fed cohort were administered 8 billion CFU *B. infantis* EVC001 suspended in 0.5 mL MCT oil once daily until 34 weeks PMA or for a minimum of two weeks, whichever duration was longer. In addition to analysis of the VLBW population in this study, a subgroup analysis of extremely low birth weight (ELBW) infants was also conducted.

Infants fed *B. infantis* EVC001 had a 73% risk reduction in NEC compared to infants not given *B. infantis* EVC001 (11% versus 2.7%) with an adjusted risk ratio of 0.27 (95% CI 0.094, 0.614, $P < 0.01$). The number needed to treat was 13. Sub-group analysis for ELBW infants demonstrated a statistically significant difference in NEC rates between cohorts (19.2% versus 5.3%) with an adjusted risk ratio among ELBW infants of 0.28 (95% CI 0.085, 0.698, $P < 0.05$). The number needed to treat was 8. Perhaps most striking, there was no NEC-related mortality in the EVC001-fed cohort, which results in a statistically significant difference compared to infants not given *B. infantis* EVC001 (0% vs. 2.7%, $P = 0.03$). The effect in ELBW infants was remarkable given the lack of prior evidence for an effect of probiotics in these smallest of patients.¹⁰ Furthermore, OHSU has not seen an in-born NEC-related death in the more than three-and-one-half years since adopting *B. infantis* EVC001 in the NICU. The low NEC rate continues to be true beyond the study period.

Expert opinions still vary regarding the use of probiotics in preterm patients, and if used, on what strains, regimens, and dosing are appropriate for NICU populations.¹¹ However, the results of our study add to the growing body of evidence in support of select probiotic strains for clinical applications in neonatology.¹²

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received the support of CEREBRA, CIBERER and AGAUR. Low birth weight is associated with birth complications and health problems. Low birth weight babies (birth weight below the 10th centile) account for 10% of all births. Low birth weight reflects growth restriction in fetal life, it is recognised by the WHO as one of the most important causes of perinatal mortality worldwide and it is linked to poorer neurodevelopment in childhood and higher risk of metabolic and cardiovascular health problems in adulthood. No treatment had existed until now that could prevent or improve this condition. The research team led by Dr Eduard Gratacós has been studying the possible causes and consequences of low birth weight for many years. “We saw that mothers of low birth weight newborns often had a suboptimal diet and high stress levels,” explains Dr Gratacós. This led to the idea of conducting a clinical trial to study whether structured interventions based on Mediterranean diet or stress-reduction could reduce fetal growth restriction and other pregnancy complications.

Neonatal Sepsis: WHO-Recommended Rx Needs a Major Rethink

First-line treatment of neonatal sepsis in low- and middle-income countries (LMICs) with ampicillin-gentamicin — as recommended by the World Health Organization (WHO) — needs to be reassessed, a retrospective, observational cohort study suggests. Rates of resistance to this particular antibiotic combination are extremely high in LMICs, and this treatment is unlikely to save many neonatal patients, according to the study's results. “The WHO guidelines are over 10 years old, and they are actually based on high-income-country data, whereas data reported from low-income countries are reported by private labs, and they do not cater to the lower socioeconomic groups within these countries, which is important data to capture,” Timothy Walsh, MD, University of Oxford, Oxford, United Kingdom, said. “The main take-home message from our data is that ampicillin-gentamicin doesn't work for most of the Gram-negative isolates we tested, and while there are alternatives, their use is confounded by [a lack of] financial support,” he added. In this substudy of the Burden of Antibiotic Resistance in Neonates from Developing Societies (BARNARDS) study, investigators focused on the effectiveness of antibiotic therapies after taking into account the high prevalence of pathogen resistance to ampicillin-gentamicin. Participating countries included Bangladesh, Ethiopia, India, Nigeria, Pakistan, Rwanda, and South Africa. “Blood samples were obtained from neonates presenting with clinical signs of sepsis,” the authors note, “and WGS [whole-genome sequencing] and MICs [minimum inhibitory concentrations] for antibiotic treatment were determined for bacterial isolates from culture-confirmed sepsis.” Between November, 2015, and February, 2018, 36,285 neonates were enrolled into the main BARNARDS study, of whom 9874 had clinically diagnosed sepsis and 5749 had antibiotic data. A total of 2483 neonates had culture-confirmed sepsis, and WGS data were available for 457 isolates taken from 442 neonates. Slightly over three quarters of the 5749 neonates who had antibiotic data received first-line ampicillin-gentamicin. The other three most commonly prescribed antibiotic combinations were ceftazidime-amikacin, piperacillin-tazobactam-amikacin, and amoxicillin-clavulanate-amikacin. Neonates treated with ceftazidime-amikacin had a 68% lower reported mortality than those treated with ampicillin-gentamicin at an adjusted hazard ratio (HR) of 0.32 (95% CI, 0.14 – 0.72; *P* = .006), the investigators

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Tetherless Techniques for Continuous Monitoring of Arterial Oxygen Saturation and Non-invasive Continuous Respiration Rate for Neonates

Leslie Altimier, DNP, RN, MSN, NE-BC

Abstract

In the last decades, photoplethysmography (PPG) has been used as a noninvasive technique for monitoring arterial oxygen saturation by pulse oximetry (PO). In addition, algorithms have been developed to extract respiration rate from these vital signs using datasets taken from adult or child respiration values so they may not accurately represent the respiration signals from infants. While oxygen saturation and respiration rate monitoring have played a key role in treating the most vulnerable patients in the NICU, wired connections can limit clinicians in the ability to improve neonatal comfort and enhance clinician workflows. As technology improves, the more we can eliminate cables and wires, and the more mobility and access to holding a baby will be available to parents of a baby in the neonatal intensive care units (NICUs). The promotion of tetherless technology will improve not only the ability of parents to easily access and hold their baby in the NICU but will also simplify clinicians' workflows.

Keywords: Photoplethysmography, PPG, wearables, noninvasive, tetherless, wireless, respiration rate, oxygen saturation, pulse oximetry, neonate

Background

The world is witnessing a rising number of preterm infants who are at significant risk of medical conditions and require continuous care in the NICU. Preterm is defined as babies born alive before 37 weeks of pregnancy are completed, and there are further sub-categories of preterm birth, based on gestational age: Extremely preterm (less than 28 weeks), very preterm (28 to 32 weeks), and moderate to late preterm (32 to 37 weeks). Preterm infants are at a significantly higher risk of medical and surgical morbidities in comparison to babies born at term (> 37 weeks). Therefore, preterm infants are specially cared for in the NICU for continuous medical monitoring of respiration rate (RR), heart rate (HR), electrocardiogram (ECG), and blood oxygen saturation (SpO₂ – also known as pulse oximetry). Medical parameters are continuously monitored in premature infants in the NICU using a set of wired, sticky electrodes attached to the body which can cause discomfort and irritation. In addition, respiration rate (RR) monitoring in the NICU faces challenges of accuracy and clinical quality because RR is extracted from the electrocardiogram (ECG) via impedance.

In 2018, the World Health Organization (WHO) reported that an estimated 15 million babies are born preterm (before 37 completed weeks of gestation) globally, and this number is rising. That is more than 1 in 10 babies. Moreover, in almost all countries with reliable data, preterm birth rates are increasing. Preterm birth complications are also the leading cause of death among children under 5 years of age, responsible for approximately 1 million deaths in 2015. Three-quarters of these deaths could be prevented with current, cost-effective interventions. Across 184 countries, the rate of preterm birth ranges from 5% to 18% of babies born. Many survivors face a lifetime of disability, including learning disabilities and visual and hearing problems.

Inequalities in survival rates around the world are also stark. In low-income settings, half of the babies born at or below 32 weeks (2 months early) die due to a lack of feasible, cost-effective care, one of which is basic care for breathing difficulties. More than three-quarters of premature babies can be saved with feasible, cost-effective, kangaroo mother care (the baby is carried by the mother with skin-to-skin contact). Suboptimal use of technology in middle-income settings is causing an increased burden of disability among preterm babies who survive the neonatal period. WHO has developed new guidelines with recommendations for improving outcomes of preterm births. This set of key interventions can improve the chances of survival and health outcomes for preterm infants. The guidelines include interventions provided for the newborn baby—for example thermal care, feeding support, kangaroo mother care, safe oxygen use, and other treatments to help babies breathe more easily.

In the neonatal intensive care unit (NICU), heart rate, respiratory rate, and oxygen saturation are vital signs (VS) that are continuously monitored in infants, while blood pressure is often monitored continuously immediately after birth, or during critical illness. Although changes in VS can reflect infant physiology or circadian rhythms, persistent deviations in absolute values or complex changes in variability can indicate acute or chronic pathology.

Although changes in vital signs (VS) can reflect infant physiology or circadian rhythms, persistent deviations in absolute values or complex changes in variability can indicate acute or chronic pathology. Recent studies demonstrate that analysis of continuous VS trends can predict sepsis, necrotizing enterocolitis, brain injury, bronchopulmonary dysplasia,

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

cardiorespiratory decompensation, and mortality. Subtle changes in continuous VS patterns may not be discerned even by experienced clinicians reviewing spot VS data or VS trends captured in the monitor. In contrast, objective analysis of continuous VS data can improve neonatal outcomes by allowing heightened vigilance or preemptive interventions.

Preterm infants in the NICU are often unstable and have fluctuating vital signs. For example, a very low or high heart rate can indicate an underlying condition such as infection, pain, or illness. Abnormal respiratory rate values are often associated with hypoxemia (low level of oxygen in the blood), hypercapnia (high level of carbon dioxide in the blood), or acidosis (high level of acidity in the blood).

Preterm infants also often require some form of respiratory support with supplemental oxygen. Hyperoxia in preterm infants is associated with retinopathy of prematurity and bronchopulmonary dysplasia, whereas intermittent hypoxia is associated with increased mortality, severe retinopathy of prematurity, and pulmonary hypertension. Therefore, regulating oxygen exposure is essential. Continuous pulse oximetry (SpO₂) measured by high-resolution pulse oximeters is more accurate than hand-transcribed SpO₂ values, and more episodes of intermittent hypoxia are detected.

Current Monitoring Methods

To monitor their physiological status, specialized medical equipment is used depending on the unique needs of neonates. The standard vital signs usually monitored include heart rate (HR), respiratory rate (RR), blood pressure, temperature, and peripheral oxygen saturation (SpO₂). Below are some current monitoring methods for standard vital signs such as heart rate (HR), respiratory rate (RR), and peripheral oxygen saturation (SpO₂) used by clinicians:

- The Electrocardiogram (ECG) computes the heart rate. A pulse oximeter attaches to the infant's hand, foot, finger, or toe, which records the photoplethysmography (PPG) signal and computes the estimates of heart rate and SpO₂.
- The impedance pneumography (IP) waveform computes the respiratory rate, obtained by measuring changes in the electrical impedance of the patient's thorax using the ECG electrodes. The clinical staff also make manual measurements every 1 to 4 hours depending on the severity of the patient's condition.
- Other methods of respiratory rate monitoring include the manual counting of breaths by a caregiver, capnography, and transthoracic impedance measurement. Manual counting of breaths (such as auscultation) is an intermittent, labor-intensive, and unreliable method of measuring the respiratory rate.
- Continuous pulse oximetry is used to monitor oxygen saturation (SpO₂) and pulse rate and has been a valuable tool for Neonatologists since the early 1980s. In the last few decades, photoplethysmography (PPG) has been used as a noninvasive technique for monitoring arterial oxygen saturation by pulse oximetry (PO). Photoplethysmography (PPG) is a noninvasive circulatory signal related to the pulsatile blood volume in tissue and is displayed by the pulse oximeter. Pulse oximeters use photoplethysmography (PPG) to not only compute oxygen saturation and pulse rate, but the PPG also contains an abundance of information related to cardiac hemodynamics. The PPG is similar in appearance to the invasive arterial waveform but is noninvasive and

ubiquitous in hospitals. Continuous monitoring of arterial oxygen saturation by pulse oximetry (SpO₂) is the main method to guide respiratory and oxygen support in neonates during postnatal stabilization and after admission to the neonatal intensive care unit. Titration of supplemental oxygen to maintain a narrow window of oxygen saturation is essential to reduce the risk of retinopathy of prematurity, bronchopulmonary dysplasia, and death. Continuous pulse oximetry (SpO₂) is superior to clinical observation alone; without it, desaturation can only be detected once arterial saturation (SaO₂) has dropped below 80% and cyanosis develops. Pulse oximetry also avoids frequent phlebotomy for blood gas analysis, which is painful and causes iatrogenic anemia.

Challenges with Current Monitoring Methods

Sensors used in current monitoring methods are attached either to the chest and/or extremities and pose several challenges that include:

- **Artifacts and false alarms:** Optical blood oxygenation and heart rate sensors are significantly vulnerable to motion artifacts such as limb movements, crying, coughing, and handling of the infant. Standard ECG electrodes also suffer from frequent false or non-actionable alarms due to loosely connected electrode leads and dry contacts.
- **Tethered connections:** Tethered, or wired connections, between sensors and equipment, can limit skin-to-skin contact (SSC)/kangaroo care (KC), which negatively impacts neonates and their parents.
- **Lack of direct respiration measurement:** Neonates also need continuous monitoring of vital signs such as respiration rate without being caused discomfort or irritation. Respiratory rate (RR) is one of the most sensitive markers of a patient's condition and a vital component of clinical assessment and monitoring. While end-tidal carbon dioxide monitors are the most accurate respiration monitoring technique, the cannulas may cause discomfort and are less well tolerated by non-intubated preterm babies. Infant respiration signals are generally extracted from ECG and pulse oximetry signals and through manual counting of chest excursions. With ECG or impedance-based respiratory rate, clinicians may not get an accurate measure of the patient's ventilation. With manual counting of the respiratory rate, clinicians are only able to get a snapshot of the vital signs and documentation may be prone to transcription errors.

Advancements in New Monitoring Solutions

Due to the ongoing needs and limitations of the current standard monitoring equipment used in NICUs, recent research has explored alternative technologies to address these issues. Advancements include improved accuracy of pulse oximeters, wearable devices, and acoustic respiration rate, which are discussed in the following sections.

Accuracy with Adaptive Signal Processing

Reliable and accurate pulse oximetry is paramount to optimal patient outcomes. The discovery of adaptive signal processing separates the true arterial signal from other sources of noise, creating the ability for pulse oximetry to measure-through motion and low perfusion. During neonatal care, accurate pulse oximetry is necessary to target SpO₂ during delivery room resuscitation, in situations associated with increased risks of hypoxemia, in the prevention of hyperoxia, and for screening of congenital heart disease. Accurate pulse oximetry has also

been shown to help clinicians better target oxygen levels and therefore reduce severe retinopathy of prematurity in neonates. In addition, accurate pulse oximeters can improve clinician confidence by limiting false positives and false negatives during CCHD screening in newborns and help improve patient outcomes. Some suggest that pulse oximetry is the fifth vital sign. Pulse oximetry sensors can have accuracy specifications down to 1.5% A_{RMS} during motion, in all patient populations, providing clinicians with even greater confidence that the SpO_2 values they rely on accurately reflect a neonate's physiological status while decreasing the number of alarms to help prevent alarm fatigue. The use of pulse oximetry can lead to fewer adverse events by capturing accurate readings, even during frequent movement and crying of babies and in low perfusion situations, such as in critically ill or unstable patients.

Wearable Technology

There is a growing demand, across the globe, for wearable health technology because of its wide-ranging benefits. It is assumed that by 2030 there will be about 100 billion network-connected devices. Medical device companies have launched wearable vital sensors at warp speed since the COVID-19 pandemic began.

Recent technological advances in pulse oximetry focusing on the morphologic analysis of the PPG waveform have defined new indices, such as the perfusion index, that are capable of assessing and monitoring the microcirculation and intravascular fluid volume status] of neonates while in the neonatal intensive care unit. Perfusion index is an assessment of the pulsatile strength at a specific monitoring site (e.g., the hand, finger, or foot), and as such is an indirect and noninvasive measure of peripheral perfusion. In recent years, the use of perfusion index has been suggested as an adjunct to pulse oximetry screening to detect non-cyanotic CCHD cases. Multiple studies have described perfusion index values in the first few days of life in term and preterm infants. Low values and reduced short-term variability of perfusion index on day 1 are associated with adverse outcomes. A lower perfusion index in neonates has been correlated with lower superior vena cava flow and shown to be a predictor of illness severity and subclinical chorioamnionitis, a major predictor of morbidity and mortality in very low birth weight (VLBW) neonates.

With recent advances in digital signal processing, PPG waveform can also be used to assess the microcirculation (perfusion index) and intravascular fluid status of neonates. Because of the success of pulse oximetry and recent advances in digital signal processing, there is growing research interest in seeking circulatory information from the PPG and developing techniques for a wide variety of novel applications.

It is well established that early skin-to-skin contact (SSC) between mother and newborn encourages bonding, facilitates early and successful breastfeeding, assists in thermoregulation and glucose control, provides cardiorespiratory stability, and decreases newborn pain. The World Health Organization and UNICEF strongly support early SSC. A tetherless pulse oximeter solution is of great interest for neonates, families, and clinicians in the NICU, since Skin-to-Skin Contact (SSC)/Kangaroo Care (KC) is the optimal environment for the care of neonates. SSC/KC involves a complex transfer process of moving the baby, with numerous wires, cables, and tubing, from the incubator to the chest of the parent. With babies in mind, an innovative and unique tetherless pulse oximetry solution have been developed,

which combined with adaptive signal processing provide superb accuracy without the need for a cabled connection to a monitor. Such sensors are lightweight, comfortable to wear, and allow for the safe movement, transport, and transfer of a baby to the parent's chest, providing uninterrupted continuous pulse oximetry monitoring.

Acoustic Respiration Rate

Thoracic impedance respiratory monitoring (IM) is widely used in the neonatal intensive care unit (NICU) for apnea detection in preterm infants. However, IM may fail to identify apneic events by misinterpreting cardiac impedance changes as breathing, particularly during bradycardia. Such false negative episodes preclude alarm initiated intervention by nurses prior to the onset of apnea-associated bradycardia and/or hypoxia. Conversely, IM may fail to recognize shallow breathing, resulting in false-positive signaling of apnoea.

There is technology that can provide continuous, non-invasive respiratory monitoring with accurate respiratory rate measurements that is automated and recorded on connected devices. Such technology obtains respiratory rate by detecting acoustic signals produced by the turbulent airflow in the upper airway that occurs during inhalation and exhalation. The respiratory signal is separated and processed to display continuous respiration rate and an acoustic respiration waveform; a visualization of the signal caused by the patient's airflow. The visual waveform analyzes both the inspiratory and expiratory phases of respiration. For example, a longer expiration phase is noted when a child has RSV or asthma. Additionally, clinicians can monitor for any pauses in breathing over the time the neonate is being monitored.

Conclusion

Accuracy of all monitoring devices (wired or wireless) for our extremely tiny and critically ill neonates is of paramount importance. Accuracy Root Mean Squared (A_{RMS}) is a statistical calculation of the difference between device measurements and reference measurements. When evaluating monitoring equipment utilized on our most vulnerable patients, it is important to choose equipment with accuracy specifications that have the highest sensitivity and specificity to help clinicians make critical patient care decisions. Accurate wireless pulse oximetry is beneficial to encourage attachment and bonding between the parents and baby. We as caregivers for these vulnerable neonates should not compromise for such patients as they deserve the best care we have to offer.

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report. In contrast, no significant differences in mortality rates were reported for neonates treated with amoxicillin-clavulanate-amikacin or piperacillin-tazobactam-amikacin compared to those treated with ampicillin-gentamicin.

Surprising Data on Neurodevelopment of Babies Born During the Pandemic

Columbia researchers found that babies born during the pandemic's first year scored slightly lower on a developmental screening test of social and motor skills at 6 months—regardless of whether their mothers had COVID during pregnancy—compared to babies born just before the pandemic. The study which included 255 babies born at NewYork-Presbyterian's Morgan Stanley Children's Hospital and Allen Hospital between March and December 2020, was published in the journal *JAMA Pediatrics*. “Infants born to mothers who have viral infections during pregnancy have a higher risk of neurodevelopmental deficits, so we thought we would find some changes in the neurodevelopment of babies whose mothers had COVID during pregnancy,” says Dani Dumitriu, MD, PhD, assistant professor of pediatrics and psychiatry at Columbia University Vagelos College of Physicians and Surgeons and lead investigator of the study. “We were surprised to find absolutely no signal suggesting that exposure to COVID while in utero was linked to neurodevelopmental deficits. Rather, being in the womb of a mother experiencing the pandemic was associated with slightly lower scores in areas such as motor and social skills, though not in others, such as communication or problem-solving skills. The results suggest that the huge amount of stress felt by pregnant mothers during these unprecedented times may have played a role. “These were not large differences, meaning we did not see a higher rate of actual developmental delays in our sample of a few hundred babies, just small shifts in average scores between the groups,” Dumitriu says. “But these small shifts warrant careful attention because at the population level, they can have a significant public health impact. We know this from other pandemics and natural disasters.”

Micro-Preemie Beats Odds to Become Busy Toddler

Unique Cardiac and Respiratory Care for Infants with BPD (CRIB) Program helps patients like Haven thrive

Three-year-old Haven Greyson Smith likes to break odds and set records—whether that’s playing at home or surviving despite being given a 10-per-cent chance. With help from his devoted mom and an army of health care professionals, Haven has beaten all odds and expectations as a “micro-preemie.”

“It hasn’t always been easy, but none of that matters. I have a thriving three-year-old, which I didn’t always believe I’d have,” Amanda says.

Born at just 25 weeks gestation, Haven earned the title of tiniest baby born at Lucile Packard Children’s Hospital Stanford in 2019. Nicknamed ‘Tiny Peanut’ by the neonatal intensive care unit (NICU) nurses, he weighed just 0.9 pounds at birth. Amanda compared him to the size of a soda can. She likes to say that when he finally left the hospital’s NICU after eight months, weighing just over eight pounds, he was “eight times the Haven he was when he was born.”

Amanda’s high-risk pregnancy was complicated by intrauterine growth restriction, leading to his early delivery. It’s common for micro-preemies this small to have challenges such as breathing and feeding problems, and Haven was no exception. The Nest at Packard Children’s, which cares for the smallest preemies, has developed specialized ventilator protocols to assist the breathing of micro-preemies to promote a gentle approach and minimize future breathing complications. This approach allowed Haven to finally breathe without ventilator support at six weeks of age and just over two pounds.

Growth-restricted babies are also at risk for developing future lung complications. Lungs are the last organ to develop, so when babies are born prematurely their lungs are not fully formed. This can cause heart-lung problems, and leave kids fatigued and short of breath.

The Packard Children’s Cardiac and Respiratory Care for Infants with BPD (CRIB) Program Care Team was established to address complications of prematurity. In 2019, CRIB began monitoring Haven’s bronchopulmonary dysplasia (BPD) and pulmonary hypertension as a newborn and continues to do so today.

Doctors at Lucile Packard Children’s Hospital Stanford created CRIB because of the constant need for communications between the cardiologists, pulmonologists, and neonatologists



Haven Greyson Smith has giggling fits, enjoys throwing things, and loves to snuggle on his mom’s lap. Photo from 2021 provided by Stanford Children’s Health.

who care for preemies who have both lung and heart disease. The coordinated, multidisciplinary effort means convenient, seamless, and exceptional care for highly complex preemies in the hospital and through the years as they grow. While there are other hospitals that have BPD follow-up programs, the true multidisciplinary approach at Stanford Children’s Health is what makes CRIB unique.

“What’s great about CRIB is that with pulmonary hypertension you need both a heart doctor and a lung doctor talking and agreeing on treatment, so you get that comprehensive look in one appointment,” Amanda says.

This article is contributed by Stanford Children’s Health.

Helping Haven go home

“Each lung has an array of blood vessels, shaped like a tree. When a baby is born early, this vascular tree is like a tree in winter. It’s missing all its little branches and the leaves in between,” says Rachel Hopper, MD, pediatric cardiologist at Stanford Children’s Health and co-director of CRIB. “This puts pressure on the heart to pump more blood and can cause high blood pressure in the lungs.”

Haven’s pulmonary hypertension demanded a specialized use of the drug treprostinil, a medication that was delivered 24/7 from a pump that he wore continuously to enhance blood flow in his lungs and make it easier for his heart to pump blood. Without this stress, his body was better able to grow and develop, and Haven transitioned off the drug last year. Treprostinil tends only to be prescribed by large pediatric heart centers with a PH program, like Lucile Packard Children’s Hospital Stanford. Amanda credits the medicine for enabling Haven to come home.

“As we support Haven’s ability to grow new lung tissue and blood vessels, we are seeing his lungs improve,” says Michael Tracy, MD, pediatric pulmonologist at Stanford Children’s Health and co-director of CRIB. “Research used to say that lungs became fully developed by age two or three. Now, we are learning that lungs continue to develop even into adolescence.”

Stanford Children’s Health, with Lucile Packard Children’s Hospital Stanford as its center, continues to expand CRIB and research efforts to further improve care for patients with BPD. The team is part of the Pediatric Pulmonary Hypertension Network, a national group of pediatric pulmonary hypertension experts, and the BPD Collaborative, a national group of multidisciplinary care teams dedicated to optimizing outcomes of infants and children with severe BPD. Participation in these organizations empowers doctors to identify trends and improve care. They hope research will eventually lead to novel treatments, like stem cell therapies that could potentially help repair damaged lungs.

“Haven is clearly a fighter, and he’s getting more fight in him as he gets older,” Dr Tracy says.

To support his heart and lungs, Haven is sometimes hooked up to oxygen at night. A victory was weaning him off oxygen during the day, giving Haven one less cord to tether him.

As Haven grows, so does his lung capacity, making it easier for oxygen to flow and creating less work for his heart. The hope is that he can eventually come off oxygen altogether. In the meantime, Haven is conquering even more milestones—most recently, going to his first day of in-person preschool.

“It’s rewarding to care for preemies like Haven. For many the first year can be dicey, especially with pulmonary hypertension,” Dr Hopper says. “But we know that if we can get babies to two years of life, many will grow and thrive.”

Nutritional Practices to Optimize Care in Small Baby Units

Sandra Sundquist Beauman, MSN, RNC-NIC

Small baby units are becoming more common within the walls of existing neonatal intensive care units. These units are designed to optimize care for the smallest infants, those under 28 weeks or 1000 grams (Kaempf & Gautham, 2022). This includes those at 23 weeks gestation or in some cases, as early as 22 weeks (Backes, Rivera et al, 2021; Holtrop, Swails et al, 2013; Rossi, DeFranco, Hall, 2021; Watkins, Dagle et al, 2020). Infants at this edge of viability present special challenges in care. Even as survival improves at these gestational ages, outcomes in growth, neurodevelopment and respiratory status present special challenges in this population and have lasting impact.

The intent of implementing a small baby unit is to provide a dedicated space where these particularly vulnerable infants can be cared for in a quiet environment that supports mother/infant bonding by healthcare providers who provide evidence-based, consistent care. Even when evidence is lacking, it is known that consistency in care improves outcomes (Tay, de la O, Finn, Fritzell, 2021). Particular areas that may be addressed in these programs include:

- Delivery Room Management
- Respiratory Care
- Cardiovascular Care
- Nutrition
- Neuroprotective/Developmental Care
- Infection Prevention
- Family involvement and support

While these practices are separated in the list here, they are actually very intertwined in overall care practices. Some programs separate care practices into phases of time such as stabilization including birth to 10 days of age, the first month of life and 30 days to discharge (Morris, Cleary, Soliman, 2015). This article will focus on nutritional care, particularly enteral, in these infants.

Infant growth is important but often challenging. The rate of growth for a fetus while in utero at the gestational ages under discussion is much higher than what is expected in term and near term infants after delivery (Pereira-da-Silva, Virella, 2014).

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



Photo supplied

This growth and the nutrition required to accomplish it is important as poor antenatal or early postnatal growth impact long-term outcomes negatively (Wight, Kim et al, 2018). Early adequate parenteral nutrition with sufficient protein intake is vital. Early enteral feeding is also known to improve outcomes and decrease the risk of necrotizing enterocolitis. Exactly when to start enteral feedings and increasing them is not yet established. However, two things are certain, a consistent approach to feedings improves outcome (Gephart & Hanson, 2013) and provision of human milk, particularly mother's own milk (Meier, Engstrom, Patel et al, 2010) whenever possible are valuable tools to improve outcome, particularly preventing NEC in these vulnerable infants.

Use of Feeding Protocols

The use of feeding protocols, and particularly consistency in approach to feeding has been shown to improve outcomes such as growth rate and feeding tolerance (Kwok, Dorling, Gale, 2019). To date, there is no good evidence that one protocol is superior to another in reaching these outcomes. However, systematic reviews show that feeds initiated within the first 3 days (Parker, Desorcy-Scherer, Magalhães, 2021) or as early as 48 hours (Kwok, Dorling, Gale, 2019) result in less time to attain full enteral feeds without increasing complications. Some protocols advocate for starting feeds in VLBW infants as early as the first 24 hours (Wight, Kim, et al, 2018). Progression of feedings is a key element in feeding protocols. Rates of

increase, after initial trophic feeds, of as high as 30 ml/kg/day do not show an increase in feeding intolerance and show enhanced growth rates (Parker, Desorcy-Scherer, Magalhaes, 2021).

Also included in feeding protocols is when to stop progression of feeding advancement and/or when to stop feeds altogether related to “feeding intolerance.” While this is important to include, there is very little evidence to support one practice over another. What we do know is that gastric residuals, commonly used as criteria to halt advancement and possibly stop feeds altogether, is an unreliable indicator of feeding difficulty, particularly necrotizing enterocolitis. Premature infants have slowed gastric motility often resulting in gastric residuals which may be interpreted as feeding intolerance and therefore result in feeding delays, impaired growth and impact length of stay (LI, Lin, Torrazza, et al, 2014). At least a consistent, conservative approach to this, based on the experience of the individual unit as well as quality outcomes over time may result in fewer episodes of feeding delays as well as improved growth indices. Nutritional Support of the Very Low Birth Weight Infant QI Toolkit (Wight, Kim et al, 2018) contains a recommendation for reporting of gastric residuals (if they are measured) of greater than 30-50% of a feeding over three feeding episodes along with changes in physical, particularly abdominal exam (Li, Lin, Torrazza, et al, 2014). Simply a residual should not result in placing an infant without feeds.

Improving provision of human milk

Providing human milk as nutrition in these small babies is probably one of the most vital interventions in the small baby unit. The implementation of “oral care” as soon as mother’s colostrums is available came into practice as part of the ventilator associated pneumonia practices (Ceballos, Waterman, Hullet, Mukic, 2013). However, there are more advantages to this practice overall. First, it is more than oral care. The antioxidants present in colostrum have been provided to the fetus via amniotic fluid (Garofalo, Caplan, 2019). These infants born at 22 weeks to 29 weeks have missed significant exposure to this. Since many of them will have limited exposure to their mother’s milk for various reasons, this can be best provided this via colostrum. This means early, regular opportunities for expression of colostrum and as able, skin to skin care.

Skin to skin care provides several advantages in bonding, thermoregulation and overall physiologic stability (Hubbard, Gattman, 2017) but particularly in assisting mothers to initiate and maintain milk supply while offering early opportunities for the infant to nuzzle or feed directly at the breast (Hubbard, Gattman, 2017). Skin to skin care has been shown to be critically important to the success of early direct breastfeeding (Lucas, Smith, 2015) and early direct breastfeeding has been shown to be effective in maintaining long term breastfeeding (Pineda, 2011; Briere, McGrath, Cong et al, 2016). A physiologic event that happens within 72 hours of birth may be triggered by placing the infant skin to skin in the absence of the infant being able to suckle at the breast. The release of prolactin along with infant suckling triggers an event to allow an increase in human milk lactose which draws water in to the lactocytes and results in the increase of milk supply or what some refer to as the milk “coming in.” This one-time event without which human milk synthesis may be impaired without appropriate stimulation (Meier, Patel, Hoban, Engstrom, 2016).

Early, frequent effective pumping is important in this population so that mother’s own milk can be provided early to these small babies who are most in need of the nutrients, antioxidants and immunity provided. It is recommended that this early pumping start within 1 hour postpartum whenever possible (World Health Organization, 2018). This early and effective pumping aids in triggering what would normally happen with early infant suckling and aids in establishing milk supply. Effective pumping is critical in the early stages of lactogenesis when an infant is not able to suck effectively at the breast. Two studies have demonstrated this by comparing pumps with an irregular suction pattern to a standard suction pattern (Meier et al, 2012; Post, Stam, Tromp, 2016). The irregular suction pattern is the usual sucking pattern seen in term infants when limited milk is available at a slower flow when compared to later in lactation. Post, Stam & Tromp (2016) found significantly earlier secretory activation and significantly higher daily milk production in the group that initiated pumping with the irregular breast pump suction pattern (Preemie+™, Medela, Baar, Switzerland).

Use of donor milk

In spite of efforts to initiate and maintain mother’s own milk supply, small babies often need additional supplementation, either in the form of donor milk or fortification of a human milk diet sufficient to meet nutritional needs of this unique population. The fetus at 23-29 weeks grows, under normal circumstances, at a much faster rate than when extrauterine. However, this growth rate should be approximated as close as possible for infants born at very early gestational ages. In order to achieve this, extra nutrients, including calcium and protein as well as calories are required over what is usually available in pumped human milk (SECTION ON BREASTFEEDING, 2012). Decisions about when to fortify the human milk diet of these small babies should be included in a feeding protocol even though evidence is of very low quality as to the exact best timing of fortification (Basu, Upadhyay, Singh, 2020).

Feeding/eating is a social experience. This is so in very small infants as much as in any population on the earth. The experience parents have feeding their infant is something that promotes bonding and care for the infant. Involving parents in every aspect of care is a tenant for these small babies. It is so important to view parents as an integral part of the of the infants care while still in the hospital and not expect them to take over once the infant is discharged. Many of these very early gestational age infants will stay in the hospital for 3-6 months and sadly, some will never go home. Parents deserve to be as much a part of their infant’s life as possible during this time. Parents bring a unique view from their NICU experience that can be quite helpful in improving outcomes, promoting parental involvement at the bedside and parental/professional relationships. Whether creating a small baby unit or seeking to enhance care of these infants in your NICU, the following will aid in a successful environment for these infants:

- a parent advisory committee
- nursing staff interested and engaged in care of these infants and willing to commit to
 - primary nursing model of care
 - certification to ensure an equal knowledge base (NCC reference)
- hospital and medical staff committed to evidence-based practice and continuous improvement

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Changing the Paradigm for Premature Infants <750 Grams: The Evolution of Specially Tailored Nutrition and Small Baby Units

Kim Carmignani, MSN, RNC-NIC, PCN, NEA-BC and Terry S Johnson, APN, NNP-BC, ASPPS, CLEC, MN

Introduction

Small baby unit (SBU) teams/programs are ways neonatal intensive care units (NICUs) describe their specialty focus on care of the preterm neonate. The SBU provides structure to core care components: use of evidence-based practices, interprofessional teamwork and shared mental model, and continuous use of quality improvement (QI) methodology.¹ Extremely low birth weight (ELBW) infants (less than 1000 g) and extremely low gestational age (ELGA) infants (less than 25 weeks gestational age) have an increased risk of death and comorbidities. These comorbidities are often referred to as “the burdens of prematurity”² and include but are not limited to bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), and late-onset sepsis.³

Statistics identify patients who require the highest level of intensive care and the most resources as those ELBW and ELGA infants. Due to the model of care practices found in SBUs, more infants delivered at what was previously thought to be below the threshold of viability are now surviving.

Fathi et al note, “[I]nfants born at 23 and 24 weeks of gestation, once considered non-viable, are now routinely surviving, and some institutions are demonstrating remarkable success even prior to 23 weeks. Unfortunately, these gains in survival have not been universal nor equally distributed across centers and geographic areas, and these differences in outcomes are not explained by differences in patient characteristics.”⁴

Kim Carmignani has a master's degree in nursing and has been a clinician for over 36 years within Maternal Child Care with most of her focus in Neonatal Intensive Care. She has worked as a staff RN, Case Manager, NICU Clinical Educator, and the Unit Director of both small community level III hospitals and at a 72 bed Level III NICU in a university setting.

Terry Johnson is a Neonatal Nurse Practitioner with over 35 years of experience in a variety of clinical settings including the NICU, Special Care Nursery, Normal Newborn Nursery and Developmental Follow-Up Services. She was a National Patient Safety Fellow and is a member of the Society of Professionals in Patient Safety. A nationally known educator, Terry is a frequent presenter at national and international nursing and multidisciplinary conferences and serves as Prolacta's Director of Clinical Education.

This bodes the questions:

- If patient characteristics cannot explain the survival of this population, what factors and clinical practices are associated with improved survival of these infants and their improved long-term outcomes?
- Is the combined interdisciplinary care required to support the extremely preterm infant at the threshold of viability unique and different from the care required for the later preterm (>27 weeks) infants?

The models for SBUs emerged in a similar time frame in different areas of the United States corresponding with the increased survival of these younger gestation/lower birth weight infants. Morris et al at Children's Hospital of Orange County, California, developed a quality initiative to address variation in clinical outcomes in infants ≤28 6/7 weeks. They utilized a pre- and post-interventional cohort design. Their model focused on standardizing practice and reducing practice variation. The SBU was physically separate from the NICU with a specialized team and standardized clinical practices.

Their data demonstrated a statistically significant reduction in the incidence of BPD, nosocomial infection, and growth restriction. There was improvement in the ability to utilize continuous positive airway pressure (CPAP) alone and, if intubated, to achieve extubation in the first week of life. The post-interventional group also had a statistically significant reduction in resource utilization measured as the total number of laboratory days and radiographs the infants required.⁵

In the same period the SBU concept of care was initiated at Nationwide Children's Hospital in Columbus, Ohio. The focus was to decrease variability in care and serve as an agent of culture change. Nationwide Children's Hospital also focused on the concept of an “infant-driven” model of care in the SBU. Fathi et al wrote, “The medical care required to support the premature infant at the threshold of viability is unique and differs from that required for the later preterm (>27 weeks) infant or the full-term infant. The ELBW infant requires a unique focus from each multidisciplinary team member and recognition of the value of providing a different approach to the care of this vulnerable patient population.”⁴ Using a similar quality improvement model, they confirmed the benefit of this model of care for ELBW infants.

"The growth and neurodevelopmental needs of the evolutionarily new population of very premature infants are best met by the appropriate fortification of human milk."¹⁰

There have been SBUs in a small number of NICUs for many years. Although there are no randomized control trials, there are two publications specifically describing the planning, development, and outcomes in pre- and post-SBU cohorts.⁵ Another report, of a Vermont Oxford Network (VON) 10-center collaborative focused on micro-premature neonates during a 6-year collaborative period, showed reductions in similar morbidities. Nearly all of the 10 centers adopted a more formalized SBU structure of small baby care during the collaborative.⁵

Institutions with SBUs believe that, given their many challenges, ELBW infants do best with a consistent, unified approach across the spectrum of care throughout their NICU experience. Standardization of care across multiple disciplines focuses on reducing unintended or unnecessary variability, and most SBUs establish institution-specific guidelines for all aspects of the care of ELBW infants. The infant-driven model of care⁶ is based on core measures incorporated in the SBU. These include a healing environment, partnering with families, positioning and handling, safeguarding sleep, minimizing stress and pain, protecting skin, and optimizing nutrition.

In particular, the feeding of ELBW infants is an aspect of care that lends itself well to consistency and standardization. In describing the finer points of Loma Linda Children's Hospital's SBU in California, Banerji et al discuss the unit's feeding protocols: "We focused on using our existing standardized feeding protocol to advance and fortify feeds more uniformly and reinforced guidelines for central line discontinuation. We also addressed more optimal support of mother's milk supply and use of donor milk when mother's milk is not available."⁷

Exclusive Human Milk Diet

The American Academy of Pediatrics has reaffirmed in its most recent breastfeeding guideline that human milk remains the appropriate nutrition for all infants, particularly those born prematurely: "The potent benefits of human milk are such that all preterm infants should receive human milk. Mother's own milk, fresh or frozen, should be the primary diet and it should be fortified appropriately for the infant born weighing less than 1.5 kg."⁸

The emergence of 100% human milk-based nutritional products during the past decade allows clinicians caring for ELBW infants to provide an exclusive human milk diet

(EHMD) from the very first days of life. An EHMD uses only mother's own milk (MOM), donor human milk, and human milk-based fortifiers to deliver essential macronutrients like protein, fat, and carbohydrates. This is accomplished without the addition of any cow milk-based components.

What constitutes appropriate fortification has been a subject of scientific inquiry. Recent research⁹ on the bioactive factors in human milk suggests that an EHMD may be even more clinically significant for the <750 g population than for infants >750 g. These ELBW infants are at the highest risk of intolerance, prolonged hospitalizations, and adverse outcomes. "The growth and neurodevelopmental needs of the evolutionarily new population of very premature infants are best met by the appropriate fortification of human milk."¹⁰

Development of the gut occurs in utero, with exposure to a series of biologic fluids. This process begins in utero with womb milk and amniotic fluid, and postnatally with mother's colostrum and mother's own milk playing key roles. Birth at extreme prematurity interrupts this crucial normal gut development. Bioactive compounds found in human milk are responsible for normal gut development.¹⁰ These bioactive components include immunoglobulins, oligosaccharides, antimicrobial factors, essential fatty acids, antibodies, anti-inflammatory substances, hormones and growth factors, digestive enzymes, and hundreds of bacterial strains.¹⁰⁻¹³ These factors reduce the risk of poor outcomes and potential comorbidities from inflammation-driven gut dysbiosis.^{14,15}

Schneider et al provided the foundation for optimizing early enteral nutrition intake in preterm neonates to promote early brain maturation. Using MRI brain imaging in 49 preterm neonates, they demonstrated that increased intake of enteral nutrition during the first weeks of life was predictive of increased volume in the brain overall. This was specifically seen in the basal nuclei and was also predictive of greater white matter maturation. The investigators surmised that the impact of early nutrition on neurodevelopment may therefore be mediated by enhanced brain growth.¹⁶

Infants born extremely prematurely have been fed an EHMD in numerous studies. This diet includes the use of Prolacta Bioscience's human milk-based fortifiers. Data from these studies demonstrate that an EHMD supports adequate growth¹⁷⁻²⁰ and a more rapid advancement to full enteral feeds.²¹ Evidence supports that infants who receive an EHMD experience reduced morbidity^{18,20-25} and improved long-term outcomes²⁶ than those who received various feeding regimens that included cow milk-based nutrition.

A recent independent study from Osmanova et al found significant clinical benefits to feeding very low birth weight infants an EHMD with human milk-based fortifier versus cow milk-based fortifier. The infants who received an EHMD had fewer comorbidities and a shorter length of stay in the NICU, which helped offset the therapeutic cost of the human milk-based fortifiers.²⁷

When examining the range of comorbidities and the impact of nutrition for infants <750 g birth weight, Hair et al evaluated four studies, two randomized and two large cohort studies, totaling approximately 375 infants. Their review outlined a "significant reduction in several morbidities of prematurity

Morbidities and Clinical Outcomes[†]

	CMBD	EHMD	p-value
Sepsis	140/368 (38)	117/388 (30.2)	0.022
ROP (Stage 3/4)	82/375 (21.9)	52/391 (13.3)	0.002
BPD	249/326 (76.4)	248/358 (69.3)	0.037
Patent Ductus Arteriosus	283/373 (75.9)	278/395 (70.4)	0.087
NEC	92/379 (24.3)	40/396 (10.1)	<0.000001
NEC Surgery	64/379 (16.9)	31/396 (7.8)	0.0001
Mortality	83/392 (21.1)	76/401 (19)	0.43
MMI	294/326 (90.2)	279/341 (81.8)	0.002

* Reported as n (%).

† Numbers varied slightly by reporting of various outcomes.

for infants receiving an EHMD compared to CMBD, as well as lower incidence of MMI.²⁸

The onset and timing of human milk fortification are crucial factors. Data have demonstrated that early fortification with an EHMD produces adequate growth.^{19,29}

In a cohort of 104 infants, donor human milk-derived fortifier was initiated at 60 mL/kg/day and advanced to provide 6 to 8 additional kilocalories per ounce.¹⁹ The authors compared the infants' growth to historical growth standards and previous human milk-fed cohorts. Weight gain was 24.8 g/kg/day, with length increases of 0.99 cm/week and head circumference increases of 0.72 cm/week. The authors concluded that an EHMD with early fortification enables premature infants to meet targeted growth standards. Additionally, they concluded that this diet leads to a lower rate of extrauterine growth restriction.¹⁹

Improved growth and a reduction of BPD was demonstrated in a cohort of 394 ELBW infants with weights of 500 to 1250 g. The infants received early initiation of human milk-based fortifiers at <60 mL/kg/day using an EHMD. Clinical findings²⁹ of improved growth metrics and a reduction in BPD was statistically significant (42.6% vs 27.6%; $P = 0.008$).

Given the challenge of minimizing comorbidities and maximizing the long-term outcome potential of ELBW infants, we were encouraged to see Hair's poster presentation at the 4th Congress of joint European Neonatal Societies.²⁸ The authors analyzed pooled data from four randomized,

controlled, and cohort studies.^{20,21,24,25} Each of these studies compared outcomes of infants who received an EHMD to those who received a control diet that included cow milk-based fortifier or formula. Among approximately 375 infants with a birth weight of <750 grams across the four studies, they saw evidence for a significant reduction in the comorbidities of ROP, NEC (both medical and surgical), sepsis, and BPD for infants who were fed an EHMD.

There is significant evidence of the benefits of an EHMD and standardized feeding protocol in managing nutritional needs of preterm infants. These include early initiation of enteral feedings, improved tolerance, and reduction of neonatal comorbidities in the SBU. The significant evidence that an EHMD benefits premature infants at all ages and stages of development clearly conveys the value of following institutional feeding protocols that feature an EHMD for all NICU patients, especially those with a birth weight of 750 g or less.

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Maternal and Fetal Effects of COVID-19 Virus on a Complicated Triplet Pregnancy: a Case Report

Maryam Rabiei, Tahereh Soori, Amene Abiri, Zohreh Farsi, Arshia Shizarpour and Reihaneh Pirjani

Abstract

Background: Coronavirus disease 2019 (COVID-19), the global pandemic that has spread throughout the world, is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Given the limited scientific evidence on the manifestations and potential impact of this virus on pregnancy, we decided to report this case.

Case presentation: The patient was a 38 year-old Iranian woman with a triplet pregnancy and a history of primary infertility, as well as hypothyroidism and gestational diabetes. She was hospitalized at 29 weeks and 2 days gestational age due to elevated liver enzymes, and finally, based on a probable diagnosis of gestational cholestasis, she was treated with ursodeoxycholic acid. On the first day of hospitalization, sonography was performed, which showed that biophysical scores and amniotic fluid were normal in all three fetuses, with normal Doppler findings in two fetuses and increased umbilical artery resistance (pulsatility index [PI] > 95%) in one fetus. On day 4 of hospitalization, she developed fever, cough and myalgia, and her COVID-19 test was positive. Despite mild maternal symptoms, exacerbated placental insufficiency occurred in two of the fetuses leading to the rapid development of absent umbilical artery end-diastolic flow. Finally, 6 days later, the patient underwent cesarean section due to rapid exacerbation of placental insufficiency and declining biophysical score in two of the fetuses. Nasopharyngeal swab COVID-19 tests were negative for the first and third babies and positive for the second baby. The first and third babies died 3 and 13 days after birth, respectively, due to collapsed white lung and sepsis. The second baby was discharged in good general condition. The mother was discharged 3 days after cesarean section. She had no fever at the time of discharge and was also in good general condition.

Conclusions: This was a complicated triplet pregnancy, in which, after maternal infection with COVID-19, despite mild maternal symptoms, exacerbated placental insufficiency occurred in two of the fetuses, and the third fetus had a positive COVID-19 test after birth. Therefore, in cases of pregnancy with COVID-19

infection, in addition to managing the mother, it seems that physicians would be wise to also give special attention to the possibility of acute placental insufficiency and subsequent fetal hypoxia, and also the probability of vertical transmission.

Keywords: Case report, COVID-19 virus, Placental insufficiency, Triplet pregnancy

Introduction

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a global pandemic that has spread throughout the world. Unfortunately, there is still limited scientific evidence on the manifestations and potential impact of this virus on pregnancy. In this article, we aim to report the maternal and fetal effects of the virus on a complicated triplet pregnancy.

Case

A 38 year-old Iranian woman with a triplet (three chorionic and three amniotic) pregnancy was hospitalized at 29 weeks and 2 days gestational age due to one-time high blood pressure at 140/90mmHg and elevated liver enzymes. A week before admission, she had been hospitalized in another hospital for about 5 days to evaluate the cause of increased liver enzymes. She had a 2-year history of primary infertility and had become pregnant by ovulation induction, and also had a 5-year history of hypothyroidism, which was euthyroid during pregnancy. She had also been diagnosed with gestational diabetes a month before admission, which was being treated with 16 units of insulin daily (6 units Levemir and 10 units NovoRapid), so her blood glucose levels were maintained in a normal range, and glycated hemoglobin concentration was 5.6 %. She was at risk for preeclampsia due to her advanced age and triplet pregnancy, so aspirin was administered. On the other hand, due to hospitalization for more than 3 days, she was at increased risk of deep vein thrombosis and was treated with enoxaparin. Additionally, given the possibility of iatrogenic preterm delivery, she had received a course of betamethasone for fetal lung maturation.

Two weeks before hospitalization, liver enzymes increased to four times the normal levels: alanine amino transferase (ALT) 218 units per liter (U/L) and aspartate amino transferase (AST) 283 U/L. After a thorough evaluation and ruling out preeclampsia, and due to a probable diagnosis of gestational cholestasis, she was treated with ursodeoxycholic acid (300 mg twice a day) from 1 week before hospitalization. Lab tests at admission

Maryam Rabiei, Tahereh Soori, Amene Abiri, Zohreh Farsi, and Reihaneh Pirjani are with the Arash Hospital, Tehran University of Medical Sciences, 1416753955 Tehran, Iran. Arshia Shizarpour is with the Medical School, Tehran University of Medical Sciences, Tehran, Iran. Full list of author information is available at the end of the article. This is an Open Access article distributed under the terms of the Creative Commons Attribution License.

included the following: ALT = 94 U/L, AST = 57 U/L, total bilirubin = 0.7, direct bilirubin = 0.1, and lactate dehydrogenase (LDH) = 276 U/L. Other tests including white blood cell count, hemoglobin, platelet, serum creatinine, and urinalysis were in the normal range. She underwent 24-hour Holter blood pressure monitoring, and among all measurements, only 18.8% of systolic and 15.6% of diastolic blood pressure exceeded the set limit of 140 and 90 mmHg, respectively. Echocardiographic findings were quite normal, and 24-hour urine protein was also reported in the normal range. On the second day of hospitalization, an ultrasound exam was performed, which showed that biophysical scores and amniotic fluid were normal in all three fetuses. One of the fetuses had increased umbilical artery resistance (pulsatility index [PI] > 95%) and estimated weight below 5%, but umbilical cord and middle cerebral artery findings were normal in the other two fetuses. On the fourth day of hospitalization, the patient developed fever and cough. The following day, due to the persistent fever and cough and also an onset of myalgia, real-time reverse transcriptase polymerase chain reaction (RT-PCR) was conducted on nasopharyngeal swabs for SARS-CoV-2 nucleic acid. All steps including sample collection, processing and laboratory testing were based on World Health Organization (WHO) guidelines. Chest X-ray and computed tomography scan were not performed due to the patient's lack of consent.

The result of RT-PCR was positive for the SARS-CoV-2 virus. However, the patient's clinical symptoms were mild. She had a mild fever, with maximum temperature of 38.3 °C. She had no complaint of shortness of breath, diarrhea, nausea or vomiting, her respiratory rate was 18-20 per minute, and oxygen saturation was above 95% at all times. On the same day that she developed clinical symptoms, an ultrasound exam was performed: the fetus who already had increased umbilical artery resistance showed an exacerbated condition involving absent umbilical artery end-diastolic flow, and another fetus showed umbilical artery resistance (PI > 95%), but umbilical cord and middle cerebral artery findings were normal in the third fetus, and biophysical scores and amniotic fluid were normal in all three fetuses. Based on these findings, the patient underwent serial ultrasound exams, and unfortunately, exacerbated umbilical flow resistance in the second fetus also progressed to absent umbilical artery end-diastolic flow (Fig. 1). However, Doppler and biophysical scores were normal in all fetuses. Finally, 6 days after the beginning of clinical symptoms, the biophysical scores declined in the two fetuses with absent umbilical artery end-diastolic flow, so the patient underwent cesarean section due to rapid deterioration of fetal conditions and exacerbated placental insufficiency. The first baby was born weighing 1320 g with umbilical cord pH 7.25, and her 5-minute APGAR [appearance, pulse, grimace, activity, respiration] score was 4; the second baby was born weighing 1600 g with umbilical cord pH 7.23, and his 5-minute APGAR score was 7; the third baby was born

weighing 1250 g with umbilical cord pH 7.21, and her 5-minute APGAR score was 6. In order to protect the babies from infection with the virus, delayed cord clamping was not performed, skin-to-skin contact of mother and babies was not practiced, and the babies were separated from the mother immediately after birth. All three babies were intubated and were admitted to the neonatal intensive care unit (NICU), where they were kept in separate, isolated rooms. RT-PCR of nasopharyngeal swabs for SARS-CoV-2 nucleic acid was carried out for all three newborns immediately after birth. The mother was discharged 3 days after cesarean section, and 2 weeks later she had recovered completely without any complications.

Two of the babies, weighing 1250 and 1320 g, each received three doses and the other baby received two doses of surfactant. All three newborns developed clinical symptoms of sepsis and pulmonary hemorrhage. The primary results of the COVID-19 test were negative for all three newborns. Because of the poor general conditions of the newborns, and considering the false-negative probability of the initial test, the COVID-19 test was repeated immediately after receiving the first test results, and the result was positive for the baby who weighed 1600 g and also had better umbilical cord and placental circulation before birth. Unfortunately, we did not examine the umbilical cord blood and amniotic fluid samples for the virus, so we cannot conclusively link the COVID-19 RT-PCR positive test in this fetus to vertical transmission, but because the babies were completely isolated and had no suspected exposure during the period between the two tests, the possibility of vertical transmission cannot be ignored.

The baby who weighed 1320 g died 3 days after birth with collapsed white lung and sepsis. The baby who weighed 1250 g also had symptoms of sepsis and died 13 days after birth. The baby who weighed 1600 g and had a positive COVID-19 test eventually recovered and was discharged in good general condition 3 weeks after birth.

Discussion

We report the case of a woman with a triplet pregnancy who was infected with COVID-19. Despite the presence of some comorbidity, she had only mild symptoms of COVID-19 infection, but rapid and progressive placental insufficiency occurred simultaneously with the peak maternal infectious disease symptoms. A COVID-19 test was positive in one baby, who was discharged in good condition 3 weeks after birth, and negative in two other babies, who died 3 and 13 days after birth.

A recently published study identified maternal age and underlying diseases as risk factors for severity of COVID-19 symptoms;¹ however, other studies have reported maternal mortality in women without underlying disease.^{2,3} In our previous prospective cohort study of COVID-19-infected pregnant women, we did not have any maternal deaths, and there were no differences in underlying disease between COVID-19-infected and non-infected pregnant women.⁴ However, studies in this area are insufficient, and further research is needed.

Available data about COVID-19 vertical transmission is still contradictory. At the beginning of the pandemic, no vertical transmission was reported;⁵ however, some cases of probable vertical transmission have recently been noted.⁶⁻⁸ In a recent review of 50 studies, the virus test was positive in 17 cases of neonatal secretions, eight cases of placental tissue, three cases

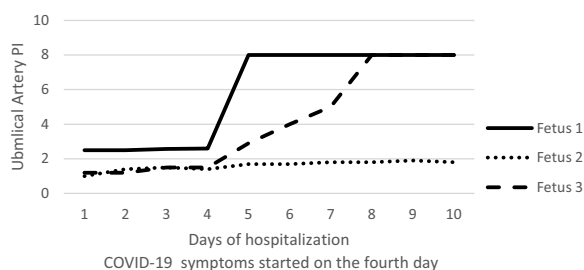


Fig. 1 Fetal umbilical artery resistance during hospitalization

of breast milk and one case of amniotic fluid, and anti-SARS-CoV-2 antibodies were positive in three infants.⁹ Therefore, the possibility of vertical transmission should be considered.

Delayed positive tests in newborns have also been reported in other studies.^{2,6-8} In most reports, the positive test occurred with a delay of 16-72 hours after birth; therefore, we recommend that all infants born to COVID-19-infected mothers be retested within the next hours if the test immediately after birth is negative. In our study, SARS-CoV-2 PCR tests for the babies were negative immediately after birth, and interestingly, changed to delayed positive in one baby who during the time between the first and second tests was completely isolated and had no suspected exposure. Unfortunately, we did not test the placenta, umbilical cord or amniotic fluid samples for the virus, and this is a limitation of our study.

Our case was a triplet pregnancy. Most previous studies are in singleton pregnancies, although there are also some reports of twin pregnancies.¹⁰⁻¹²

Some have hypothesized that maternal respiratory failure and hypoxia may transiently reduce uterine placental blood flow,^{13,14} but in our case, the mother did not have severe illness. However, there was severe placental insufficiency in two of the fetuses, both of whom had negative COVID-19 test results. Interestingly, it was the largest fetus with better placental circulation who was infected. On the other hand, although this woman had several underlying factors for placental insufficiency, and umbilical artery resistance was noted in one of the fetuses before maternal infection, the rapid and progressive placental insufficiency occurring during the last days of pregnancy and simultaneously with the peak maternal infectious disease should be taken into account. Although this pregnancy was a complicated one and there were several risk factors for placental insufficiency, the conceivable and hypothetical impact of COVID-19 on uterine circulation and fetal hypoxia should also be considered.

Conclusion

There are still insufficient data about COVID-19 in pregnancy. Our case was a complicated triplet pregnancy; however, COVID-19 symptoms in the mother were mild. Given the rapid and progressive placental insufficiency after COVID-19 infection, it seems prudent that in cases of pregnancy with COVID-19 infection, in addition to assessing and managing the mother, special attention should be given to the possibility of acute placental insufficiency and subsequent fetal hypoxia. The possibility of vertical transmission should also be considered.

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Authors' contributions

MR, AA and RP are perinatologists, and TS is an infectious disease specialist, all of whom managed the patient. ZF is a neonatologist who managed the newborns. RP and ASH drafted and revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Tehran

University of Medical Sciences (Ethical number IR.TUMS.VCR.REC.1398.1057), and written informed consent was obtained from the patient.

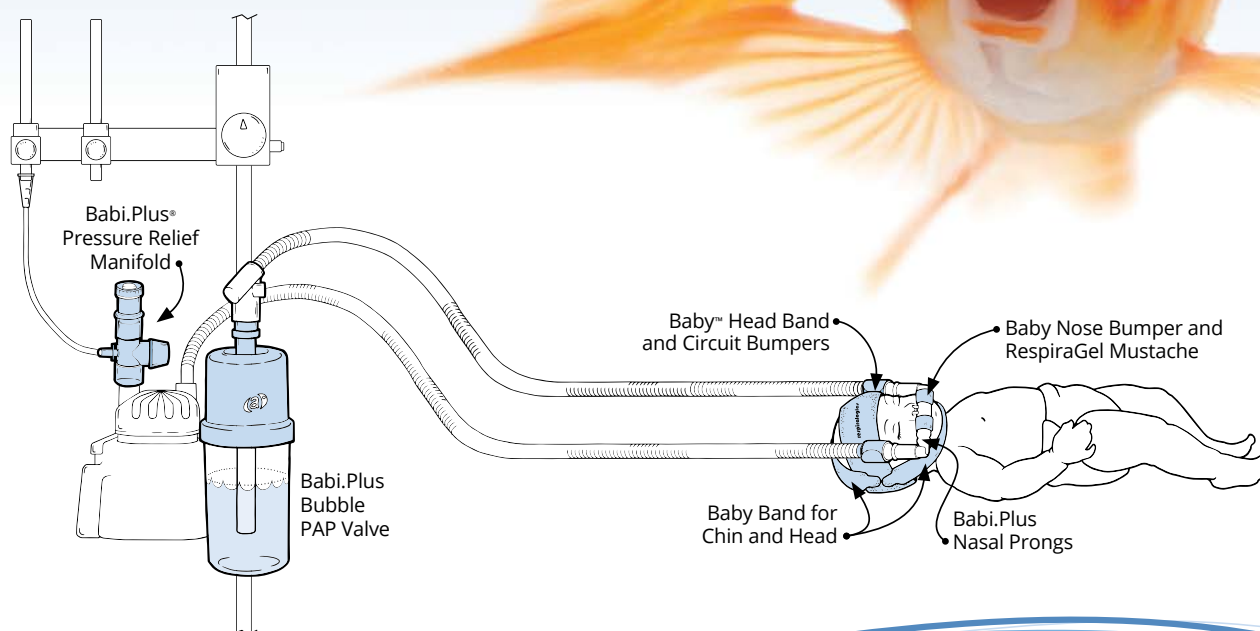
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