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The Journal of Perinatology-Neonatology

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The American Academy of Pediatrics' (AAP) policy recommends the use of human milk for all preterm infants, whether mother's own milk (MOM) or pasteurized donor human milk when mother's own milk is unavailable.[1]

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1. American Academy of Pediatrics. Breastfeeding and the Use of Human Milk. Section on Breastfeeding. [originally published online February 27, 2012]. Pediatrics. DOI: 10.1542/peds.2011-3552

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Neonatal nurses have concerns about oxygen toxicity*

Though FiO_2 is necessary and often beneficial at appropriate doses, elevated levels can put patients at risk of hyperoxia and may result in[1-4]:

- Generation of reactive oxygen species
- Cytotoxicity
- Damage to lung tissue

Currently, no published national guidelines exist for hyperoxia management.[5]

Mallinckrodt Pharmaceuticals is working to link the ongoing dialogues around effective use of oxygen supplementation. Look for more information this fall from Mallinckrodt Pharmaceuticals.

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*Eighty-six percent of neonatal nurses surveyed at an Ikaria-sponsored symposium entitled Oxygen Toxicity: Hyperoxia and the Risks to the Pulmonary System had concerns about oxygen toxicity.

References: 1. Kulkarni AC, Kuppusamy P, Parinandi N. Oxygen, the lead actor in the pathophysiologic drama: enactment of the trinity of normoxia, hypoxia, and hyperoxia in disease and therapy. *Antioxid Redox Signal.* 2007;9(10):1717-1730. **2.** Lakshminrusimha S, Steinhorn RH, Wedgwood S, et al. Pulmonary hemodynamics and vascular reactivity in asphyxiated term lambs resuscitated with 21 and 100% oxygen. *J Appl Physiol.* 2011;111(5):1441-1447. **3.** Kannan S, Pang H, Foster DC, Rao Z, Wu M. Human 8-oxoguanine DNA glycosylase increases resistance to hyperoxic cytotoxicity in lung epithelial cells and involvement with altered MAPK activity. *Cell Death Differ.* 2006;13(2):311-323. **4.** Yee M, Vitiello PF, Roper JM, et al. Type II epithelial cells are critical target for hyperoxia-mediated impairment of postnatal lung development. *Am J Physiol Lung Cell Mol Physiol.* 2006;291(5):L1101-L1111. **5.** US Food and Drug Administration. The Food and Drug Administration Safety and Innovation Act. http://www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf. Published July 9, 2012. Accessed June 30, 2015.

neonatal
INTENSIVE CARE

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Fall 2015

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DEPARTMENTS

ARTICLES

Editorial Advisory Board

In term and near-term neonates with hypoxic respiratory failure (HRF)...

When do you stop the cascade?

Early intervention with INOMAX® (nitric oxide) for inhalation upon confirmation of pulmonary hypertension may help:

- Avoid higher levels of supplemental oxygen
- Improve oxygenation[1]
- Potentially prevent the progression of HRF[2]

Learn more at www.inomax.com

Indication

INOMAX® is a vasodilator, which, in conjunction with ventilatory support and other appropriate agents, is indicated for the treatment of term and near-term (>34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, where it improves oxygenation and reduces the need for extracorporeal membrane oxygenation.

Utilize additional therapies to maximize oxygen delivery with validated ventilation systems.

Important Safety Information

- INOMAX is contraindicated in the treatment of neonates known to be dependent on right-to-left shunting of blood.
- Abrupt discontinuation of INOMAX may lead to increasing pulmonary artery pressure and worsening oxygenation even in neonates with no apparent response to nitric oxide for inhalation.
- Methemoglobinemia and NO_2 levels are dose dependent. Nitric oxide donor compounds may have an additive effect with INOMAX on the risk of developing methemoglobinemia. Nitrogen dioxide may cause airway inflammation and damage to lung tissues.
- In patients with pre-existing left ventricular dysfunction, INOMAX may increase pulmonary capillary wedge pressure leading to pulmonary edema.
- Monitor for PaO_2, methemoglobin, and inspired NO_2 during INOMAX administration.
- Use only with an INOmax DS_{IR}®, INOmax® DS, or INOvent® operated by trained personnel.

Please see Brief Summary of Prescribing Information on adjacent page.

References: 1. INOMAX [package insert]. Hampton, NJ: Ikaria, Inc.; 2013. **2.** González A, Fabres J, D'Apremont I, et al. Randomized controlled trial of early compared with delayed use of inhaled nitric oxide in newborns with a moderate respiratory failure and pulmonary hypertension. *J Perinatol*. 2010;30(6):420-424.

Mallinckrodt Pharmaceuticals

INOmax® (nitric oxide) FOR INHALATION

Stop the cascade

INOMAX® (nitric oxide) for inhalation
Brief Summary of Prescribing Information

INDICATIONS AND USAGE

Treatment of Hypoxic Respiratory Failure
INOMAX® is a vasodilator, which, in conjunction with ventilatory support and other appropriate agents, is indicated for the treatment of term and near-term (>34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, where it improves oxygenation and reduces the need for extracorporeal membrane oxygenation.

Utilize additional therapies to maximize oxygen delivery with validated ventilation systems. In patients with collapsed alveoli, additional therapies might include surfactant and high-frequency oscillatory ventilation.

The safety and effectiveness of INOMAX have been established in a population receiving other therapies for hypoxic respiratory failure, including vasodilators, intravenous fluids, bicarbonate therapy, and mechanical ventilation. Different dose regimens for nitric oxide were used in the clinical studies.

Monitor for PaO_2, methemoglobin, and inspired NO_2 during INOMAX administration.

CONTRAINDICATIONS
INOMAX is contraindicated in the treatment of neonates known to be dependent on right-to-left shunting of blood.

WARNINGS AND PRECAUTIONS

Rebound Pulmonary Hypertension Syndrome following Abrupt Discontinuation
Wean from INOMAX. Abrupt discontinuation of INOMAX may lead to worsening oxygenation and increasing pulmonary artery pressure, i.e., Rebound Pulmonary Hypertension Syndrome. Signs and symptoms of Rebound Pulmonary Hypertension Syndrome include hypoxemia, systemic hypotension, bradycardia, and decreased cardiac output. If Rebound Pulmonary Hypertension occurs, reinstate INOMAX therapy immediately.

Hypoxemia from Methemoglobinemia
Nitric oxide combines with hemoglobin to form methemoglobin, which does not transport oxygen. Methemoglobin levels increase with the dose of INOMAX; it can take 8 hours or more before steady-state methemoglobin levels are attained. Monitor methemoglobin and adjust the dose of INOMAX to optimize oxygenation.

If methemoglobin levels do not resolve with decrease in dose or discontinuation of INOMAX, additional therapy may be warranted to treat methemoglobinemia.

Airway Injury from Nitrogen Dioxide
Nitrogen dioxide (NO_2) forms in gas mixtures containing NO and O_2. Nitrogen dioxide may cause airway inflammation and damage to lung tissues. If the concentration of NO_2 in the breathing circuit exceeds 0.5 ppm, decrease the dose of INOMAX.

If there is an unexpected change in NO_2 concentration, when measured in the breathing circuit, then the delivery system should be assessed in accordance with the Nitric Oxide Delivery System O&M Manual troubleshooting section, and the NO_2 analyzer should be recalibrated. The dose of INOMAX and/or FiO_2 should be adjusted as appropriate.

Heart Failure
Patients with left ventricular dysfunction treated with INOMAX may experience pulmonary edema, increased pulmonary capillary wedge pressure, worsening of left ventricular dysfunction, systemic hypotension, bradycardia and cardiac arrest. Discontinue INOMAX while providing symptomatic care.

ADVERSE REACTIONS
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from the clinical studies does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Controlled studies have included 325 patients on INOMAX doses of 5 to 80 ppm and 251 patients on placebo. Total mortality in the pooled trials was 11% on placebo and 9% on INOMAX, a result adequate to exclude INOMAX mortality being more than 40% worse than placebo.

In both the NINOS and CINRGI studies, the duration of hospitalization was similar in INOMAX and placebo-treated groups.

From all controlled studies, at least 6 months of follow-up is available for 278 patients who received INOMAX and 212 patients who received placebo. Among these patients, there was no evidence of an adverse effect of treatment on the need for rehospitalization, special medical services, pulmonary disease, or neurological sequelae.

In the NINOS study, treatment groups were similar with respect to the incidence and severity of intracranial hemorrhage, Grade IV hemorrhage, periventricular leukomalacia, cerebral infarction, seizures requiring anticonvulsant therapy, pulmonary hemorrhage, or gastrointestinal hemorrhage.

In CINRGI, the only adverse reaction (>2% higher incidence on INOMAX than on placebo) was hypotension (14% vs. 11%).

Based upon post-marketing experience, accidental exposure to nitric oxide for inhalation in hospital staff has been associated with chest discomfort, dizziness, dry throat, dyspnea, and headache.

OVERDOSAGE
Overdosage with INOMAX will be manifest by elevations in methemoglobin and pulmonary toxicities associated with inspired NO_2. Elevated NO_2 may cause acute lung injury. Elevations in methemoglobin reduce the oxygen delivery capacity of the circulation. In clinical studies, NO_2 levels >3 ppm or methemoglobin levels >7% were treated by reducing the dose of, or discontinuing, INOMAX.

Methemoglobinemia that does not resolve after reduction or discontinuation of therapy can be treated with intravenous vitamin C, intravenous methylene blue, or blood transfusion, based upon the clinical situation.

DRUG INTERACTIONS
No formal drug-interaction studies have been performed, and a clinically significant interaction with other medications used in the treatment of hypoxic respiratory failure cannot be excluded based on the available data. INOMAX has been administered with dopamine, dobutamine, steroids, surfactant, and high-frequency ventilation. Although there are no study data to evaluate the possibility, nitric oxide donor compounds, including sodium nitroprusside and nitroglycerin, may have an additive effect with INOMAX on the risk of developing methemoglobinemia. An association between prilocaine and an increased risk of methemoglobinemia, particularly in infants, has specifically been described in a literature case report. This risk is present whether the drugs are administered as oral, parenteral, or topical formulations.

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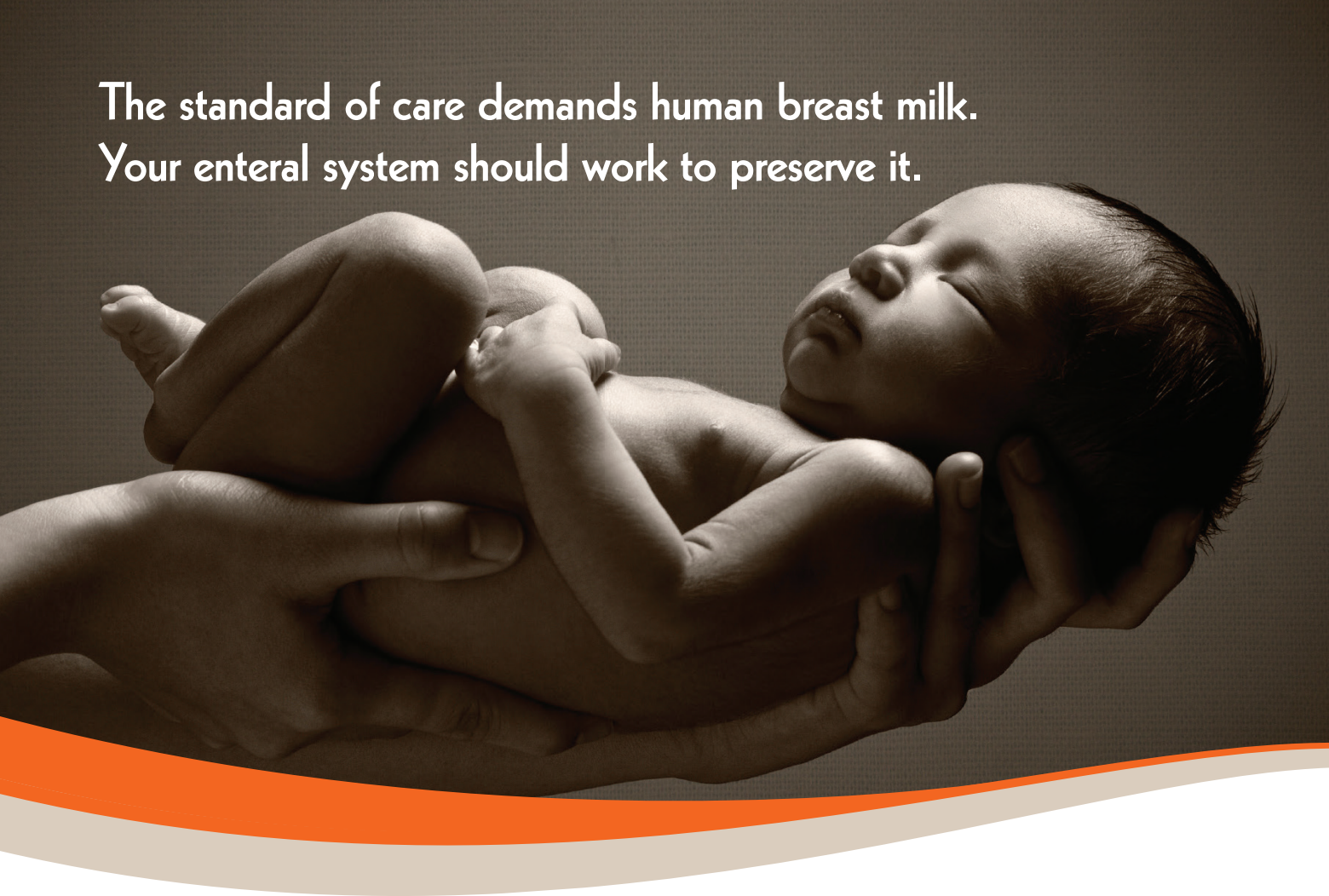
Maquet is proud to have partnered with our customers to reinforce our commitment to patients by supporting Make-A-Wish® with a donation in the amount of $150,000 to help fulfill the wishes of children with life-threatening medical conditions across the USA. For more information about Make-A-Wish visit wish.org.

The standard of care demands human breast milk. Your enteral system should work to preserve it.



5% of breast milk is fat, fat-soluble vitamins, and nutrients.[1] That 5% contains about half of the calories in human breast milk.[2] That's why NeoMed focuses on the details that impact nutrition delivery.

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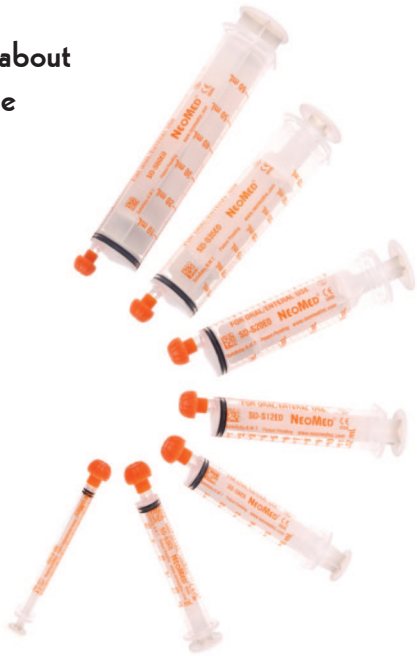

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News

☐ Fall 2015

Vaccination in Pregnancy

Pregnant women should be vaccinated against pertussis during each pregnancy to protect their infants from the infection, according to new recommendations from the Global Pertussis Initiative (GPI). The GPI is an expert scientific forum charged with addressing the global burden of pertussis. Families can also use a second, less-effective preventive strategy known as cocooning, which entails vaccinating all individuals who will have close contact with the infant. Pertussis is transmitted via aerosol droplets. Although vaccines are available and coverage is high in most regions of the world, the disease remains a global health problem, the authors write. "Many countries with long histories of routine pertussis vaccination have experienced a recent resurgence of the disease, particularly among older children, adolescents, and adults," the authors explain. "One factor that may be contributing to this is waning immunity, which has been observed despite vaccination." Infants aged 6 months and younger are at increased risk for pertussis-related complications and death. In addition, infants are at increased risk of contracting the disease because the youngest infants, those aged 0 to 6 weeks, are too young to be vaccinated, and older infants are at risk until their vaccinations have been completed. Vaccination during pregnancy is the primary and most important preventive strategy because it offers direct protection to the infant through the passive transfer of pertussis antibodies from the mother to the fetus, the authors write. It is safe and effective and has logistic advantages over the cocooning strategy. Cocooning provides indirect protection to infants. Families who use this strategy should undertake complete cocooning or full immunization of the family. When this is not possible, immunizing only the mother will provide limited protection for the infant. The authors note that cocooning can be costly and resource intensive to implement because of the need to secure increased staffing and obtain reimbursement or alternate funding. In addition, it may be difficult to gain the acceptance of families.

Enteral Syringes Cleared

NeoMed, Inc., which makes neonatal nutrition/enteral safety devices, announced that it received FDA 510(K) clearance from the United States Food and Drug Administration (FDA) for its NeoConnect Enteral Syringes with ENFit connector (K143344) on April 8, 2015. NeoMed is currently one of only two enteral syringe manufacturers that have received FDA 510(K) clearance for enteral syringes with ENFit connectors. The NeoConnect syringes are an important part of the NeoMed solutions for the ISO 80369-3 (ENFit) Small Bore Connector Standard, being implemented to help reduce the risk of tubing misconnections and improve patient safety. NeoMed designed the first comprehensive enteral safety system to comply with the recommendations of the Joint Commission, FDA, ASPEN, and AAMI to help prevent tubing misconnections and is proud to support the ENFit initiative. Aaron Ingram, President of NeoMed, Inc. says, "Our commitment to our customers is our continual participation with GEDSA, the trade association created to help introduce the new standards. We will continue our support of the new ISO 80369-3 standard through implementation, practice, and beyond."

Neonatal Consortium Formed

The Critical Path Institute (C-Path), a pioneering non-profit organization dedicated to accelerating the pace and reducing the costs of medical product development by facilitating unique partnerships among a wide range of stakeholders, formed its ninth consortium, the International Neonatal Consortium (INC). The launch took place at the European Medicines Agency (EMA) during a widely attended workshop focused on the needs of the neonate. Dr Jordi Llinares Garcia (Interim Head, Human Medicines Research & Development Support Division,

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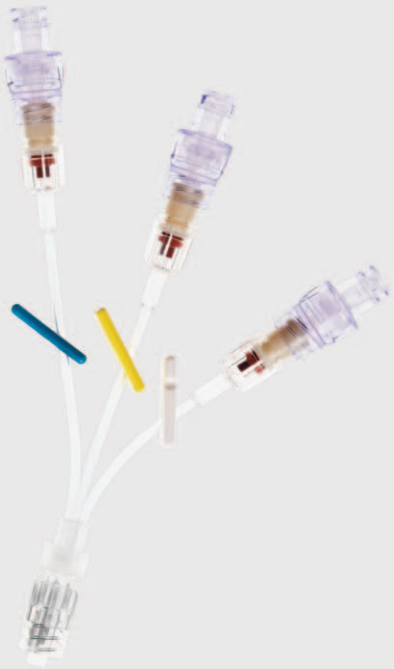

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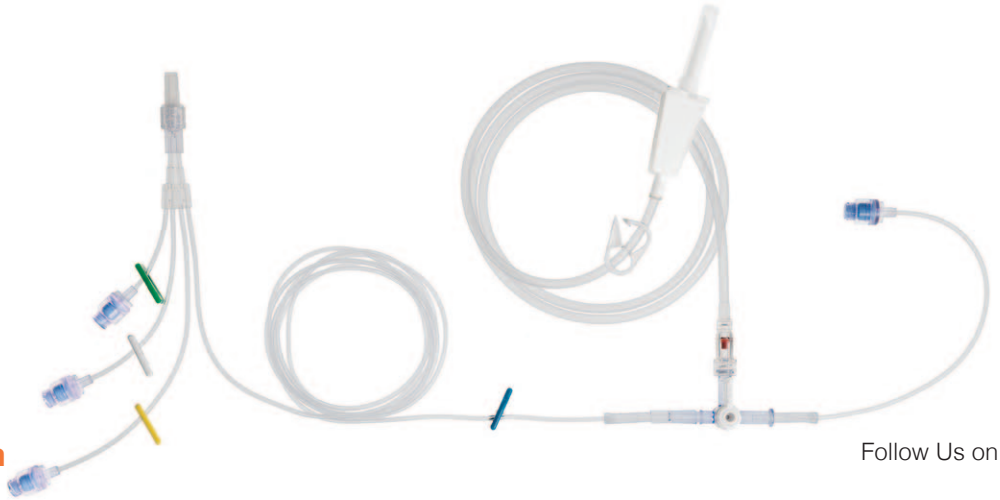

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EMA) welcomed the collaborative efforts to create novel and improved methods to evaluate treatments that will one day benefit a vulnerable and underserved population. Dr Janet Woodcock, Director of the US Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER), added that "By uniting stakeholders from research institutions, drug developers, regulatory agencies, patient advocacy and other organizations, INC can develop practical tools that can be incorporated into clinical trials for neonates, which will then lead to more successful, efficient trials and provide this population with better treatments." INC is the latest in a series of successful developments for C-Path, which include the celebration of its 10th anniversary and the opening of a new office in London. "Individual organizations simply do not have the data, resources, or expertise to address the many gaps in regulatory science that exist for the neonatal population," explained C-Path President and CEO Dr Martha Brumfield. "By utilizing our consensus science model and working directly with regulators, we will forge a more efficient regulatory pathway for much-needed neonatal treatments." The C-Path-appointed Executive Director of the new consortium is Dr Alan Bedrick, who will continue to serve as Chief of Neonatology and Developmental Biology at the University of Arizona College of Medicine – Tucson. "The International Neonatal Consortium embodies the collaborative nature of the Arizona Health Sciences Center, which has major multi-disciplinary initiatives in health disparities, population health, pediatrics, translational medicine and many other areas," said Dr Joe GN "Skip" Garcia, UA Senior Vice President for Health Sciences. "We welcome the opportunity to partner with C-Path to more rapidly develop better treatments for this vulnerable population."

INC will concentrate on conditions commonly observed in neonatal intensive care units (NICUs). Therapeutic areas include neonatal brain, lung, and gastrointestinal injury; neonatal sepsis; retinopathy of prematurity; and neonatal abstinence syndrome. Workshop participants prioritized an array of high-impact initiatives, such as developing clinical trial endpoints to assess efficacy of treatments. The workshop was supported in part by contributions from the Burroughs Wellcome Fund, the March of Dimes Foundation, Graham's Foundation, and grant 1U18FD005320-01 from the FDA.

Preemies Worth Fighting For?

Should doctors make more effort to save the very youngest preemies, even if they are at high risk for serious impairments? Hundreds of readers debated that question after research showing that a tiny percentage of babies born in United States hospitals at 22 weeks—a gestational age most doctors had not considered viable—lived. Some of the most affecting opinions came from readers with deeply personal experience: They were parents of preemies or born prematurely themselves. Kristen from California, born at 26 weeks, is now 30 and said she was lucky that her parents fought hard for her survival. "At that time, 26 weeks was just on the edge," she said. "While the doctors did treat me, they came to my parents multiple times and told them that I would be severely handicapped and should be taken off life support. I am now 30, in perfect health, have my Ph.D. in science and am married. These preemies are worth fighting for."

Study Looks at Breastfeeding Impact on Leukemia

Children who are breastfed as infants have a lower risk of developing childhood leukemia, a new study suggests. Leukemia

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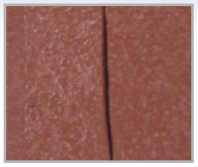

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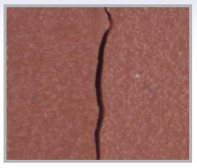

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is one of the leading killers of children and adolescents. Scientists have long suspected that breast-feeding might have a protective effect against the blood cancer because breast milk contains many antibodies and immune-strengthening compounds. In the new study, published in JAMA Pediatrics, scientists found that children who were breast-fed for at least six months had a 19 percent lower risk of the disease compared with those who were not breast-fed at all or were breast-fed for shorter periods of time. The research showed only an association, not a cause and effect, and more research is needed to confirm the link and explain the biological mechanisms involved. The study was based on data from 18 studies that involved about 28,000 children, including roughly 10,000 who went on to develop leukemia. The American Academy of Pediatrics recommends that mothers exclusively breast-feed their children for at least six months, saying it lowers the risk of infections, allergies and sudden infant death syndrome, among other things.

Drugs for Children Studied

The Pediatric Trials Network, an alliance of clinical-research sites around the country, is studying a number of drugs in a series of clinical trials. Many of the medications are already the standard treatment in small children, so the trials are trying to determine the safest, most effective doses and regimens for the drugs rather than to explore new uses. About 3,500 children have participated in the trials at some 90 locations in the U.S., primarily children's hospitals to discover the right dose for the right children, to be given at the right time for the right problem. The research project, which is funded by the National Institutes of Health, is beginning to have an impact. The Food and Drug Administration in December revised the prescribing label for the antibiotic meropenem to add that it can be used in infants younger than 3 months of age to treat complicated intra-abdominal infections. Although the drug already was widely used in these babies, doctors didn't have sufficient clinical-trial data to guide dosing decisions. Some of the trial findings have been surprising. Traditionally, doctors would extrapolate dose levels for babies and children based on findings from studies in adults, using the same dose per pound of body weight. But recent research has found that babies, especially premature ones, metabolize drugs differently because of immature organs and sometimes need a higher dose per pound than adults. A national network of pediatricians is testing the effectiveness and safety of several drugs commonly used in infants and preemies. Even premature babies with the same body weight might need different doses of a medication, if they were born at different weeks of gestation and their organs matured differently. In the past, drug manufacturers often didn't test their products in children because they viewed the pediatric market as much smaller than that for adults. Also, normal clinical-trial procedures such as drawing blood are more difficult with children, and young people often can't communicate information about adverse events, such as side effects. Medical ethics pose an issue, too, and parents or guardians must give consent.
A series of U.S. laws beginning in the late 1990s required pharmaceutical companies to study new drugs in children and offered incentives to do so, such as a longer period of patent exclusivity. The Pediatric Trials Network is testing mostly older drugs that hadn't previously been studied in certain age groups, especially premature infants. In considering ethical concerns, the researchers discuss among themselves whether they, as

parents, would consent to have their own children participate in a prospective trial, before seeking consent from the actual parents. Because many of the drugs are well known after years of use, often the only parental consent required is to take blood samples from the children. Frequently, only a small drop of blood is needed.

Study Looks at Maternal Use of Antidepressants

Use of antidepressants late in pregnancy has been controversial since the FDA issued a Public Health Advisory in 2006 warning that the use of antidepressants in late pregnancy may increase risk of persistent pulmonary hypertension of the newborn (PPHN), a condition that typically occurs in term or near-term infants and presents within hours of birth with severe respiratory failure requiring intubation and mechanical ventilation. The 2006 public health advisory was based on a single epidemiologic study. To shed more light on the issue, researchers from Brigham and Women's Hospital (BWH) and the Harvard T.H. Chan School of Public Health examined the risk of PPHN associated with both SSRI and non-SSRI antidepressants in a large cohort of publicly insured pregnant women across the United States. In new findings, researchers demonstrate that while the possibility of an increased risk of PPHN associated with maternal use of antidepressants in late pregnancy cannot be entirely excluded, the absolute risk is small and the risk increase, if present, appears more modest than suggested in previous studies. The cohort study included 3,789,330 pregnant women enrolled in Medicaid from two months or less after the date of last menstrual period through at least one month after delivery, of which 128,950, or 3.4 percent, filled at least one prescription for an antidepressant late in pregnancy. Among these women, 102,179 or 2.7 percent used an SSRI and 26,771 or 0.7 percent a non-SSRI antidepressant. The reference group consisted of women without exposure to antidepressants at any time during pregnancy. Overall, 20.8 per 10,000 infants not exposed to antidepressants during the last 90 days of pregnancy had PPHN compared with 31.0 per 10,000 infants exposed to antidepressants. This higher risk among exposed infants was observed for both SSRI (31.5 per 10,000 infants) and non-SSRI (29.1 per 10,000 infants) antidepressants, representing a 40 to 50 percent increase in risk. After accounting for differences in the characteristics of women who did and did not take antidepressants, there was no longer a significant increase in the risk of PPHN associated with SSRI or non-SSRI antidepressants.

There's an App for Embryos

A new smartphone app could allow doctors and would-be parents receiving in vitro fertilization treatment to monitor the growth of embryos in a lab thousands of miles away. The technology, being developed by Sydney-based Genea, is the latest example of how innovation in the global IVF industry—tipped by some analysts to be worth US$14 billion in 2020—is gathering pace. It could enable a more efficient approach to boosting the quality of embryos and the chances of successful implantation. Merck KGaA said it plans to sell a suite of Genea's products to IVF clinics around the world. Included is Gavi, the world's first machine to snap-freeze human eggs and embryos for later use, removing human error in the temperature-reducing process. There is also Geri, an incubator for fertilized eggs that uses time-lapse photography to eliminate the potentially hazardous procedure of removing the eggs for inspection as they are forming into embryos. The agreement includes funding

toward developing new technology, including to help livestream the images from Geri to smartphones so doctors, or even patients, can monitor embryos around the clock. The assisted-reproduction industry has grown rapidly since the first baby was born through IVF in 1978. There are now around 4,000 clinics world-wide, according to the International Federation of Fertility Societies, performing about 1.5 million treatments annually. An estimated 350,000 such babies are born each year, says the European Society of Human Reproduction and Embryology, or ESHRE.

Study Questions PUFA Supplements

In very low birth weight (VLBW) infants, giving milk fortified with long-chain polyunsaturated fatty acids (LCPUFAs) had no effect on cognitive function or brain macrostructure at eight years of age, researchers reported May 18 online in Pediatrics. VLBW infants have changes in brain structure and development that correlate to their cognitive and motor function, Dr Astrid Nylander Almaas and colleagues from the University of Oslo in Norway note in their report. Given that docosahexaenoic acid (DHA) and arachidonic acid (AA) play a key role in nervous system development, and that preterm babies miss much of the DHA and AA accumulation in the brain that occurs later in pregnancy, several investigators have looked at supplementation with LCPUFAs in these infants. Dr Almaas and her colleagues previously found in a randomized, controlled trial of 129 VLBW infants that DHA/AA showed positive effects on cognition at six months (as measured with event-related potentials) and at 20 months as measured by attention capacity during free play. To investigate whether supplementation has lasting effects, they followed up with 98 children from their original study when the children were 8.6 years old, on average. The children underwent cognitive testing, and 81 had brain magnetic resonance imaging (MRI) tests adequate for analysis. The investigators found no difference between the supplemented and non-supplemented group on any measure of cognitive function, nor was there any evidence of differences between the groups in brain volumes, cerebral cortex volume, area or thickness. They conclude: "Further RCTs with MRI-derived end points are warranted to clarify the effects of LCPUFAs on long-term brain development and hence preclude neurocognitive sequelae for next generations of premature children."

Growth Restriction Found in Protocol

An evidence-based premature infant feeding 'bundle' of practices can safely reduce postnatal growth restriction (PNGR) among very low birth weight (VLBW) infants, new findings show. VLBW babies face a high risk of PNGR for many reasons. Their nutritional stores are low, while their metabolic demands are high, which can lead to protein catabolism and "metabolic shock." Protein-enhanced parenteral nutrition soon after birth can help them catch up metabolically, but it can't provide enough nutrition to reverse these effects, the Albany Medical Center researchers added. Several studies have shown that early enteral feedings can improve growth safely, but they are not used consistently. Graziano and her colleagues developed a bundle of evidence-based feeding practices for VLBW infants after observing that enteral nutrition use was inconsistent at their center, and rates of PNGR were high. Elements of the bundle included use of fortified breast milk, initiation of enteral nutrition within 24 hours of birth, and daily feeding increases if tolerated. The bundle also provided standardized definitions of

feeding tolerance and intolerance. For extremely LBW infants, weighing less than 1,000 grams, the bundle recommends minimal enteral nutrition for the first five days of life, followed by increases of 10 to 20 ml/kg per day if tolerated. The investigators gathered data on 482 infants admitted their neonatal ICU in 2010 through 2012, including 119 who were treated before introduction of the feeding bundle.

Prolacta Forms National Nutrition Advisory Committee

Prolacta Bioscience – a producer of human milk-based neonatal nutritional products – has announced the formation of a national Nutrition Advisory Committee. The NAC is comprised of leading registered dietitians including professionals certified in nutrition support and board-certified specialists in pediatric nutrition. The goal of is to provide neonatal intensive care units (NICUs) with clinical expertise, research, insights, and guidance on premature infant nutrition and the use of an exclusive human milk diet. "We've heard from countless hospitals and neonatologists about the need for education and support around neonatal nutrition and the growing use of an exclusive human milk diet, so we brought together experts in the field to serve as a resource to their fellow clinicians," said Scott Elster, president and CEO of Prolacta Bioscience.

Critically ill and premature infants have special nutritional needs requiring higher levels of fat, protein and calories, and a different approach to nutrition support, than full-term babies need. Nutrition Advisory Committee members stay current on clinical data and trends within the NICU. They are actively involved in nutrition research within their own institutions, and many have published in peer reviewed medical and nutrition journals, and frequently serve as advocates for the health, well-being and survival of premature infants. Beginning in June 2015, members of the Nutrition Advisory Committee will be hosting monthly webinars to share information directly with fellow clinicians. Topics will focus on premature infant nutrition and will include guidance on standardizing feeding protocols in the NICU, growth and macronutrients for premature infants, and implementing donor milk in the NICU. To view the webinar schedule and register, visit www.prolacta.com/webinars. Growing scientific evidence supports the health benefits of an exclusive human milk diet for premature infants in the NICU, as opposed to cow milk-based nutrition or formula. A report published in 2014 in the journal Breastfeeding Medicine found an increase in the likelihood of developing necrotizing enterocolitis (NEC), NEC requiring surgery, or sepsis, as the amount of cow milk-based protein fed to the infants in the control group increased. NEC is one of the leading causes of mortality among preterm babies. Another study published in the Journal of Pediatrics found that successfully incorporating a human milk caloric fortifier made from pasteurized human milk cream into premature infants' diets improved their growth outcomes in the NICU. Since human breast milk is highly variable, a significant percentage typically contains less than 20 calories per fluid ounce. Adding a human milk-derived cream supplement to mom's own or donor breast milk, when less than 20 calories are present, provides the nutrition these preemies need for growth.

Benefits of Cerclage Placement

Cerclage placement, when indicated by physical examination, significantly increases neonatal survival and extends pregnancy by an average of 33.98 days compared with expectant management, according to a published systematic review and meta-analysis. The researchers also found fewer preterm births

and higher birth weights associated with physical exam-indicated cerclage, although only one randomized trial was available for the analysis. "A concern with physical examination-indicated cerclage is that it may prolong pregnancy long enough only to result in an extremely preterm delivery," note Robert Ehsanipoor, MD, from the Department of Gynecology and Obstetrics at Johns Hopkins University in Baltimore, Maryland, and colleagues. "However, we found that expectant management was associated with a more than fourfold increased risk of delivery between 24 and 28 weeks of gestation." They continue, "The current literature suggests that physical examination-indicated cerclage is associated with markedly improved outcomes." Still, an important caveat of their analysis includes the limited quality and small size of the included studies. The researchers searched six databases for studies published between 1966 and 2014 that compared cerclage with expectant management for treating cervical insufficiency. Cervical insufficiency, defined as painless second semester cervical dilation, occurs in less than 1% of pregnancies, and few data exist for assessing the benefit of cerclage to prevent pregnancy loss.

Maternal PCOS Linked to Problems

Maternal polycystic ovary syndrome (PCOS) may have long-lasting adverse health consequences for offspring, according to a study published online May 11 and in the June issue of Obstetrics & Gynecology. Offspring of affected mothers had higher odds of congenital anomalies than peers of unaffected mothers and were 14% to 69% more likely to be hospitalized for various health conditions, with the elevated risk persisting into at least young adulthood. "In view of our findings and the purported association of periconception, metabolic derangements with poor implantation and placentation[,] strategies to improve periconception health in women with PCOS may be expected to improve reproductive outcomes," write Dorota A. Doherty, PhD, from the School of Women's and Infants' Health, University of Western Australia in Subiaco, and colleagues. Both normal-weight status and metformin therapy have been linked to better pregnancy outcomes in this population, they note. "Hence, preconception identification of women with PCOS may enable early intervention to improve long-term outcomes, although it is not clear if all women with PCOS have this increased risk for adverse outcomes or whether there are certain features of PCOS that are associated with particular outcomes for the mother and her offspring," they maintain. The study is important as it is apparently the first to report a link between maternal PCOS and health outcomes of offspring in early life, according to Kathleen Hoeger, MD, a professor of obstetrics and gynecology and director of the Reproductive Endocrine Division, University of Rochester Medical Center, New York. In addition, PCOS is common among women of reproductive age but is often underappreciated in general pregnancy care.

Newborns and CF

Eleven percent of infants who had inconclusive results for cystic fibrosis (CF) as newborns went on to develop the disease by age 3 years, underscoring the need for additional tests by skilled clinicians, including monitoring of sweat chloride and searching for disease-causing mutations, according to a prospective longitudinal study. The study, by Chee Y. Ooi, MBBS, PhD, from the Discipline of Pediatrics, School of Women's and Children's Health, Faculty of Medicine, University of New South Wales, Sydney, Australia, and colleagues, is one of two

articles published online May 11 in Pediatrics that examine how to care for children who are CF screen positive but receive an inconclusive diagnosis (CF screen positive inconclusive diagnosis; CFSPID). CF is a genetic disorder that shortens the lifespan of up to 1 in 2500 white infants and results in sticky mucus gumming up the body's organs and air passages, according to the National Institutes of Health. Dr Ooi and colleagues enrolled 162 newborns from June 2007 to August 2013 from seven CF clinics in Canada and Italy. Eighty-two infants were found to have CFSPID at newborn testing, and 80 had CF. The last clinical review was conducted at a median age of 24.8 months for the CF cohort and 24 months for the CFSPID cohort.

SSRIs and Newborns

Persistent pulmonary hypertension of the newborn (PPHN) was present in slightly more births among women who had taken selective serotonin reuptake inhibitors (SSRIs) in late pregnancy compared with in women who had a diagnosis of depression but were not prescribed antidepressants (34.4 vs 24.9 per 10,000), according to a cohort study of nearly 3.8 million women. However, after adjustments for confounding factors, the association diminished. Although the condition is serious, "the absolute risk was small and the risk increase [from taking SSRIs] appears more modest than suggested in previous studies," write Krista F. Huybrechts, PhD, from the Division of Pharmacoepidemiology and Pharmacoeconomics in the Department of Medicine at Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, and colleagues.

"This is an extremely useful study...it is the largest study on this issue to date," said Patrick O'Brien, MD, a spokesperson for the Royal College of Obstetricians and Gynaecologists, in a statement released to the media. "It has used a robust methodology and careful efforts have been made to account for any confounding factors. The findings therefore, are certainly the best evidence we currently have on antidepressant use in late pregnancy and the risk of PPHN. In a sense, these results are reassuring," he continued. "The findings suggest a very small absolute risk. The chances of a baby getting PPHN when its mother was not taking an SSRI are around 2 in 1000, compared to around 3 in 1000 when the mother had taken an SSRI antidepressant medication in the last 90 days of pregnancy." Moreover, both the authors and Dr O'Brien noted that any risk associated with antidepressant use must be weighed against the risk for untreated depression during pregnancy.

Predicting Outcomes in Pregnant Women

Good outcomes were found in pregnant women with inactive or stable mild or moderate systemic lupus erythematosus (SLE) and no specific risk factors, according to findings of a prospective, multi-center cohort study in the Annals of Internal Medicine. Various clinical and laboratory parameters can identify patients at high risk for adverse pregnancy outcomes (APOs). Using a multi-ethnic cohort of 385 women with SLE with inactive or stable mild or moderately active disease during the first trimester of pregnancy, the investigators aimed to identify predictors of APOs. These were fetal or neonatal death; birth before 36 weeks' gestation caused by placental insufficiency, hypertension, or preeclampsia; and small-for-gestational-age neonate, defined as birth weight below the fifth percentile. Nearly half (48%) of participants were non-Hispanic white, and 31% had a history of nephritis. The study included women with a singleton pregnancy of up to 12 weeks' gestation. Exclusion criteria were urinary protein–creatinine ratio exceeding 1000 mg/g, serum creatinine level exceeding 1.2 mg/dL, prednisone use exceeding 20 mg/day, diabetes, and uncontrolled hypertension. Nearly one fifth of the women (19.0%; 95% confidence interval [CI], 15.2% - 23.2%) had one or more APOs. Most of these APOs were small-for-gestational-age neonate (10%) or preterm delivery (9%). Fetal death occurred in 4% and neonatal death in 1%. Only 2.5% (95% CI, 1.1% - 4.7%) of the women had severe SLE flares in the second trimester, and 3.0% (95% CI, 1.4% - 5.6%) in the third trimester, as determined with the SLE Pregnancy Disease Activity Index and the Physician's Global Assessment (PGA).

Blood Flow and Umbilical Milking

Umbilical cord milking (UCM) resulted in higher systemic blood flow than delayed cord clamping among preterm cesarean-delivered infants, according to the findings of a randomized controlled trial led by Anup Katheria, MD, director, Neonatal Research Institute Team, Sharp Mary Birch Hospital for Women and Newborns, San Diego. The study included 197 infants born with a mean gestational age of 28 weeks. Forty-three infants were delivered vaginally, with 23 randomly assigned to UCM and 20 to delayed clipping. Another 154 were delivered by cesarean, with 75 randomly assigned to UCM and 79 to delayed clamping for at least 45 seconds. The infants underwent echocardiogram at between 6 to 12 hours of life, and continuous hemodynamic recordings were made at one of the two study centers for 140 subjects: 70 in each group. The clinicians were blinded with respect to the infants' study group. The investigators found higher superior vena cava blood flow and higher right ventricular output in the first 12 hours of life among cesarean-delivered infants in the UCM group, which was the primary endpoint of the trial, compared with infants who had delayed clamping. Hemodynamic testing also documented improved hemoglobin, higher delivery room temperature, and higher blood pressure in the first 15 hours of life, as well as higher urine output in the first 24 hours among cesarean-delivered infants in the UCM group.

Senators Urge Action

A bipartisan group of US senators, led by Sherrod Brown (D-OH) and Kelly Ayotte (R-NH), is urging the US Department of Health and Human Services (HHS) to expedite its review of updated guidelines aimed at preventing preterm birth. "We cannot afford further delay in moving forward on initiatives—many of which can be implemented with relative ease through the use of existing technologies—that have the potential to lower the rate of preterm birth in our country," the senators wrote to HHS Secretary Sylvia Mathews Burwell in a letter dated June 12. The updated guidelines were submitted to HHS in August 2014 by the Society for Maternal-Fetal Medicine (SMFM), the American College of Obstetricians and Gynecologists (ACOG), and the American College of Nurse-Midwives (ACNM). They include the use of routine, universal screening for premature cervical shortening midpregnancy and equitable access to progesterone treatment as one strategy for reducing preterm birth.

Teens Not Getting Pregnant as Often

New data suggest an uptick in the number of babies being born in the United States, but not among teenagers. The preliminary number of births in 2014 was 3,985,924, an increase of 1% (or 53,743 births) from 2013. This is the first increase in births since 2007, ending the recent downward trend, according to the report from the Centers for Disease Control and Prevention's National Center for Health Statistics (NCHS). The number

of births increased 1% for non-Hispanic white, non-Hispanic black, and Hispanic women from 2013 to 2014. Births among Asian or Pacific Islander women rose 6% in 2014, while births to American Indian or Alaska Native women fell 2%. The preliminary general fertility rate (GFR) also increased 1% in 2014, to 62.9 births per 1000 women aged 15 to 44 years, up from 62.5 in 2013. This is the first increase in GFR since 2007. Yet, fewer adolescents are having babies. The preliminary birth rate among 15- to 19-year-olds in 2014 was 24.2 births per 1000—"yet another historic low for the nation," Brady Hamilton, PhD, and colleagues with the NCHS Division of Vital Statistics, note in their report. The preliminary numbers show that 249,067 babies were born to women aged 15-to-19 years in 2014. The 2014 birth rate among this age group, 24.2 births per 1000, is down 9% from the 2013 rate of 26.5 births per 1000 and has dropped more than 7% annually since 2007. Since the most recent peak in 1991 (61.8 births per 1000), the rate has declined a total of 61%, the authors note.

Warmer Cleared by FDA

Creche Innovations has announced that the Food and Drug Administration (FDA) has granted 510(k) clearance for the Penguin In-Line Enteral Warmer, which is intended to maintain the body temperature of breast milk that is fed enterally over extended periods of time. This addition to the Penguin line of warmers provides caregivers a solution that now assures 100% of all feedings will be easily and safely administered at "mom's temperature". The proprietary low heat technology utilized in the Penguin assures the entire nutritional value is delivered with every feeding. More importantly, the Penguin protects the babies from unwanted chemical transfers that are potentially leached into the feedings when exposed to high heat environments currently offered by competitive solutions. Unlike current enteral warmers, the Penguin In-Line Warmer is the only warmer that supports universal compatibility and is interchangeable with ALL brands of feeding pumps, extension sets, and accessories. The company plans on making the Penguin In-Line Warmer commercially available in the United States prior to the fourth quarter of 2015.

NANN PREVIEW

Accriva Diagnostics

Booth 1014

What products do you plan to exhibit at NANN?
Accriva Diagnostics will be featuring our Tenderfoot® line of infant heel incision devices. For over 25 years, our patented Softsweep technology creates high-quality incisions resulting in a sample with maximum blood flow to reduce the need for re-sticking. When used as intended, Tenderfoot produces a consistent incision arc that is controlled to a depth just above the nerve fibers. This benefits a device that is safe, easy to use, and virtually pain-free with less bruising as compared with traditional lancet devices.

What's new this year?
At this year's NANN we will be launching our new Tenderfoot Educational Kit. The kit will include everything necessary to perform a heel stick test, and is intended as an educational tool when training Neonatal Nurses. The Tenderfoot Educational Kits will include:

- Sample devices in all four incision depths from micro-preemie to toddler.
- Full-term infant foam foot to be used for demonstrating the product.
- Instructional Video.
- Literature for clinical professionals.
- An informational guide for parents.

Why should our readers stop by your display?
In partnering with the National Association of Neonatal Nurses, Accriva Diagnostics will be sponsoring the Passport Program with prizes drawn to those who collect all the necessary stamps. Visit us at Booth #1014 to receive your passport stamp, and find out more information about our Tenderfoot Educational Kit. If you would like to receive a kit for your hospital, please visit www.tenderfootcares.com.

Argon Medical

Booth 614

What products do you plan to exhibit at NANN?
Argon Medical is an industry leader in neonatal and pediatric PICCs, offering silicone and polyurethane catheters in a comprehensive array of sizes from 28G (1.2F) to 16G (5F). Argon also offers a maximum barrier neonatal/small pediatric insertion tray that meets all industry standards and a range of midlines and safety MST kits.

What's new this year?
Argon is working on new products to enhance the current product line.

What educational or training materials will be available?
We will feature product catalogs and have demonstrations of our neonatal products. We will also have our popular educational neonatal vein guide cards on lanyards as our booth giveaway. These are a big hit among attendees each year.

Why should our readers stop by your display?
Argon Medical is an industry leader in the world of neonatal and pediatric PICCs and insertion trays. If you work in this space, you owe it to yourself to trial Argon products.

CODAN

Booth 408

What products do you plan to exhibit at NANN?
CODAN, a leading medical device manufacturer of high quality IV delivery systems, will feature Closed Medication Administration Sets specifically designed for the NICU and PICU at NANN. The sets focus on infection prevention and offer an alternative to standard open medication delivery systems that present a serious health concern and contribute to increased infection rates.

All-in-one CODAN neonate/pediatric sets eliminate the need to assemble multiple sets, increase efficiencies of line change outs and decrease CLABSI rates. Made in the USA product line

includes completely sterile burettes for truly sterile procedures.

- Pre-Assembled System Saves Precious Time
- 0.2 micron Air Eliminating Filter Sets
- Needlefree Adapters and Stopcocks
- MiniBore and MicroBore Tubing for Low Priming Volume
- Available for Use with Any Syringe Pump
- Color-Coded Clamps for Verification of Medication Use
- Bifurcated, Trifurcated and Quad Furcated Sets
- Reduced Material Management Cost
- Back Check Valves Prevent "Free Flow"
- TPN and Custom Sets
- Non-DEHP and Latex Free

Why should our readers stop by your display?
CODAN is an environmentally conscious manufacturer of clean, safe and simple specialty products for the Infusion Therapy Market. CODAN Label product lines include high quality IV sets and components for neonatal, pediatric, pharmacy, anesthesia, oncology and cytotoxic drug delivery. Through decades of experience and working closely with clinical practitioners, CODAN is committed to innovative applications and new product development. Our manufacturing schedule is flexible and we respond quickly to client needs. Custom sets are available in 4 weeks. For further information, visit www.codanuscorp.com.

Draeger

Booth 207

What products do you plan to exhibit at NANN?
During the NANN conference this year, Draeger will showcase several of our elite NICU technologies: the Isolette 8000 infant warmer, the GT5400 Neonatal Transport System, the Babylog VN500 Neonatal Ventilator and our JM-105 Jaundice Meter.

What's new this year? Tell us about your latest products or future plans.
Since last year's NANN conference, Draeger added two products to our Neonatal portfolio, the GT5400 Neonatal Transport System and the JM-105 Jaundice Meter. These two products enhance our comprehensive line of infant care solutions. The JM-105 is a handheld jaundice screening tool with advanced features such as bar code scanning technology and EMR connectivity. The GT5400 is Draeger's solution to inter-hospital transport that addresses the wide variety of clinical needs of the baby, the practical needs of clinicians, and the logistical requirements of the transport team.

What educational or training materials will be available?
In early 2015, Draeger extended its popular ICON resource, which has offered a high level of clinical support to ventilation customers for 10 years, to the full line of neonatal care products. ICON provides customers with a support system and resource center that can enhance patient safety by helping to reduce the number of errors that can occur in the NICU. In addition to the clinical hotline, ICON also offers online support through the "members only" section of its website. Draeger customers enjoy access to online clinical documents and case studies, as well as educational web conferences, symposiums with continuing education units, and respiratory care and neonatal care modules for respiratory care practitioners and registered nurses.

Tell us about any speakers or in-booth promotions.
NANN provides Draeger the opportunity to showcase our technology and interact with clinicians. We will have knowledgeable staff at our booth with operational devices, to allow neonatal practitioners to view the latest advances in technology. Our educational resources such as www.babyfirst.com will also be on display to demonstrate Draeger's commitment to supporting both clinicians and parents alike.

Why should our readers stop by your display?
As we talk to clinicians throughout the year, two topics that routinely are discussed are education and innovation. We will showcase the latest technologies in jaundice screening, infant warming, and neonatal ventilation. Clinicians can hear about the rationale and evidence for volume ventilation or better understand jaundice screening. Draeger appreciates the opportunity to meet you this year in Dallas.

International Biomedical

Booth 101

What products do you plan to exhibit at NANN?
We will feature the Airborne Voyager transport incubator, 750i in-house transport incubator, AeroNOx INO delivery system, Lifeborne infant warmer, Tecotherm infant body cooling system, Neo-Restraint infant positioning system, Puffin infant resuscitator.

What's new this year? Tell us about your latest products or future plans.
We are now the distributor in the US for the transport use of the Tecotherm infant cooling system. The Tecotherm is compatible with all Airborne transport incubators.

What educational or training materials will be available?
We will have product sell sheets, our sales team and videos available to provide information.

Tell us about any speakers or in-booth promotions.
We will feature the Tecotherm infant cooling system.

Why should our readers stop by your display?
To learn more about the products available from International Biomedical such as our neonatal transport life-support systems.

NeoMed

Booth 509

What products do you plan to exhibit at NANN?
As implementation of the ISO Enteral Connector approaches, NeoMed is committed to providing our customers with strategic guidance to navigate through these changes. Our unique understanding of the specialized needs of the neonatal/pediatric patient and pharmacy allows us to provide a comprehensive approach that meets clinical and product needs.

NeoConnect is the NeoMed trademark for our ENFit compliant and compatible enteral devices. NeoConnect products will feature new SKU numbers and different product and package graphics for easy identification.

NeoMed will be exhibiting our existing line of enteral/oral syringes, feeding tubes and extension sets, along with our NeoConnect product line with ENFit connectors.

What's new this year? Tell us about your latest products or future plans.
NeoMed supports the international movement to the ENFit design which helps eliminate the possibility of small-bore misconnections in the NICU and is excited about the NeoConnect solutions. Like our existing product line, our ENFit syringes will continue to feature an off-centered tip and solid plunger design that are known to minimize loss of lipids and vital micro/macro nutrients, as well as facilitate lipid delivery first during horizontal enteral pump feeds.

We will also provide syringe tip caps that are compatible with our ENFit syringe while retaining our existing hands-free and self-righting design, promoting compliance with aseptic technique. All NeoConnect products with ENFit connectors will be available in both orange and purple.

The NeoMed pharmacy solution includes both filling and dispensing accessories engineered to maintain dose accuracy when delivering through a placed feeding tube or directly into the mouth, saving cost, time, complexity and reducing the risk of errors.

The NeoConnect line will include Pharmacy Syringes, Straws, Pharmacy Caps, Transfer Lids, Syringe-to-syringe Coupler, and the Oral Administration Tip.

What educational or training materials will be available?
As implementation of the ISO Enteral Connector approaches, NeoMed is committed to provide our customers the strategic guidance to navigate through these changes.

Our unique understanding of the specialized needs of the neonatal/pediatric patient and pharmacy allows us to provide a comprehensive approach that meets clinical and product needs.

Why should our readers stop by your display?
NeoMed has considered neonatal specific needs necessary for enhancing clinical outcomes for each of our ISO 80369-3 compliant enteral devices.

The NeoConnect enteral system incorporates feeding tubes with our open hub design which was developed to reduce residual nutrition from accumulating at the bottom of the threaded hub cavity while also allowing full visualization and maintaining compliance to ISO 80369-3. The feeding tube cap is a plugged device which closes the tube yet allows airflow through the hub. The NeoConnect system also includes a patent-pending hub "cleaning tool" designed to help remove any residual material from the threads.

NeoMed is an industry leader of innovative patient safety devices for the pharmacy, NICU, and PICU. Our commitment is our continual participation with GEDSA, the trade association created to help introduce the new standards. We will continue our support of the new ISO 80369-3 standard through implementation, practice, and beyond.

Prolacta Bioscience

Booth 507

What products do you plan to exhibit at NANN?
As the world leader in providing donor breast milk products to hospitals, Prolacta Bioscience will exhibit its full line of Neonatal Nutritional Products for premature babies in the NICU:

- **Prolact+ H²MF™ Human Milk Fortifier** (HMF) is the only commercially available 100 percent human milk-based liquid HMF designed to help meet the nutritional needs of preterm infants. The product is made exclusively from human milk, as opposed to cow's milk, and is proven to make a difference in the lives of preterm infants.
- When mother's own milk is unavailable, **Prolact HM™ Human Milk** meets nutritional needs with pasteurized and standardized 100 percent breast milk for preterm infants. It is formulated to deliver a minimum of 20 Cal/fl. oz.
- **PremieLact™ Human Milk for Trophic Feeds** may be used as the initial feeding of a 100 percent human milk diet when a mother's own milk is unavailable, or it may be used as a trophic feed to "prime the gut" for larger enteral feeds.
- **Prolact RTF™ Human Milk-Based Premature Infant Formula** is a new "ready-to-feed" product made from 100 percent human milk. It provides an easy and convenient way to provide 100 percent human milk-based fortified nutrition when a mother's own milk is unavailable, and delivers standardized caloric content of 24, 26, or 28 calories per ounce. This is the first formula for premature infants made from human milk as opposed to cow's milk.
- **Prolact CR™ Human Milk Caloric Fortifier** is pasteurized human milk cream derived from human milk that increases the caloric content of nutrition for extremely premature infants in the NICU. Prolact CR is formulated to contain 2.5 kcal per ml. which is used to fortify human milk—either mother's milk or donor human milk—to achieve a 20 Cal/fl. oz. solution to which human milk fortifier may then be added.

What's new this year? Tell us about your latest products or future plans.
Preemies in the NICU are in need of safe, human milk-based formulations when mother's own milk is unavailable. In an effort to provide standardized donor milk to at-risk premature NICU infants, Prolacta Bioscience now offers a contracted donor milk program developed to enable hospital NICU's to achieve three specific goals:

- Provide standardized donor milk to their most vulnerable preterm infants to reduce medical complications and subsequent costs
- Ensure the donor milk provided meets industry-leading quality standards
- Secure an adequate and guaranteed supply of donor milk to avoid shortages

What educational or training materials will be available?
At the request of many hospitals, Prolacta provides hospitals with a series of brochures to assist hospitals with their education initiatives on the importance of human milk nutrition for babies in the NICU. The series of brochures, which are also available in Spanish, facilitates hospital education programs on topics such as:

1. Premature Babies. What to expect in the NICU.
2. Nutrition for Premature Babies.
3. 100% Human Milk Nutrition. The Best Nutrition.
4. What is Necrotizing Enterocolitis?

Tell us about any speakers or in-booth promotions.
Prolacta Bioscience will be sponsoring a breakfast symposium on Sunday, October 25th on "100% Human Milk Diet—Meeting the Challenges of Infant Nutrition in the NICU." This symposium will present the latest data on the benefits of a 100% human milk diet to meet the nutritional needs of very low birth weight (VLBW) premature infants. In this session, the faculty will summarize the mounting body of compelling evidence demonstrating that an exclusively human milk diet leads to improved health outcomes and cost savings in this fragile patient population, through a reduced incidence and severity of comorbidities. The advantages of an exclusive human milk-based diet for VLWB infants in a community Level III NICU, which include lower total hospitalization cost and physician charges regardless of the cost of human milk-based fortifiers and donor breast milk, will also be discussed.

Speakers and topics include:

1. Terry S. Johnson, APN, NNP-BC, CLEC, MN, Director, Education & Professional Development, Prolacta Bioscience, City of Industry, CA. In this session, Terry will discuss the benefits of a 100% human milk-based diet for extremely premature infants. She will summarize the mounting body of compelling evidence demonstrating that an exclusively human milk diet leads to improved health outcomes and cost savings in this fragile patient population, through a reduced incidence and severity of comorbidities.
2. Melinda J. Elliott, MD, FAAP, Neonatologist and Faculty, The Herman and Walter Samuelson Children's Hospital at Sinai Hospital, Baltimore, MD. In this session, Dr Elliott reports that the advantages of an exclusive human milk-based diet for VLWB infants in a community Level III NICU include lower total hospitalization cost and physician charges regardless of the cost of human milk-based fortifiers and donor breast milk. These findings complement a decrease in necrotizing enterocolitis (NEC) and feeding intolerance, and shorter time to full feeds and length of stay with human milk vs. bovine-based fortifier and formula.

Why should our readers stop by your display?
Clinical evidence supporting the improved outcomes of an exclusive human milk diet continue to mount. Visit the booth to register for the Sunday morning breakfast symposium titled "100% Human Milk Diet—Meeting the Challenge of Infant Nutrition in the NICU" and obtain copies of the many published studies on human milk nutrition. Increasing clinical evidence has led to greater hospital demand for exclusive human milk nutrition for premature infants. As the pioneer in human-milk based nutritional products, Prolacta has built the only pharmaceutical-grade manufacturing facility for human breast milk products. Visit the booth for a look into the state-of-the-art human milk processing and find out how you can sign-up for an in-person tour the facility in California.

To further advance the science of human milk, Prolacta founded the International Conference on Human Milk Science and Innovation, a forum covering the latest in scientific and clinical research related to human milk. Renowned scientists and neonatologists from around the world attend this annual event to present and discuss the scientific potential of human milk and raise awareness of its clinical applicability. Visit the booth to learn more about this year's conference and to obtain copies of the conference proceedings.

USDTL, Inc.

Booth 117

What products do you plan to exhibit at NANN?
Umbilical cord tissue testing for in utero exposure to alcohol and substances of abuse.

What's new this year? Tell us about your latest products or future plans.
USDTL continually offers the most efficient methods to ensure reliable, easy sharing and retrieval of client results, including HL7 interfacing and online portals.

What educational or training materials will be available?
Our representatives will be available to answer questions concerning all USDTL approved specimen collection procedures. Our delegates are available to assist with specimen collection training in person and online. Collection instructions are available as videos or downloadable pdfs from our website, USDTL.com.

Why should our readers stop by your display?
Umbilical cord tissue drug testing offers many benefits over meconium testing. Universal availability, simple one-step collection, and improved turn-around time are just some of the benefits of umbilical cord testing over meconium or urine. USDTL pioneered the use of umbilical cord testing for in utero alcohol and drug exposure.

Utah Medical Products, Inc.

Booth 319

What products do you plan to exhibit at NANN?
We plan to display our entire neonatal line, which includes: Dialy-Nate, PICC-Nate, Nutri-Cath & Nutri-Lok systems, Umbili-Cath, Uri-Cath, General Procedure Trays, Thora-Cath, Disposa-Hood, Pala-Nate, Deltran Plus, Hemo-Nate, and Myelo-Nate.

What's new this year? Tell us about your latest products or future plans.
This year we will be launching/reintroducing our new and improved enteral feeding system, Nutri-Cath/Nutri-Lok, also we will launching PICC-Nate with Tungsten as well as PICC-Nate with an additional size of 1 FR.

What educational or training materials will be available?
We will have brochures and DVDs available for educational purposes.

Why should our readers stop by your display?
UTMD supports developmental care. Developmental care is a patient-focused treatment approach that focuses on the special needs of premature babies. Developmental care minimizes the amount of stress, discomfort and distruption to which babies are exposed. UTMD provides only latex-free devices, and avoids PVC materials with the potentially harmful additive of DEHP.

Parabase Genomics

Chris Campbell

Describe your product(s) and its unique features

Congenital abnormalities and genetic diseases are the leading cause of infant death in the United States and elsewhere in the world.[1,2,3,4,5,6,7,8,9,10] Sequencing of the human genome has paved the way toward developing and delivering "the right drug, for the right patient at the right dose" also known as "Precision Medicine." Despite its great potential, these novel approaches have not significantly impacted patient care in most Neonatal Intensive Care Units (NICU) in the U.S., which annually admit nearly 475,000 babies.[11] About 10-25% of these babies have been shown to carry a genetic disorder.[12,13,14] Due to their non-specific clinical and genetic presentation many infants are unable to receive a definitive diagnosis in a timely fashion because many health care professionals still rely on severe symptomology to nominate genes of interest for testing. As a result, the functional disability of the affected child could be exacerbated due to needless delays in medical interventions where on average an infant goes 5 years between disease onset and diagnosis. Despite there non-specific presentation an examination of the 4,300 genes in the Online Mendelian Inheritance in Man database (OMIM) shows that there are a set of 500-1000 genes with known specific disease phenotypes that disproportionately affect newborns. This suggests that targeted next-generation sequencing (TNGS) of a panel of genes may provide a more precise approach to diagnosing a majority childhood disorders. Gene sequencing, coupled with the use of minimally invasive sampling using dried blood spots, a rapid 7-10 day turnaround time and the use of both proband and parental samples (trios) could offer a cost effective method for differential diagnoses of neonatal disorders. Several studies have already reported that an appropriate NICU treatment is among the most cost-effective methods of high-cost health care.[15,16,17,18] Parabase Genomics has pioneered the application of dried blood spots, commonly used in Newborn Screening (NBS), to rapid TNGS. The company has already demonstrated the potential to expand elements of NBS to molecular diagnosis (MDx) following the precision medicine model to hundreds of undiagnosed or under diagnosed genetic diseases. For the highly penetrant and lethal disorders, such a TNGS panel provides close to 70% of the same diagnosis as whole genome sequencing would, but the TNGS is devoid of the burden of collecting and processing large volumes of blood, long-turnaround times and associated expenses as well as many ethical issues.

Chris Campbell is the Senior Editor of Neonatal Intensive Care.

An initial panel called NewbornDx, offered by Parabase Genomics (http://www.parabasegenomics.com), is designed to query 554 genes. This panel of genes has been curated and clinically validated at the Clinic for Special Children and the Brigham and Women's Hospital in Boston.[19] The panel itself shows analytical sensitivity of 99.8% observed across known mutation hotspots (Figure 1). Concordance calls with or without clinical summaries were 94% and 75%, respectively. Extraction of high quality and high yield double stranded DNA from dried blood spots have also been validated and can be submitted using a sample collection kit. The panel itself is composed of 554 genes representing 25 disease categories including: 1) NBS related – 126 metabolic genes plus 12 genes for immune deficiency disorders, cystic fibrosis and other non-specific endocrine disorders, 2) NICU related – 100 for hypotonia, 97 for hypoglycemia and other categories such as hepatosplenomegaly.

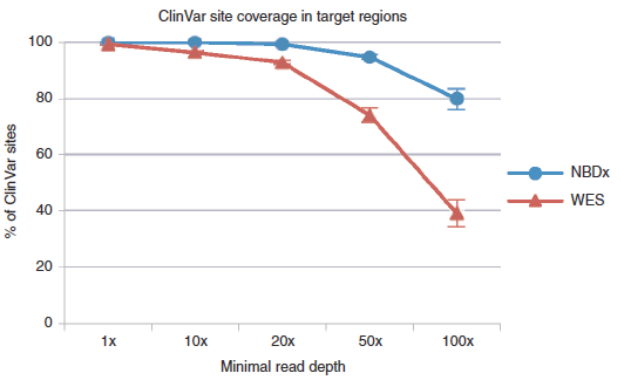

Figure 1. Comparison of % ClinVar Sites coverage with TNGS (NBDx panel) vs clinical exome.

We expect that a majority of genetic disorders can be detected with the TNGS panel at 1/3 the price compared to whole genome sequencing. Most importantly, the test could be performed while the child is still in the hospital. Payors such as Blue Cross Blue Shield also agree that "a relatively unbiased sequencing application that examines most genes without requiring prior knowledge of the potential diagnosis would be advantageous."[20] Molecular diagnosis of genetic diseases in infancy can dramatically decrease morbidity and mortality, as evidenced by many newborn screening (NBS) programs.[21] A rapid focused TNGS panel will not only yield a timely MDx in NICU infants, but can transform empiric, phenotype-driven management

into robust, genotype-informed treatment plans that improve outcomes as advanced by the precision medicine initiative.

In short, the Parabase NewbornDx test is the first comprehensive genetic test specifically designed for critically ill neonates and infants. The test utilizes DNA extracted from Dried Blood Spots to interrogate 554 genes using Next Generation Sequencing (NGS) across 25 disease categories and results are reported to the physician within 7-10 days. The NewbornDx molecular profiling approach, empowers medical professionals to determine the best possible treatment option within the appropriate therapeutic window, in the shortest amount of time.

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Capnography Use in the NICU

In this feature, Neonatal Intensive Care interviews clinicians and healthcare providers about the actual application of specific products and therapies. Participating in the interview is Prof. Amir Kugelman, a Clinical Associate Professor of Pediatrics in the R&B Rappaport Faculty of Medicine, Technion, Haifa, Israel.

Neonatal Intensive Care: Dr Kugelman, how are you currently using capnography?
Dr Amir Kugelman: In our neonatal intensive care unit (NICU) we use capnography routinely to trend the CO_2 levels in the blood for intubated infants. We don't use it instead of blood gases, but complementary to blood gases to get continuous non-invasive measurement of CO_2 levels. The idea is to prevent hypocarbia and hypercarbia because both can result in sequelae to the infant, especially for premature infants. A baby who is exposed to hypocarbia, because of hyperventilation, is at greater risk of lung and brain injury (decreases brain perfusion and increases ischemia). Hypercarbia secondary to hypoventilation may cause respiratory acidosis or brain injury, because if you have high levels of CO_2 and an increased circulation to the brain, you increase the risk of intraventricular hemorrhage.

NIC: With which infants are you using capnography?
AK: We use it as a routine in intubated babies. It would be great if you could use it in non-invasive ventilation, but currently it's problematic because you may get dilution of the CO_2 reading. So currently we use it primarily in intubated babies. It's also possible to use it in infants who are not ventilated, like infants with bronchopulmonary dysplasia (BPD). We are not using it for non-intubated infants routinely.

NIC: How long have you been using and publishing on capnography?
AK: We published on capnography starting back in 2002. In a 2008 publication in Pediatrics,[i] we used a novel method for sampling end-tidal CO_2. In the study published in Pediatrics we used the Microstream technology[ii] and we used it with a special double lumen endotracheal tube so we could sample etCO_2 at the distal end of the ET tube. We also published in 2010 using capnography with high-frequency ventilation[iii] and have ongoing studies.

The idea of using distal end-tidal CO_2 is to improve sidestream capnography because mainstream capnography is typically preferred and considered a more accurate mode for monitoring intubated patients. If we could improve the sidestream by using Microstream capnography monitoring and distal sampling, it will allow us to get as good as or even better measurements compared to the mainstream technique. The distal sidestream capnography is easier to use in intubated infants because if you use mainstream in small infants you get more dead space and you might get kinking and increased risk of tube displacement in the small ET tubes due to the weight and bulk of the mainstream sensor which is in-line with flow sensors. Using this method, we get very nice measurements using Microstream capnography monitoring with very good agreement with $PaCO_2$ levels.

NIC: Is it your routine now to use dual lumen ETT with Microstream technology for capnography sampling?
AK: Since 2008 and even before, we have used the double lumen ET tube and Microstream capnography monitoring as a routine in our unit. We continue to use it routinely for other studies and during routine care within the department and in the delivery room. I would say that in 80 to 90 percent of the infants we use Microstream capnography monitoring via the double lumen tube. For others, we may use mainstream capnography or transcutaneous CO_2 monitoring. Yet, this routine has some limitations. While this tube allows us to get distal measurements, it's a bit softer than other tubes and sometimes you might have to use a stylet when placing the tube. It shouldn't be a problem, but you have to get used to it. And the outer diameter is 0.1 - 0.2 millimeters wider than the single lumen tube. So if there is any difficulty in introducing the tube then we put a single lumen tube in and we can't use the double lumen tube to get measurement of distal capnography. With the double lumen ET tube we can measure distal capnography and we are giving also surfactant by the extra port of the double lumen tube.

NIC: You mentioned using capnography in conjunction with arterial blood gases (ABG). What are the benefits of using capnography in this manner?
AK: When we are taking blood gases it's not continuous measurement of CO_2. You can take it according to the acuity of the baby. You can take it every 4, 8, or 12 hours according to the routine of the department and the acuity of the clinical situation. But in between you don't know what happens with the CO_2 and if the baby has secretions and the tube is occluded or if the baby is moving and the ET tube becomes lodged on the side of the trachea, the CO_2 can go up or down and you won't know that's happening. So the baby can be outside of the safe range of CO_2 in between ABGs.

For monitoring oxygenation we have continuous measurement of pulse oximetry, but for CO_2 at the current time we don't

This interview was conducted by Greg Spratt BS RRT CPFT, the Director of Clinical Marketing in Patient Monitoring Market Development at Medtronic-Covidien. If you would like to participate in this feature, as a company or healthcare provider, please contact Steve Goldstien at s.gold4@verizon.net.

have continuous measurement unless you use end-tidal CO_2 or transcutaneous CO_2. So the benefit is that you have continuous measurement and if the CO_2 is trending up you can make a change in the vent settings, suction, or change the position of the baby and make sure that the CO_2 returns to the safe range. If you don't monitor CO_2 continuously, there may be long periods when CO_2 was out of the safe range and you don't know it.

NIC: Some point out that the difference between $etCO_2$ and $PaCO_2$ (gradient) makes capnography difficult to use in patients with significant lung disease. What are your thoughts?
AK: We have good agreement between $etCO_2$ and $PaCO_2$ for most infants; $etCO_2$ is typically two to five millimeters of mercury lower than $PaCO_2$ for most babies. For infants where the gradient is higher, such as those with higher ventilation/perfusion (V/Q) mismatch, we get an idea of the agreement and as there may be fluctuations as the baby's condition changes, we still periodically check the blood gas to ensure the gradient is staying relatively consistent.

It really depends on the baby. If the baby is stable and does not have significant lung disease, then gradient will be relatively small and consistent, but sometimes if there is a big ETT leak or significant lung disease with V/Q mismatch, then the gradient is not as consistent so you have to periodically recheck to make sure that the $etCO_2$ measurement correlates with the blood gas.

When the end-tidal to arterial CO_2 gradient is increased, it also gives you a clue on the severity of the lung disease and whether measures you are taking are working to improve the baby's condition. If you have a large gradient, then you know whether an intervention is effective when the gradient decreases.

But the idea is that in a baby who is very sick, in the first day or two if the baby had respiratory distress syndrome (RDS) we always use blood gases. And we use the end-tidal CO_2 for trending. After a few days when the baby is becoming better and the RDS is improving, typically the gradient is going to be smaller and then we don't take a lot of blood gases because the baby's doing better. At this stage, some babies do not have arterial lines anymore. But we are able to continuously assess and trend CO_2 levels by having the end-tidal CO_2. It's in that way that the blood gases and the end-tidal CO_2 are complementary.

NIC: Have you measured or looked at how much you were able to reduce the number of blood gases that you draw now compared to before you had these continuous measurements?

AK: We did not, but there is a study that was published by Rowan[iv] for the Pediatric Intensive Care Unit in the US and they compared the time period before and after using end-tidal CO_2 and they showed a reduction in the number of blood gases.

NIC: Could you estimate what percentage of babies that the gradient is acceptable to use the end-tidal CO_2 to do your ventilator management?
AK: It's difficult to say but most of the time you get good correlation and agreement based on the first study that was published in Pediatrics.[i] Even in babies who had severe lung disease the gradient was still adequate. So in most of the babies you could trust the measurements.

If the gradient is higher, you can still use $etCO_2$ for trending because if you know that you have, for example, $PaCO_2$ of 60 mm Hg the end-tidal CO_2 of 50 mm Hg, the gradient is around ten. But if you see that end-tidal CO_2 is going up and is now at 70 or 80, you know that the $PaCO_2$ is also going up, and might now be 80 or 90. So in this situation you would intervene with suctioning, changing position, or changing the vent settings or you might take a blood gas to confirm the elevation and then make a change.

So even when you have an increased gradient, the $etCO_2$ trending can help you. And I believe the main goal of the continuous CO_2 monitoring is not to get the exact measurement of CO_2 level, but to be able to monitor the trending.

NIC: In your hospital, which clinicians are responsible for using capnography monitoring?
AK: The doctors write the orders, but the nurses are involved all the time. We don't have a Respiratory Therapist in our unit so it's the senior physicians, residents, and nurses. If the nurse is watching the capnography and sees that the CO_2 is going up, he or she suctions the baby, changes the position of the baby, or calls the doctor to listen to the baby to see if the ET tube is blocked. All the medical team responds to the end-tidal CO_2 measurements.

NIC: You mentioned that you look for changes in CO_2 trends that may indicate you have secretions in the airway. Do you also use capnography to confirm ETT placement and monitor for tube migration or dislodgement?
AK: Yes. It's very useful in that way because when you use end-tidal CO_2 you use it partially to observe for technical problems and in part for physiologic problems. If you are looking for technical problems, it's to make sure that the tube is in place and to make sure that the tube is not occluded with secretions. And we look for physiologic changes that may indicate respiratory, hemodynamic, or metabolic conditions. So to your question it's very important to make sure that the tube is in place all the time and the end-tidal CO_2 is very helpful because if you lose your $etCO_2$ reading, you have to make sure that the tube is in place.

NIC: Do you find that the capnography waveforms are helpful in neonates?
AK: Theoretically it should help. The problem is when you are doing end-tidal CO_2 in small premature infants you don't always have adequate end-tidal plateau, like in older children or in adults when you have very nice end-tidal breathing. Small infants breathe fast so you don't always get a very nice plateau. For the time being we have not explored to see if the capnography waveform can help us in managing the baby. It is helpful in ensuring that the end-tidal CO_2 is in place and if you don't have adequate waveform or adequate repetition of the waveforms then you have to ensure that the sampling line and ETT is properly placed or that there are no secretions in the tubing. It's the same as when you are doing pulse oximetry; you look at the waveform to make sure that readings are adequate. The same is true with the end-tidal CO_2; if you don't see a nice waveform, it could indicate that the $etCO_2$ measurement won't be accurate or there's a problem.

NIC: You've talked primarily about use with intubated neonates in the NICU. Do you use capnography in any other applications at your facility?
AK: We always use capnography in the operating room and if we're transporting a ventilated baby from the emergency room to

intensive care unit or another hospital. Again, to make sure that the tube is in place on the way.

NIC: Do you use capnography with non-intubated infants?
AK: You can use the end-tidal CO_2 measurement for non-intubated infants even when the baby is getting oxygen. You can follow the level of CO_2 in the same way that you follow the pulse oximetry in a baby. So that's an option, especially if the baby is an older baby. For example, if they have BPD, they don't have any arterial lines anymore if you want non-invasive monitoring you can use pulse oximetry for oxygenation and end-tidal CO_2 for ventilation. Theoretically you can use it all the time, but it's not routine in our unit.

NIC: Are there any other studies you've completed where the use of capnography was helpful to you and your patients?
AK: We did a study using it to see how the position of the baby affects the level of CO_2 and apneas as infants mature. As you know, when babies are discharged from the hospital, parents are instructed to lay them on their back. For babies who are in the NICU and more premature, it's better for them to lie on the abdomen. And when using capnography, you can change the position and see the changes in CO_2 in different positions. That study was published in 2002.[v]

NIC: Do you believe that the benefits of using capnography justify the cost and have you looked at any data in that regard?
AK: It's a good question and I'll just say that we are in the process of submitting a study that looked if it's beneficial to do capnography in the NICU and we have shown that monitoring etCO_2 trends allows us to maintain the baby in a safer zone of arterial CO_2. I think this is very important. We didn't check the economic cost of doing it because it wasn't the aim of this study.

NIC: What do you think the future holds for capnography in the NICU?
AK: With new ideas of how to use capnography more effectively and with improved capnography technology, I think that in the future it might become a routine to measure CO_2 continuously and non-invasively, the same way that you measure pulse oximetry now. It may improve safety of care in regard to respiratory and central nervous system, it may allow to take less blood gases, decrease infections, and increase the comfort of the infants in the NICU.

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Approaches to Preterm Infant Enteral Feeding: New Insights from Research and Evidence

Jean Rhodes PhD, CNM, IBCLC

Introduction

Many enteral feeding decisions seem to impact feeding intolerance; however, consistent evidence to support one aspect of feeding strategies over another is lacking. Conflicting practices without evidence-based answers include those related to continuous versus bolus feeds;[1] scheduled feeds versus demand;[2] amount and schedule for feeding progression;[3-14] appropriate fortification and methods;[15-28] how to progress nipple feedings with enteral feedings;[29-33] type of enteral tubing material; and locus of tube placement—nasogastric (NG) or orogastric (OG).[34-38] One of the few absolutes in enteral feeding recommendations is the superiority of human milk, in particular mothers' own milk, over infant formulas in reducing related short and long-term morbidities in preterm infants.[39-50]

Infant feeding progression—from total parenteral nutrition to trophic feeds, through enteral feeding progression to full oral feeds—is a delicate balance of outcomes from unfettered progression on one side to physiologic risks of feeding intolerance and necrotizing enterocolitis on the other. In addition, parents and caregivers must endure almost constant psychological stressors associated with caring for very vulnerable NICU infants as they progress from one feeding phase to the next.

This article examines three issues related to enteral feeding of NICU (neonatal intensive care unit) infants: continuous versus bolus feedings, measurement of enteral feeding tubes and infant responses to unpleasant experiences. The purpose is to inform clinicians of helpful research concerning preterm infant feeding practices.

Continuous versus Bolus Feeds

In 2005, Dsilna and associates[35] published a randomized controlled trial (RCT) to evaluate the effects of continuous feeding to intermittent feeding in 70 very low birth weight (VLBW) infants less than 1200 grams with gestational ages between 24-29 weeks. In this study, the experimental group was continuously fed and all infants were fed via NG tubes. There were two control groups that were intermittently feeding—one group by OG tubes, the other with NG tubes. Nasogastric tubes in both experimental and control groups were left in place between feedings while OG tubes (in one of the control groups) were placed and removed with each feeding every three hours.

The primary outcome of this study was time to achieve full enteral feeding. Infants in the continuous feeding group—all of whom had NG tubes—had a significantly shorter average time to achieve full enteral feeds (20.1 days, compared to 26.1 days in the intermittent NG and 28.8 days in the intermittent OG groups). Infants in the continuous feeding group also had better feeding tolerance and weight gain. Furthermore, infants ≤ 850 grams who received continuous feeds achieved full enteral feeding considerably faster than those infants in the same weight strata fed intermittently.

These authors concluded that continuous feeding of infants less than 1200 grams between 24-29 weeks improved feeding tolerance and decreased the time to achieve full enteral feeding compared to intermittent bolus feeding. Infants ≤ 850 grams demonstrated the greatest benefit with continuous feeds.

This research[35] compared continuous versus intermittent feeds in a VLBW population. Since its publication, Premji and Chessell[1] in a 2011 Cochrane review of seven clinical trails concluded there is not enough evidence to support one method over the other. However, variables in the study by Dsilna et al illustrate the complexity of enteral feeding questions.

Recently, issues related to enteral feeding of small for gestational age (SGA) or in-utero compromised infants with poor end-diastolic flow have emerged. For example, Arnon et al[4] in 2013 conducted a RCT of early enteral feeds (within the first 24 hours of life) versus delayed enteral feeds (after 24 hours) in a total of 60 SGA preterm infants with antenatal absent or reverse diastolic flow. Their findings suggested earlier feeds reduced the time to full feeds and to discharge to home. On the other hand, Kempley et al[51] in 2014 published a larger RCT of preterm infants with compromised antenatal umbilical artery blood flow born. Infants were categorized by gestational age at birth, less than or greater than 29 weeks, then randomized within groups to early enteral feeds at two days of life or, later, on day six. They found infants born less than 29 weeks did not tolerate early enteral feeds as well as those born greater than 29 weeks; these more vulnerable infants took longer to advance to full enteral feeds. Of interest, neither Arnon et al nor Kempley et al included type of feeding tube (OG or NG) as a variable in their discussion or analysis.

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Type of Feeding Tube (OG or NG)

While enteral feeding tubes are necessary until preterm infants are able to take full oral feeds, there is little definitive information in the research literature to support one locus of insertion over another. Both tube insertion sites, nasogastric (NG) and orogastric (OG), have advantages and disadvantages: nasogastric tubes are believed to be more stable and less likely to become dislodged than those inserted orally but they block one nostril so are not appropriate for infants with respiratory distress; while orogastric tubes leave both nares open but may be associated with bradycardia during insertion and are more likely to become dislodged.[37,52,53]

Until recently, type of feeding tube—OG or NG—has been based on practitioner or institutional preference when there was no clear-cut reason for one over the other. However, in 2013 the National Association of Neonatal Nurses' (NANN) Infant-Directed Oral Feeding for Premature and Critically Ill Hospitalized Infants: Guideline for Practice recommended "advancement of oral feeding while an infant maintains an indwelling nasogastric feeding tube...."(p.7)[54] Newer enteral tubes now provide the option of leaving them safely in place for longer periods of time, in some cases up to 30 days.[55-57] But before enteral feeding tubes are placed nurses need evidence-based guidance on how to measure enteral tube length for proper placement.

Enteral Tube Placement

The literature on enteral feeding explores several methods for determining optimal NG or OG tube length to ensure proper placement in infants' stomachs. The majority of studies have focused on term or older infants and children up to 19 years of age. Few studies have examined the newborn population, with even fewer concentrating on preterm infants in the NICU. Previous studies have shown that approximately half of feeding tubes in neonates are misplaced. Enteral feeding tubes can be too long, causing curling in the stomach or placement of the tip into the small intestine, leading to complications such as malabsorption and poor weight gain. Conversely, feeding tubes can be too short, resulting in the tip placement in the esophagus causing risks of and aspiration and pneumonia. [58-64] Predicting correct enteral tube length and even identifying correct placement are challenges for those practicing in the NICU. X-ray is the gold standard for enteral tube placement verification, but interpreting results can be difficult for even experienced clinicians.[59] Other methods of tube placement such as listening for injected air bubbles and/or aspiration of gastric contents have been shown to be inaccurate in pediatric patients and neonates and are not recommended by the Agency for Healthcare Research and Quality.[52]

Historically, practitioners have used one of two methods, the direct distance nose-ear-xiphoid method (NEX) [63,64] or the direct distance nose-ear-mid-umbilicus method (NEMU). The NEX method is associated with more placement errors but neither method is consistently accurate.[63,64] Other methods have been proposed: in 1993 Gallaher et al[65] recommended minimal insertion lengths for OG tubes in VLBW infants based on weight categories while Beckstrand et al[58] in 2007 developed a regression equation using infant age-related, height-based measurements (ARHB). This method, developed and tested on VLBW infants (with the smallest measuring 44.5 cm in length), was found to be more accurate than either of the NEX or NEBU methods, but the regression equations were not easy to use in practice.[66] Additionally, NG tubes are used more commonly than OG tubes.

In 2012 Cirgin-Ellett and associates[66] conducted a randomized control trial to determine which of three methods (NEX, NEMU or ARHB) was the most accurate or had the lowest error rate for predicting enteral tube length in neonates who were less than one month corrected age. Ninety-seven percent of the subjects were preterm and three percent were term. Since the ARHB method had not been tested on infants less than 44.5 cm, infants fewer than 44.5 cm long were randomly assigned to either the NEX or the NEMU method.

With input from x-ray measurements, the authors calculated a final regression equation for ideal insertion of NG tubes for infants from birth to one month corrected age of 1.95 + 0.372 multiplied by the infant's length in centimeters. From this equation, the authors developed a table with ideal NG tube insertion length based on infant length categories, e.g., 35-35.5 cm, 36.0-37.0 cm. The table calculates ideal placement if all enteral tubes had pores within 1.5 centimeters of the tip. Unfortunately, there were not enough infants with OG tube insertions to develop a regression model for orogastric tubes.

Also in 2012 Ellett et al[62] evaluated ARHB, MEMU and NEX methods in children one month to 17 years of age. These findings confirmed the ARHB method to be slightly better than NEMU methods for predictions of feeding tube placements into the stomachs of non-premature infants (88.9% verses 85.7%).[62] They concluded the NEX method for predicting OG or NG insertion length should no longer be used, as it is generally too short and places infants at risk for aspiration and/or pneumonia. They also concluded further studies are needed to compare NG tube predictions using ARHB to the Gallaher method, which uses infant weight instead of length.[65]

However, Cordero and associates[60] developed an enteral tube prediction model for ELBW infants based on the NEX method with a regression formula based on infant weight. Their findings suggested the weight-based NEX formula was significantly better when compared to NEX alone. It also seemed to obtain better results than any method used by Cirgin-Ellett.[66] Cordero et al obtained enteral tube tip placement diagonally in the stomach 96% of the time with no placements in the esophagus, duodenum or reversed in the stomach. Unfortunately this method was tested only on ELBW infants with OG tubes, and no conversion formulas were suggested for infants with NG tubes.

Although many issues are yet to be resolved regarding enteral feeding options, enteral feedings are a necessary component of preterm infant care. As infants progress from total enteral nutrition to enteral feeds to full feedings by mouth, their path may be influenced by care respectful of their developmental and physiologic needs.

Infant Feeding Tolerance, Stress and Trauma-Informed Care

For many infants, adaptation to extrauterine life is stressful; for preterm infants the challenge is much greater. Beyond separation from their mothers, preterm infants must cope with a foreign environment replete with new stimuli and uncomfortable procedures including respiratory support, assessments, laboratory tests and enteral tube placements.

Studies of adverse neonatal experiences and alterations in brain development, behavior, stress responses, cortisol concentrations and other biological markers for stress or allostatic load in human infants have been present in the literature for over a decade. Moore and associates[67,68] proposed a theoretical model of allostatic stress in preterm infants based on the work of McEwen in 1998.[69,70] Four maladaptive responses referred to as conditions of allostatic load are:

1. Repeated hits (or over-activations of the stress response caused by multiple concurrent stressors)
2. Lack of adaptation, demonstrating an inability to habituate to stress
3. Prolonged response involving the absence of a recovery period
4. Inadequate response to stress.[67,69,70]

A 2012 study, Moore and associates[68] suggested feeding intolerance in NICU infants is a symptom of stress overload. Other researchers have studied NICU stressors and infant responses. Peng et al[71] recorded 4164 observations in NICU settings. Environmental stressors such as sounds, light and nursing interventions were associated with infant physiologic changes in heart rate, respiratory rate and O_2 saturation as well as nine other specific stress response behaviors including grimacing, sucking, finger splay and yawning. Compounding types or intensities of stressors increased the intensity and numbers of stress behavioral responses in preterm and hospitalized neonates.

In a recent keynote address to the National Association of Neonatal Therapists 2014 Conference, Mary Coughlin discussed "trauma-informed care" for preterm and hospitalized infants.[72] Using the theory of allostasis and allostatic load, she discussed evidence, like that outlined above, to remind neonatal therapists and nurses to be mindful of their contributions to infant stress and to manage their care with every attempt to make each encounter with the infant as comfortable and pleasant as possible. Examples of mindful-care include kangaroo care, non-nutritive sucking at breast during heel sticks, allowing infants to suck on a pacifier dipped in mothers' milk during enteral tube placements or smelling mothers' scent after the procedure. Such actions are attempts to soothe infants in a developmentally appropriate manner as they go through uncomfortable procedures. Needless to say, whenever possible, parents should be involved in their infant's care, enhancing the healing properties of the maternal-infant-family triad.

Concluding Remarks

Managing enteral feedings for preterm infants involves awareness of current research, new feeding technologies, infant developmental care and coordination with the entire health care team, including parents. While many questions remain unanswered and practice guidelines are currently in flux, what will not change is the need to support infants safely as they transition to full oral feeds in a manner that is extremely sensitive to their need for comfort and sleep to enhance their growth and development.

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Is the Donor Milk Used in Your NICU Commercially Sterile?

Elena Taggart Medo

Vegetative cells, spores and toxins can and do survive pasteurization. Medical professionals may be unaware of the differences between commercial sterility and pasteurization and the methods used by process authorities to professionally process a wide range of food, now including human donor milk. This article is intended to guide the medical professional through the technical and legal aspects of thermal processing methods as well the scientific literature that supports the need for commercially sterile milk for fragile neonates.

The foundation for the next generation of human donor milk products is commercial sterility. My company made this decision to improve safety for preterm infants as well as the economy of scale and ease of use by adopting the same professional processing method utilized by the infant formula industry for many years to process commercially sterile preterm infant formula. The process is not new, nor is it experimental.

Since introducing Co-Op Donor milk, over 1,000 preterm infants have received the product with good results. Growth and tolerance studies are complete and data will be released shortly. This type of process has never been used for human milk only because there has never been enough volume of donor milk to make it possible. The founding of the Mother's Milk Cooperative has changed all that. Nursing mothers have voted with their membership and an unprecedented volume of qualified donor milk has been collected as a result.

The type of sterile processing utilized at Medolac Laboratories is called retort processing and is based on well established scientific evidence. The temperature used to process Co-Op Donor milk is higher than the holder method but held for a much shorter time. Along with higher temperature, pressure is utilized, allowing for a more efficient thermal treatment than temperature alone. The holder method, also known as the holding method, used for many years by the dairy industry, is used by donor milk providers and by non-profit milk banks today but does not result in a commercially sterile product.

In December 2010, the FDA Pediatric Advisory Committee convened a Working Group to "obtain a better understanding of Human Milk Banking—current practices, infectious disease risks, state regulations and mitigation strategies currently used to avoid contamination of donated milk."[1] During this full day event, representatives from the milk banking industry presented their standard operating methods.

Testimony was given by many experts including William Rodriguez, MD, PhD, Science Director, Office of Pediatric Therapeutics, Office of the Commissioner, United States Food and Drug Administration. Dr Rodriguez identified the potential areas of risk for human donor milk, which included:

- Infectious disease
- Non-infectious contaminants
- Nutrition

The infectious disease risk originates from two sources:

- Intrinsic (coming from the mother)
- Extrinsic (introduced after milk is expressed)

Thus, infectious contaminants, such as Staphylococcus aureus (SA) and Group B Streptococcus (GBS) may be present in the breast milk of the mother due to mastitis or it can become contaminated after it leaves the breast from a wide variety of sources during pumping, storing and handling at a milk bank. Published research exists to support this, but in our own laboratory, our microbiologists have confirmed it by culturing hand expressed breast milk samples from donors who persistently provide donor milk that is unfit for use due to high bacterial cultures, after ruling out potential causes of extrinsic contamination (collection kits, pooling containers and pumping environment).

Using Dr Rodriguez's testimony as a guideline along with other credible sources, the infectious disease risk of donor breast milk from both sources will be examined through the lens of thermal treatment efficiencies. Two methods of thermal treatment for human milk will be explored; pasteurization and commercial sterilization. The focus is on the ability of each thermal treatment method to remove or inactivate heat resistant vegetative cells, spores and toxins that could pose a threat to hospitalized preterm infants.

A separate aspect of this issue which will not be explored here but should be noted is the intrinsic contamination of mother's own milk and the lack of routine culturing when the mother of a baby in the NICU has clinical mastitis. Foxman and her co-investigators published a study in the Journal of Epidemiology reporting that during the 12 week period of the study, 9.5% of the women had received at least one clinical diagnosis of mastitis by their medical professional and 65% had received the diagnosis

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by phone.[2] The issue becomes more complicated when one considers the issue of subclinical mastitis that would be unlikely to be identified in a non-symptomatic mother but could result in intrinsically infected milk.

This warrants further research because of the prevalence of Staphylococcus sp. and Streptococcus sp. as primary pathogens present in postpartum mastitis, the lack of routine culturing when a lactating woman presents with clinical mastitis, the lack of preprocess culturing or toxin testing in most milk banks, and the risk of neonatal sepsis in preterm infants.

An Overview of Pasteurization and Sterilization

The best explanation of pasteurization and sterilization follows: "The heat processes devised to give different degrees of shelf life to food products are usually classified either as pasteurization or sterilization. The former is a partial treatment, in that it destroys only the more labile fraction of microbial population. The latter is a complete one, because the level of surviving organisms is lowered beyond any value detectable by usual analytical practices. The two treatments differ greatly in the size of the lethal agent (heat) applied. Pasteurization is usually done at temperatures lower than 80-100°C [176°- 212°F]. Sterilization is applied at temperatures ranging from 115°C to 145°C [239°-293°F].[3] Because of the difference in temperature between the two methods, a much shorter treatment time is possible with sterilization.

Pasteurization

Milk banking has grown tremendously in the past few years since a growing body of evidence supports its use for preterm infants in clinical settings. Brazil claims the record for the largest number of human milk banks in the world. This large milk banking system utilizes pasteurization as their thermal treatment. Numerous academic studies on the pasteurization of human milk have resulted. One such study conducted by the Department of Microbiology, Immunology, Parasitology and Pathology of Patologia Tropical Institute and Public Health at the Federal University of Goiás examined the microbiological quality of human milk from a Brazilian milk bank. The findings were troubling. "The presence of Staphylococcus spp., Streptococcus spp., yeasts and molds, and Enterobacteriaceae was verified in the raw milk samples." This was no surprise although for years, many promoted the idea that human milk was sterile in its raw form. "Staphylococcus aureus were isolated in 10 (5.2%) samples, Staphylococcus epidermidis in 28 (14.4%) samples, Streptococcus spp. in three (1.6%) samples, yeasts and molds in 43 (22.2%) and Enterobacteriaceae in 49 (25.3%) samples. In a hundred and forty four (144) samples which underwent thermal treatment Staphylococcus aureus was detected in five (3.5%) samples, Staphylococcus epidermidis in 15 (10.4%), Staphylococcus lugdenensis in two (1.4%), Streptococcus spp. in four (2.8%), yeasts and molds in 37 (25.7%), and Enterobacteriaceae in nine (6.3%)."[4]

Many milk banks now rely solely on post-pasteurization culturing to confirm the absence of vegetative cells of Staphyococcus sp. and Streptococcus sp. among other potential pathogens. In a study commissioned by Food Standards Australia and New Zealand, Juffs and Deeth named SA as one of the most common causes of food poisoning and identified the endotoxin produced by SA as the central cause of illness rather than the vegetative cells. The cautionary note from this study gives reason to explore this issue further as it relates to preterm babies. "Thus absence or low numbers of S. aureus in a heat treated food product does not guarantee its safety; absence of the enterotoxin must also be demonstrated. Species of Staphylococcus other than S. aureus can produce enterotoxins, but the overwhelming majority of staphylococcal food poisoning outbreaks have been caused by S. aureus."[5]

The reliance on pasteurization by milk banks to assure the absence of SA, combined with the lack of pre-process microbiological testing creates the potential for heat stable enterotoxins, which are the root cause of foodborne illness in processed foods, including milk. Karthikeyen et al reported on SA and its strong association with neonatal sepsis[6] and Romano-Bertrand[7] reported on a one year review of SA carrier, colonized or infected patients in neonatal care centers in which the investigators also screened isolates for genes encoding staphylococcal enterotoxins A(sea). They noted that both Coagulase negative staphylococci (CoNS) and Staphylococcus aureus (SA) are the main and often sole bacteria colonizing the digestive tract of low birth-weight infants during the 3 first weeks of life. Furthermore, CoNS and SA are responsible for most infections in hospitalized preterm infants. Holmes[8] and Delgado[9] cited SA as one of the main etiological agents of mastitis while Reddy[10] reports a growing trend of postpartum mastitis now seen in "as many as one third of breastfeeding women in the United States and leads to breast abscess formation in ≈10% of cases. Although breast milk cultures are not routine in PPM management, the growth of potentially pathogenic bacteria (such as β-hemolytic streptococci or Staphylococcus aureus) is associated with longer time to recovery and more frequent abscess formation. S. aureus is the most common bacterium isolated from such cultures, representing 37%–50% of isolates."

Other potential pathogens and their related toxins identified in the Brazilian study by Serafini that remain after pasteurization include the following:

Staphlococcus epidermis is one of the leading causes of neonatal sepsis and the ability of this organism to form biofilms make this potential pathogen of great concern.[11]

Streptococcus spp. A recent article by LeDoarea K and Kampmanna[12] addressed the somewhat paradoxical issues regarding, on one hand the protective components in human milk and on the other hand, the presence of potentially lethal pathogens. Low incidence is described in mothers of extremely preterm infants of 0.4%[13] and term infants of 0.82%. Higher incidence in raw milk ranged from 3.5%[14] to 10%[15] reported in donor breast milk." "The variety of delivery, treatment and storage methods of breast milk offers potential for GBS contamination. Human breast milk may contain 103 to 109 cfu/mL of GBS at any point, representing a reservoir of potential infection for the neonatal gut."[16] When mother's own milk was pasteurized before feeding her own preterm infant, researchers found no reduction in late onset sepsis.[17] Although this seems paradoxical, the inability of pasteurization to eradicate staphylococcus sp. in human milk may be the reason.

Yeast and Mold. Blachke-Hellmesen, et al analyzed 37,000 human milk samples over twenty one years and found the incidence per year of Candida albicans was found in breast milk between 8.5% and 5.2% of samples. 14.8% of the donors had delivered contaminated milk to the human milk.[18] Considering the frequency of donor milk contaminated with Candida

albicans, the researchers made recommendations about transporting donor milk at safe temperatures and to store at -20 degrees C until the laboratory analysis is complete to exclude samples contaminated by Candida albicans. This supports the need for pre-process microbiological screening in milk banking.

Enterobacteriaceae

Researchers used "deep pyrosequencing to examine the gut associated microbiome of extremely low birth infants during the first postnatal month with a first time determination of the eukaryote microbiota such as fungi and nematodes, including bacteria and viruses that have not been previously described."[19] The researchers concluded, "Together, these data reveal surprising eukaryotic and viral microbial diversity in ELBW enteric microbiota dominated bytypes of bacteria known to cause invasive disease in these infants." Many of these pathogens have been addressed herein, but others identified by these researchers need further investigation regarding the ability of pasteurization to remove them.

"Heat processing is done by the Holder method in HMBANA banks. This method can legally be used to pasteurize cow's milk (the primary method of pasteurization used for cow's milk is High Temperature Short Time—161.0 F for 15-20 seconds) and will kill or inactivate many infectious disease agents but neither the Holder method nor the High Temperature Short Time method is a sterilization procedure." (FDA Pediatric Advisory Committee, Working Group on Banked Milk Backgrounder.)

Commercial Sterilization

"Sterilization is a process employed to deprive microorganisms of their ability to multiply. The most reliable Sterilization process is obtained by application of Heat." Heat destruction of microorganisms is a gradual phenomenon: the longer the treatment time at lethal temperatures, the larger the number of killed microorganisms. Higher treatment temperatures result in a shorter time required to kill microorganisms and the heat induced damage to food products is decreased.[20]

The first commercially sterilized human donor milk, Co-Op Donor Milk™ was introduced to the hospital market last year in an effort to overcome significant barriers that have kept donor milk in short supply, resulting in rationing in neonatal intensive care units. These barriers include chronic shortages from the existing milk banking network, expensive shipping costs due to overnight shipping of frozen donor milk, waste due to short shelf life after thawing, and total cost. Because of these barriers, neonatal intensive care units and caregivers of babies at home suffering from significant feeding issues have difficulty securing a consistent supply or are unable to obtain donor milk for use after discharge. This is driving such a demand that many parents have turned to informal sources of donor milk, including those available online or through casual social networks. The risks of procuring raw milk in this way have been widely reported. Additionally, in neonatal intensive care units, powdered infant formula is not recommended because it is not sterile and the same should be required of donor milk because of the many opportunities for contamination. Infant formula used in neonatal units must now be commercially sterile due to the risk of infection from cronobacter sakazaki.[21]

Co-Op Donor Milk is thermally processed using retort processing which has been used for many years by food manufacturers and, more importantly, by manufacturers of commercially sterile preterm infant formula. "A retort is simply a vessel that is capable of withstanding extreme pressures. It is essentially a pressure cooker or autoclave. The objective of retorting is to produce a commercially sterile food. Commercially sterile food refers to a state where all pathogens and non-pathogens that could grow during the normal, unrefrigerated storage of the finished product have been eliminated. The reference standard: The spores of C. botulinum type A are normally the target organism, since they are the most durable form of any food-borne pathogen."[22]

Packaging plays a key role in retort processing. The development of flexible, multi-layer pouches for retort processing has opened the door to shorter processing times due to the improved heat permeability of the package. The package must have a hermetic seal which prevents contamination after thermal processing. Donor milk should be collected only after donors have been qualified through blood testing done at a centralized laboratory with results sent through a secure laboratory information management system. Donors should be tested for HIV 1 and 2, HTLV I and II, HBV, HCV, Syphilis, West Nile Virus and Chagas Disease. All milk should be tested for a wide range of pathogens, adulteration and other safety and quality markers prior to thermal treatment. Large pools of 1,000-2,000 gallons made up of 200-400 donors provide a wider range of immune factors such as human milk oligosaccharides.

Validation studies to develop commercially sterile donor milk must be performed by people with the experience, training and equipment to do them properly, or what is known as a process authority. Commercially sterile products fall under FDA's low acid food regulations, 21 CFR 113.

Packaging Commercially Sterile Donor Milk

Co-op Donor Milk product is packed in a flexible, retortable pouch.[23] Our retort pouch is made from several layers. The pouch is BPA free and the material that has contact with the milk is approved for such use.

According to the Codex Alimentarius Commission, commercial sterility of thermally processed food means the condition achieved by application of heat, sufficient, alone or in combination with other appropriate treatments, to render the food free from microorganisms capable of growing in the food at normal non-refrigerated conditions at which the food is likely to be held during distribution and storage. The Codex Alimentarius also calls for the exclusive use of commercially sterile, liquid feeds with premature, immune compromised infants in clinical settings, because of risk of bacterial contamination when using non-sterile feeds.[24]

The data presented here is not intended to clinically prove that there is any new risk with respect to most milk banks currently supplying hospital neonatal units. Considering the rapid increase in the use of donor milk, it is offered to encourage critical thinking and analytical review by neonatal departments charged with the wellbeing of preterm infants.

There are more questions than answers. Some need to be reviewed internally by neonatal intensive care units. Do mothers with clinical or subclinical mastitis produce milk that could put their preterm infant at risk due to high colony counts of pathogens such as S. aureus? Does the current practice of not culturing milk from nursing mothers of fragile neonates have

sufficient data to support that practice? And finally, does the current evidence support the continued use of non-sterile donor milk for preterm infants?

While it is widely accepted that the exclusive use of human milk reduces mortality and morbidity in preterm infants, hospitals should develop their own standards for assessing the quality and safety of donor milk for use when mother's milk is not available.

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High Frequency Oscillation in Polish Newborn ICUs: Standard Practices

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Abstract

Introduction: The use of high frequency oscillatory ventilation (HFOV) has been a standard of care in managing infants with severe respiratory distress in highly developed health systems for decades. More recently its use has been adopted in the tertiary care centers in Poland. Our aim for this report is to share that clinical experience.

Methods: Using a web-based registry, data on the indications for use, baseline status, course of treatment and outcomes of infants managed with HFOV were collected concurrent to its use at 26 tertiary care centers.

Results: Over a four-year period 473 infants were managed with HFOV. More than a third were less than 1,000 grams and a quarter more than 2,500 grams. The primary use was for infants failing on conventional respirator support. HFOV intervention generally occurred in the first few days of life, and lasted less than a week. The duration was the longest for those infants treated for air leak. Baseline parameters did not predict successful treatment, but an improvement in oxygenation in the first days of treatment was associated with success. Failure to respond to HFOV intervention was associated with very high mortality and also significant morbidity in survivors.

Conclusions: Introduction of the use of HFOV in the tertiary centers in Poland appears to have been successful. This information will help to us refine our practices and hopefully those in other countries with developing healthcare systems.

Introduction

High frequency ventilation is widely used in the US and Western Europe. Nearly one in four premature infants needing respiratory support are managed with it at some point.[1,2] Some feel High Frequency Oscillatory Ventilation (HFOV) provides theoretically optimal lung protective respiratory support for the neonate.[3] While good clinical evidence supports this position[4-6] its use as the initial form of respiratory support in preterm infant has not been widely adopted. Accordingly in most centers it is employed to treat infants with severe respiratory failure, regardless of gestational maturity, often after conventional support has proved inadequate.[7] Such use is supported in the 2011 European Neonatal Respiratory Distress Guidelines.[8]

Over 10 years ago a major initiative was undertake to upgrade the respiratory support capabilities in Poland's newborn ICUs. The effort has been directed by the Polish Neonatal Society and funded in large part by the Great Orchestra of Christmas Charity. Initially this involved pervasive adoption of the use of modern nasal continuous and bilevel respiratory support systems.[9] As a second step the program has also phased in the availability of HFOV and modern conventional ventilators at tertiary centers. As part of this process, efforts were made to monitor the use and impact of these enhancements. The positive impact of the noninvasive initiative has been widely reported.[10,11] In 2010 a web-based registry of HFOV use was initiated to capture the experience of its use and impact. In the highly developed countries, HFOV has been used routinely for decades and the last generation of young neonatologist was widely exposed to its use as part of their training. This was not the case in Poland, or surely not in other countries with developing healthcare systems. The goal of this report is to document the standard practice of the use of HFOV in Polish tertiary care newborn ICUs.

Methods

Under the direction of the Polish Neonatal Research Board, a web-based database of HFOV use was developed at the Medical University of Silesia. The Great Orchestra of Christmas Charity donated the ventilators (model 3100a HFOV, CareFusion, Yorba Linda, California USA). A condition of the donation was participation in the registry. Statistical evaluations were made using chi-square or Mann-Whitney or t tests or analysis of variance (ANOVA or Kruskal-Wallis) depending on the distribution and nature of the data. These analyses were conducted using SigmaXL (version 6.1 Toronto Canada). P values <0.05 were considered statistically significant.

Results

Over a 55-month period (January 2010 and July 2014) 473 infants from 26 centers were managed with HFOV, and their clinical baseline, indication for use, treatment and outcome were recorded in the web registry.

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The median birth weight of the infants was 1,400 grams (IQR 840-2,545). More than one-third (36%) were less the 1,000 grams. HFOV was generally initiated early in their admission (age 1.3 days [IQR 0.2-3.5]). The median length of their HFOV treatment was 3.2 days (IQR 1.2-6.4). The longest treatment was 44 days.

The indications for use are categorized in the Table 1. Failing conventional ventilation was the primary indication. The difference between the indications for use in very low birth weigh infants (251) as compared to the larger infants (222) was significant (P<0.001). An analysis of variance also revealed that the duration of HFOV was related, independently, to both the weight category (p<0.05) and the indication for HFOV (p<0.001). The duration of HFOV support was 2.6 days longer in the VLBW infants. The duration was nearly 8 days for infants treated for air leak syndrome and 3-4 days shorter for the other indications. There was a shift (P<0.001) in the distribution of indications from the beginning 18 months when compared to the last 18 months. The most dramatic changes were in the use for the management of air-leak syndrome (4% to 15%), early intervention (28% to 11%) and failing conventional ventilation (49% to 58%).

Table 1

HFOV Indication	<1,500 kg	≥ 1,500 kg
Failing conventional ventilation	61.3%	45.9%
Early intervention	17.1%	27.0%
Air leak syndrome	11.6%	9.0%
other	10.0%	18.1%

other includes: failing other HFO, MAS, CDH
P<0.001- difference among indications .

HFOV intervention was subjectively deemed successful in 66% of the cases. The distribution of this varied, however, between the two weight categories and with success more likely in the larger infants (P<0.001). Details are shown in Table 2. There was also a marked difference (P<0.001) in the success rate associated with the indication for use (failing CMV 56%, early intervention 67%, other 82% and air-leak 92%).

Table 2

HFOV Outcome	<1,500 kg	≥ 1,500 kg
SUCCESS	57.4%	74.8%
Weaned to respiratory support	35.5%	42.8%
Planned due to procedure	19.1%	30.6%
Unplanned due to procedure	2.8%	1.4%
FAILURE	42.6%	25.2%
No response to HFOV	15.5%	8.6%
Death or withdrawal of support	27.1%	16.7%

P<0.001- difference between success and failure was.

An analysis of variance also revealed that the duration of HFOV treatment was related independently to both the weight category (p<0.001) and the HFOV intervention outcome (p<0.001). The duration was 2.4 days for infants that died or whose support was withdrawn and 2-3 days longer for the other indications.

In the initial phase of the registry, 12 centers provided more comprehensive data on 94 infants. This included their baseline status and their physiological response to HFOV. The timing of the HFOV intervention was markedly different depending on the indication for use (p<0.001), as shown in Table 3.

The median of the PaO_2-FiO_2 ratio prior to initiating HFOV was 58 (IQR 42-99). Analysis of variance revealed that there was a difference (p<0.05) associated with the indication for HFOV, but not with the weight category. The lowest PaO_2-FiO_2 ratios were in those infants failing conventional ventilation (48 [IQR 37-72]), followed by air-leak syndrome (55 [IQR 52-92]), early intervention (78 [IQR 54-138], and infants failing combined conventional combined with high frequency (95 [IQR 49-167]).

Table 3

HFOV Indication	Age at Intervention- Hours
Failing conventional ventilation	36 (13-60)
Early intervention	5 (1-21)
Air leak syndrome	47 (27-212)
Failing combined CV and HF	82 (21-274)
other	56 (11-73)

Median and (IQR), other includes failing other HFO, MAS, CDH,
P<0.001- difference among indications.

The FiO2 setting when HFOV was initiated was identical to the last setting prior to initiation. There were differences, however, in the HFOV settings between those initially set and two hours later after settings were optimized and the infant stabilized. These small differences were decreases in mean airway pressure, delta-P and FiO_2, as shown in Table 4. Three different approaches to lung recruitment were reported. A fixed increase in mean airway pressure was the most commonly used (56%) followed by incremental increases in 33% and sustained inflations in 11%. Analysis of variance found no differences in their relative effect on reducing FiO2 or mean airway pressure in this two-hour stabilization period associated with the different recruitment approaches.

Table 4

HFOV Settings	initial	+2 hours
mean Airway Pressure	16 (14-20)	15 (13-18)***
FiO_2	80 (40-100)	70 (39-99) ***
Delta-P	40 (35-49)	40 (30-35) *
Hz	13 (11-15)	12 (11-15)
% I-Time	33 (33-33)	33 (33-33)

*P<0.05. *** P<0.001.

HFOV intervention was rated successful in 77% of these cases. The median oxygenation index of these successful interventions, when they were transitioned from HFOV, was 5.5 (IQR 3-9). Shown in Table 5, the HFOV settings when weaned from HFOV reflect significant reductions from the initial settings. Following successful HFOV interventions many of the infants (41%) were extubated and placed on noninvasive support. In addition 14% continued on inhaled nitric oxide therapy with their transition from HFOV.

A lower maximum oxygenation index during HFOV treatment was associated with successful HFOV outcome (23 [IQR 9-44] vs 30 [IQR 21-63] p<0.05). However, neither the maximum mean airway pressure or the initial HFOV settings or the PaO_2-FiO_2 ratio prior to HFOV predicted successful HFOV treatment. The median duration of HFOV for the infants that were deemed HFOV successes was 4.4 days (IQR 1.9-6.8), while the unsuccessful HFOV treatment were generally shorter (1.6 days [0.4-3.5] p<0.001).

As shown in Table 6, the 40-week PCA outcome of those successfully treated with HFOV was markedly better than those that failed. Unsuccessful HFOV treatment was associated with

74% mortality. Further in the 26% who survived, most (81%) had significant morbidity.

Table 5

HFOV Settings	+2 hours	at weaning
mean Airway Pressure	15 (13-18)	10 (9-13)
FiO_2	60 (30-90)	25 (21-35)
Delta-P	39 (30-45)	27 (20-34)

Differences in settings Baseline and Weaning in Successful Treatments.
All differences were P<0.001.

Table 6

	% Died	% Survived with Bad Outcome	% Survived without Bad Outcome
Successful HFOV	8%	19%	73%
Unsuccessful HFOV	74%	21%	5%

P<0.001- difference in outcome between successful and unsuccessful intervention.
Bad outcome was defined as severe chronic lung disease or severe ROP or severe neurological outcome.

Discussion

We provide a descriptive report about the experience in the use of HFOV in Poland's tertiary care NICUs. This includes the timing of intervention, indications for use, physiological response, duration of support and outcomes. While data from many randomized controlled trials on the use of HFOV in infants is available, we believe this is the first descriptive report of its general use.

In Poland, neonatal HFOV is clearly used as a second line rescue intervention for those not doing well with conventional respiratory support. While more than a fifth of the use was categorized as early intervention, this is potentially misleading. It is certainly not a reflection of use at some centers as an elective lung protective modality. In this early intervention group, while HFOV was initiated in the first day of life, the oxygenation reflects severe respiratory dysfunction. We speculate that these infants exhibited much more severe respiratory failure than those who initially were placed on conventional ventilation support, but who later deteriorated. It is also interesting that the status of those infants who were failing combined conventional and high frequency support, were experiencing the least severe oxygenation at initiation of HFOV. Only a few of the centers have systems with this combined capability, and we speculate, because of the relatively better oxygenation and the longer time to intervention, that they were switched as soon as they didn't respond and the HFOV system was available.

We found no correlation of successful HFOV treatment with status prior to intervention or initial settings. However the oxygenation response as measured by oxygenation index, was an indicator of successful treatment, as has been consistently reported by many others. Failure to respond to HFOV was generally obvious in the first day or two. Successful HFOV intervention was generally complete within a week. We saw an increased use of HFOV for managing air-leak syndrome, which was probably a direct result of the high success rate experienced. In contrast the decrease in the use for early intervention and slight increase in failing HFOV, is contrary to their experienced relative success rates, and may warrant reevaluation of the timing of intervention.

Most of the infants responded to HFOV intervention, and those that did experienced relatively high survival and limited severe morbidity. In contrast of those failing HFOV, only a few survived without severe morbidity. This suggests that our use of HFOV is effective in Poland's NICU's.

Conclusion

Introduction of HFOV into the tertiary centers in Poland appears to have been successful. Its use is consistent with practices elsewhere. That is, as an intervention in infants with severe respiratory failure in the first day of life or subsequently with deterioration during conventional respiratory support therapy. The sharing of this information among the NICUs in Poland will help to refine our practices. We hope that in other countries with developing healthcare systems our experience will provide helpful guidance.

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Plasma Cytokine Levels Fall in Preterm Newborn Infants on Nasal CPAP with Early Respiratory Distress

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Abstract

Introduction: Early nCPAP seems to prevent ventilator-induced lung injury in humans, although the pathophysiological mechanisms underlying this beneficial effect have not been clarified yet.

Objective: To evaluate plasma levels IL-1β, IL-6, IL-8, IL-10, and TNF-α immediately before the start of nCPAP and 2 hours later in preterm infants.

Methods: Prospective cohort including preterm infants with 28 to 35 weeks gestational age with moderate respiratory distress requiring nCPAP. Extreme preemies, newborns with malformations, congenital infections, sepsis, surfactant treatment, and receiving ventilatory support in the delivery room were excluded. Blood samples were collected right before and 2 hours after the start of nCPAP.

Results: 23 preterm infants (birth weight 1851±403 grams; GA 32.3±1.7 weeks) were treated with nCPAP. IL-1β, IL-10, TNF-α levels were similar, IL-8 levels were reduced in 18/23 preterm infants and a significant decrease in IL-6 levels was observed after 2 hours of nCPAP. All newborns whose mothers received antenatal steroids had lower cytokine levels at the onset of nCPAP than those whose mothers didn't receive it; this effect was not sustained after 2 hours of nCPAP.

Conclusion: Early use nCPAP is not associated with rising of plasma pro-inflammatory cytokines and it seems to be a less harmful respiratory strategy for preterm with moderate respiratory distress.

Introduction

The early use of mechanical ventilation (MV) has been shown to induce pro-inflammatory cytokine expression [1,2]. Noninvasive ventilation and early initiation of continuous positive airway pressure (CPAP) in the delivery room seem to be promising strategies to prevent MV-induced injury in extremely preterm infants [3–5].

Individual trials of early CPAP therapy versus invasive ventilation in the delivery room [4–5] have not resulted in a reduced rate of bronchopulmonary dysplasia (BPD), but pooling data on combined mortality and BPD has suggested a benefit [6]. CPAP seems to facilitate spontaneous breathing, maintain alveolar recruitment, and reduce the need for MV in preterm infants [4]—pathophysiological mechanisms underlying the beneficial effects of CPAP have not yet been clarified and may be due mainly from the avoidance of invasive ventilation or inadvertent exposure to high tidal volumes and hyperventilation [7].

The mechanisms behind the protective effect of nasal CPAP (nCPAP) in ventilator-induced lung injury (VILI) have only been studied in animals [8]. One study designed to analyze cytokine levels in the first week of life in non-infected infants using nCPAP showed some small median decrease between blood samples collected on birth and until 4 hours of life [9]. Lista el al. [10] compared cytokine levels between preterm newborns at the first and seventh day of nCPAP or nasal intermittent positive pressure ventilation (NIPPV), suggesting that both ventilatory modes are protective. It seems that the use of nCPAP, even for a short period of time, might prevent harmful pro-inflammatory stimuli to the lung.

Thus, the aim of this study was to determine plasma levels of interleukin (IL)-1β, IL-6, IL-8, IL-10, and tumor necrosis factor (TNF)-α in preterm newborns in their first hours of life, right before start of nCPAP and 2 hours later.

Methods

A prospective cohort study included preterm infants admitted between September 2011 and May 2013 to the neonatal intensive care unit (NICU) of Hospital de Clínicas de Porto Alegre, a tertiary referral medical center located in Southern Brazil. Gestational age (GA) ranged from 28 to 35 weeks and all participants used nCPAP as the initial support in the first 24 hours of life. Exclusion criteria were extreme preemies, congenital malformations or chromosomal syndromes, STORCH infections, proven sepsis, meningitis, need for ventilatory support with any type of positive airway pressure therapy in the delivery room, and use of nitric oxide and surfactant prior to enrollment in the study.

Study was approved by Research Ethics Committee of Hospital de Clinicas de Porto Alegre (project number 11–0325). Written informed consent was obtained from the parents or guardians prior to enrollment of participants. The following data were collected: gestational age (based on the date of the last period and confirmed by ultrasound in the

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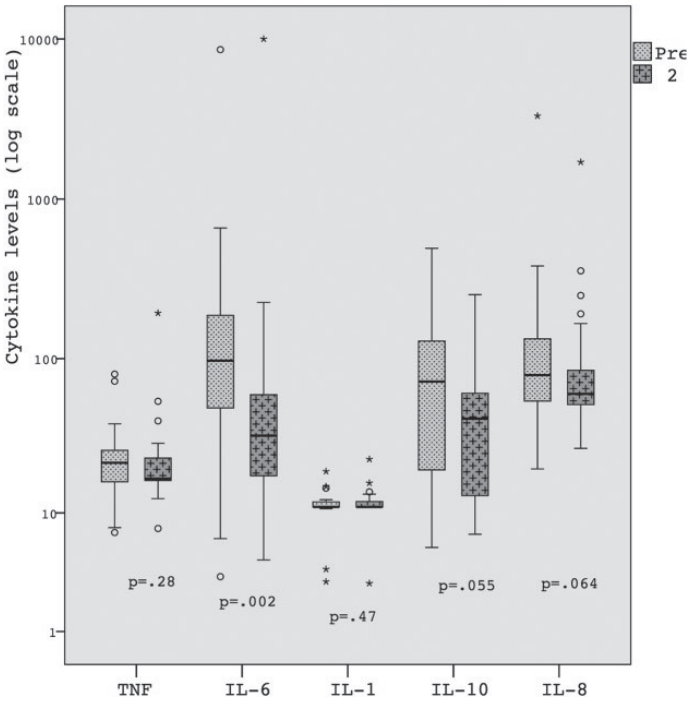

Figure 1. Cytokine levels immediately after the onset of nCPAP and after 2 hours—Wilcoxon's test.

first trimester and/or neonatal clinical examination), birth weight, gender, Score for Neonatal Acute Physiology Perinatal Extension II (SNAPPE-II), delivery room resuscitation, type of delivery, and presence of preeclampsia, amniorrhexis, and/or chorioamnionitis. Preterm infants whose mothers had received two doses of betamethasone prior to delivery were considered to have received antenatal steroids. Moderate respiratory distress was defined by the presence of grunting, tachypnea, respiratory effort and oxygen need.

Newborns were followed from birth to the start of nCPAP, blood samples were collected for arterial blood gas analysis according to the routine of the NICU, and an additional 500µL aliquot was obtained in Ethylenediamine tetraacetic acid (EDTA) tubes for later cytokine analysis. No additional venous or arterial blood punctures were performed strictly for research purposes. After two hours on nCPAP, another sample was collected for arterial blood gases and cytokine levels. The blood samples were immediately centrifuged for 10 minutes at 3,000 rpm to yield 300 µL of plasma, which was frozen at—80°C for later laboratory analysis of cytokines. Number and time of collection identified all samples.

Cytokines were measured using a commercially available kit (MILLIPLEX Human Cytokine/Chemokine MPXHCYTO-60K, Millipore Corporation, Billerica, MA USA). The readings were performed with Luminex 100 in duplicate (Austin, Texas, USA) with appropriate software. Samples and standard curve were processed

The alveolar-arterial oxygen gradient—P (Aa) O2—and the arterio-alveolar oxygen ratio (a/ApO2) were calculated from arterial blood gas analyses before and 2 hours after the start of nCPAP.

Statistical analysis

Sample size was calculated based on a previous study with animals [8], which compared three groups regarding to cytokine increase after a two-hours interval blood collection—MV, CPAP and none. To test the hypothesis that nCPAP does cause an increase of 37% in cytokine levels during its use, which would be smaller than MV increase, 19 newborns would be required ($\alpha = 0.05$ and 80% power). The results were expressed as mean ± standard deviation (SD) or median and range (p25-p75). The Wilcoxon signed-rank test was used to compare cytokine levels immediately before the onset and 2 hours after nCPAP. Mann-Whitney's test was used for the other comparisons. A delta value between pre and post nCPAP was created for each interleukin and transformed to log10 for additional testing, allowing logistic regression performing and parametric tests. Analyses were performed with Statistical Package for Social Sciences (SPSS), version 18.0, and the level of statistical significance was $p < 0.05$.

Results

Twenty-three newborns met the inclusion criteria. Of these, 7 (30%) patients were small for gestational age, 13 (56%) males, 18 (78%) delivered by C-section and 6 (23%) delivered by preeclamptic mothers. A full antenatal steroid course was given to 15 mothers (65%). Mean birth weight was 1851±403 grams, and mean gestational age was 32.3±1.7 weeks. Median SNAPPEII score was 7 (0–9). The median time for collection of samples for cytokine measurement and nCPAP onset was 2 (1.5–2.5) hours of life.

The median alveolar-arterial oxygen gradient was lower after 2 hours on nCPAP: prior = 62.4 mmHg (33.2–105.8) and after = 33.6 mmHg (13–70) ($p = 0.057$).

IL-6 median plasma levels were significantly reduced after 2 hours of nCPAP (Table 1 and Fig. 1). IL-8 levels were reduced after 2 hours of nCPAP in 18 of 23 preterm infants (78%), as

Table 1. Cytokine median levels immediately before onset of nCPAP and after 2 hours.

Cytokine (pg/dL)	Pre-nCPAP	After 2 hours n-CPAP	p
N	**23**	**23**	
IL-6	97.1 (43.1–188)	32.4 (17.6–62)	**0.002**
IL-8	78.8 (52.8–133.8)	59.9 (51–87.5)	0.064
IL-10	71.6 (14–145)	41.7 (13–63.2)	0.055
IL-1β	11 (11–11.9)	11 (11–12)	0.47
TNF-α	21.6 (15.7–26.4)	17 (16.5–23.7)	0.28

Median (p25-p75).
Wilcoxon signed-rank test.

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Table 2. Impact of antenatal steroid use on cytokine levels immediately before the onset of nCPAP and after 2 hours.

Cytokine (pg/dL)	IL-6			IL-8			IL-10			IL-1β			TNF-α		
Antenatal steroid	Pre-CPAP	After 2h	p *	Pre-CPAP	After 2h	p *	Pre-CPAP	After 2h	p *	Pre-CPAP	After 2h	p *	Pre-CPAP	After 2h	p *
Yes	63	23	**0.009**	95	70	0.17	50.5	40	0.53	11	11	0.12	18	19	0.53
(n = 15)	(15–111)	(8–45)		(55–135)	(51–166)		(10.5–114)	(11–94)		(11–12)	(11–12)		(15–24)	(16–24)	
No	216	59	0.161	75	57	0.12	82	46.5	**0.02**	11	11.5	0.46	26	17	**0.01**
(n = 8)	(149–392)	(26–84)		(52–112)	(42–77)		(49–327)	(26–62)		(11–14)	(11–13)		(19–36)	(15–24)	
p"	**0.002**	0.076		0.46	0.35		0.16	0.46		0.42	0.9		**0.034**	0.39	

* Median (p25-p75), Wilcoxon signed-rank test.

"Median (p25-p75), Mann-Whitney test.

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well as TNF- α in 13 (56%), and IL-10 in 16 (69%) and only four patients showed a reduction in IL-1β.

The median plasma levels of pre-nCPAP IL-6 and TNF-α were lower in the 15 infants whose mothers received antenatal steroids. However, this effect was not sustained after 2 hours of nCPAP (Table 2 and Fig. 2). After logistic regression, there was no relationship regarding post-natal age in hours (IL-6 OR 0,6; IC 95% 0,15–2,3, TNF- α OR 0,3; IC 95% 0,07–1,8), delivery mode (IL-6 OR 2,1; IC 95% 0,2–21, TNF- α OR 0,6; IC 95% 0,05–6,8) and cytokines decrease (IL-6 OR 6,2; IC 95% 0,5–66, TNF- α OR 73; IC 95% 0,5–10000).

Discussion

A protective and/or inhibiting effect of early nCPAP on the pro-inflammatory cascade in preterm newborns is suggested in this study. IL-6 plasma levels were significantly lower after two hours of nCPAP; and both IL-8 and TNF- α levels were reduced in more than 50% of preterm infants after two hours of nCPAP—all of those are proinflammatory cytokines involved in VILI.

Animal studies have shown that positive end-expiratory pressure (PEEP) ventilation reduced edema formation and cell damage [7], as well as inflammatory cell recruitment, during prolonged ventilation [11]. However, even the available experimental data are controversial: preterm lambs receiving tracheal CPAP presented only slightly lower cytokine levels after 2 hours as compared to those receiving MV [8]. Similar increased levels of IL-1β were recorded with both ventilation modes, whereas IL-6 and IL-8 were elevated only in the MV group [12]. Conversely, Polglase et al. [13], using a lipopolysaccharide infection model, did not observe decreased inflammatory response with the use of CPAP, suggesting a limited effect of this ventilation mode in the presence of both immature lungs and infectious injury. Timing of sample collection is an important factor in the evaluation of inflammatory response; cytokines half-life is very short, and their circulating levels increase rapidly after stimulation [14]. The strength of our study is that the collection of samples prior to and 2 hours after the stimulus provided a safe interval to prevent the onset of other potential inflammatory events, which are characteristic of preterm newborns and that could interfere with or alter the exclusive role of nCPAP on inflammatory cascade.

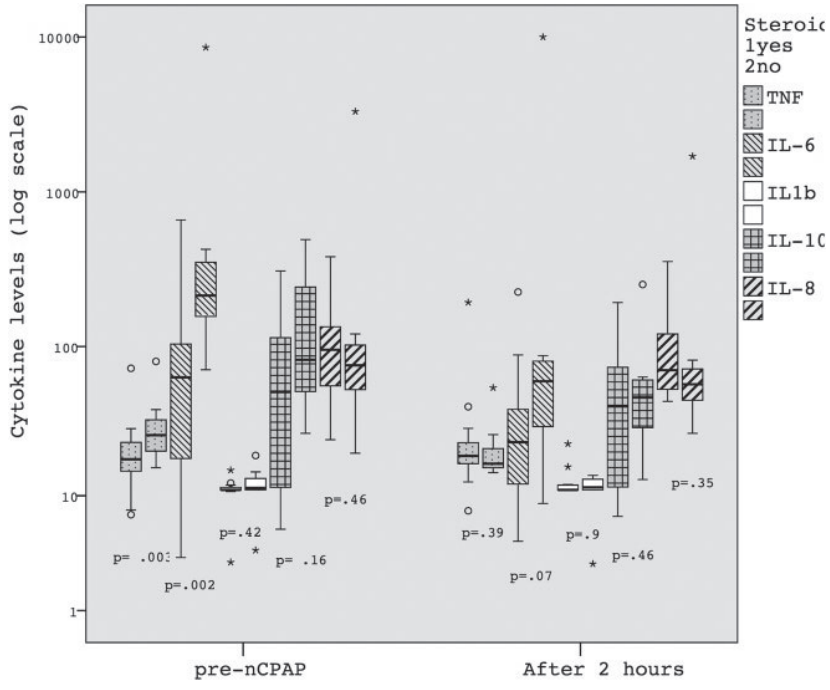

Figure 2. Comparing cytokine levels regarding to antenatal steroid use immediately before the onset of nCPAP and after 2 hours, Mann-Whitney test.

Procianoy et al. [14] observed that IL-6 levels, in newborns which blood was collected as early as 17 hours of life, were higher than in those who collected at 36 hours, suggesting a decrease in cytokine levels late in the first 24 hours of life. Other studies demonstrated that IL-6 levels increased after birth until 24 hours of life in healthy neonates [15,16], decreasing over the following second day. A randomized clinical trial comparing nCPAP with no nCPAP or nCPAP with mechanical ventilation would be the ideal study design but each ventilatory therapy has its own precise indication. Despite the absence of a non-nCPAP control group—justified by ethical issues involving blood collection in patients that do not need an exam—we believe our results do not represent the natural course of cytokines release.

Because IL-6 is the main cytokine involved in the development of the fetal inflammatory response syndrome [17], it has been described as an early marker of BPD [18] and neonatal sepsis [19, 20]. Therefore, we excluded all cases of neonatal sepsis and STORCH infections, as well as neonates requiring any type of ventilatory support in the delivery room, who might have elevated baseline IL-6 levels—a situation that might impact the evaluation of the behavior of IL-6.

Interestingly, the levels of inflammatory cytokine IL-10 were reduced in 69% of the newborns 2 hours after nCPAP. Anti-inflammatory expression of IL-10 occurs later [21], after the release of IL-8, especially in preterm infants with gestational age below 30 weeks [22]. The production of down regulatory interleukins, such as IL-10, may be insufficient in preterm newborns, which leaves them more predisposed to an exacerbated inflammatory response [23]. The very low levels of IL-1β may also be explained by kinetics, since the rate of IL-1β increase is slower in the first 24 hours of life, the period in which all our samples were obtained [24].

In a previous study, preterm newborns with less than 35 weeks of gestational age had similar levels of IL-6, IL-8, and TNF-α at the first and seventh day of nCPAP or NIPPV, which suggests that both ventilatory modes are protective—evaluating a sustained inflammatory response [10]. Our data shows that after a short period of only a couple of hours, the inflammatory response associated with protective ventilation is significantly different.

The inhibitory action of antenatal steroid administration on inflammatory response and ventilation-induced injury is well known [25]. Using antenatal steroid in women during preterm labor has been associated with a significant reduction in the baseline production of IL-6 in the umbilical cord [26]. Our preterm newborns receiving nCPAP who had been exposed to intrauterine steroids had significantly lower pre-nCPAP IL-6 and TNF-α plasma levels as compared to non-exposed newborns. However, the levels of these markers were similar in all nCPAP newborns two hours later, showing a transient anti-inflammatory action of antenatal steroid administration.

The improvement in gas exchange after nCPAP demonstrated a proper use of this support to moderate respiratory stressed newborns. We did not include extremely premature newborns, with gestational age below 28 weeks, because the success rate in applying nCPAP in that group was low in our service, during the study period. Extremely preterm newborns are more often treated with MV and affected by systemic inflammation than other preterm populations; however, their exclusion from the present study is also justified by the fact that these baseline inflammations would possibly impact interleukin levels [27]. Another study limitation was our small sample size, with enough power to detect some change in cytokine levels but unable to test other clinical relevant outcomes. A larger sample size would be necessary to draw more conclusions.

Conclusion

We suggest that early use nCPAP is not associated with release of plasma pro-inflammatory cytokines, especially considering the reduction in IL-6 plasma levels. Thus, our results propose that nCPAP is a less harmful initial ventilatory strategy for preterm infants with moderate respiratory distress.

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A Therapist that Gets the NICU Experience and Helps Families Heal

Deb Discenza

Kara Wahlin, MFT, a former licensed marriage and family therapist and trained art therapist, never realized the extent of NICU trauma for parents until she herself became pregnant with twins in 2011 and delivered them at 26 weeks and 3 days. Taking her training and her unique experience, she has created NICU Healing (www.nicuhealing.com) and has helped many families nationally heal from their NICU experience and changing lives for the better. I sat down with Kara and gathered her unique insight into the preemie parent mentality in the NICU with some excellent takeaways for staff members.

Deb Discenza: Tell me about your background both personally and professionally and how the two have intertwined.
Kara Wahlin: I am a licensed marriage and family therapist and trained art therapist, who studied person-centered care as a student and put that into practice in clinical placements. I've worked in residential care settings for most of my career, in placements ranging from a residential high school for pregnant and parenting moms, moms being released from the prison system and being reunited with their young children, and at a placement for homeless, transitional aged youth. "Person-centered care" refers to the notion that sometimes the dominant discourses, or cultural belief systems, can impair our way of seeing ourselves, and oftentimes the language that we have to describe different experiences is limiting. For example, if a person has always been characterized as a "juvenile delinquent" and all of their qualities, good and bad, have been attributed to that categorization, it can be challenging for said individual to move beyond that descriptor in understanding themselves or facilitating change in their lives. I found in my work that it was incredibly useful to align myself with my clients, and to use unique ways of accessing their perceptions of their experience, such as art and different ways of using language, questioning assumptions. Clients found ways of "freeing" themselves from less useful discourses, feeling empowered, and thus changing their lives, long after our work together was done.

While working at the placement for homeless youth, I became pregnant with my twin sons. A surprise to my husband and I both, we were jubilant with the notion that such an incredible surprise had come into our lives. At 26 weeks and 3 days into my pregnancy and without warning, I began contracting with preterm labor. After failed attempts to stop its progression, I gave birth three days later. My sons William and Elliott were placed into the neonatal intensive care unit at our hospital, where they began their incredible fight for their lives. On Bastille Day in 2011, my son, twin A, William, succumbed to complications of prematurity, dying in my husband's and my arms after a valiant struggle with fate. Elliott continued on in the NICU, fighting for three months. Undergoing a PDA ligation, respiratory support, blood transfusions, infections, learning to coordinate the suck swallow breathe reflex and coping with reflux, Elliott had a fairly eventful NICU stay, but thankfully left wire-free. The experience left my husband and I shell-shocked. We found that months after Elliott's discharge the very real and profound emotional and mental effects of having gone through this trauma were still making significant waves in our lives.

The grief not only of having lost William, but also that of losing a "normative" birth experience and first year home with Elliott (being on quarantine, being hyper-vigilant about developmental and feeding issues, being unable to socialize with friends and family), was as engulfing as it was overwhelming. It struck me that there were very few clinical resources for NICU families beyond some terrific online peer support groups. I started to peruse research about NICU parents and the psychological challenges they face, and found that the rates for PTSD and depression among both NICU mothers and fathers were staggering. In honor of my boys, I knew then that I would shift my career to meeting the needs of and helping these parents who more often than not, had no preparation for a significantly traumatic experience, the ramifications of which could potentially affect their attachment with their babies as well as their partnerships with each other, forever.

DD: Your experience and story is very relevant – what do you see as the mechanism behind parent stress in the NICU? What do you feel are some key tools to NICU professionals helping parents through this time on an emotional level?
KW: The way I see it, parent stress in the NICU is a normative, functional reaction to an extraordinary circumstance. To see your child on life support is an experience unlike any other, and it most definitely sweeps the ground from beneath your feet. Nothing is predictable, many of the medical interventions have side effects, and you're expected to cope with life and death circumstances affecting your precious baby on a minute-to-minute basis. At once you are thrust into a world where you have to learn a whole new, medical language. Nurses and doctors are essentially providing the primary care for your infant. You

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have to make decisions that could have major consequences for your baby. Oftentimes, you have to be able to weigh what you're willing to risk, often the risk of long-term developmental issues, in securing the survival of your child. It's an impossible circumstance for most that face it. Transitioning from the fast-paced world of the NICU into a world where you find yourself providing primary care for your medically fragile infant, as well as feeling the pressure of being able to be "the best" at parenting can be overwhelming.

NICU professionals can help prevent risky long-term outcomes by gently asking parents about their experience. Parents' experience is often forgotten in exchange for the obvious priority of the infant's health. However, parents play a crucial role in the outcomes for their babies. Studies have shown that the level of attachment parents have with their baby can change the baby's developmental outcome for the better (Nicolaou et al., 2009; Reynolds et al. 2013). Thus, it's important to check in with parents and find out if they'd be interested in a support group (free online support groups can be incredibly helpful), whether they need a referral to a therapist or psychiatrist, and whether there is some support in their own lives upon whom they'd be able to call should things become stressful. It's important to be aware that in many cases, fathers don't show signs of PTSD until far after the discharge of their infant (Shaw et al. 2009). Using conversation to normalize the idea of mental health issues and the importance of seeking out help if it's needed is crucial at this juncture, as parents may not have any further contact with medical professionals beyond their pediatrician or OB/GYN after their baby is discharged from the NICU. It's also important to remember that gestational age at the time of birth doesn't make a significant difference in terms of the likelihood that mental health issues could come up for a family: the parents of a 35-weeker who has been in the hospital for 2 weeks are almost at the same level of risk as the parents of a 24-weeker with a much longer stay (Borghini et al. 2006; Gambina et al. 2011). It's important not to assume that because a family didn't have as "difficult" of a NICU stay by NICU standards, that their experience could have been just as completely overwhelming and difficult to contend with.

I think an important thing to remember when dealing with any mental health issue is to create a space for talking about it that is void of stigma or judgment. As I said, in my opinion what might be diagnosed as "acute stress disorder" according to the DSM V, is actually a normative response to an extremely disconcerting circumstance, the hospitalization of your infant child. Rather than looking for "clues" to unlock the key as to whether someone may or may not develop PPD or PTSD, talking with parents about their experience and encouraging them to talk about it in the future can be extremely valuable (Whittingham et al. 2014). It's important to give parents the freedom to not have to be "strong", but rather to be real, to normalize the fact that all parents, not just those who have lost a child, go through a grieving process after the hospitalization of a child.

DD: I agree, it is important to avoid stigma or judgment as that will only push a parent away from wanting help. Also whether or not the parent seeks help, in time, they will notice that they are unable to cope with life normally and get stuck. So with that in mind, what does a mental health professional provide to the NICU parent, and therein to the infant not only for short-term support but also long-term healing?

KW: I developed NICU Healing from the notion that parents need outlets in order to process their grief and trauma, in a way that's not only easily accessible (i.e. online and not necessitating leaving a potential quarantine situation) but quick. Utilizing some of the ideas I've learned about in art therapy and person-centered care, a lot of the work focuses around creating a narrative "story" about what happened in the family after the baby was born, hospitalized and eventually discharged. To be able to create a consolidated memory, or coherent narrative, of this experience has shown to have positive outcomes for individuals faced with any kind of trauma, and in a lot of ways, the way we sew together our own stories can help inform our children's ways of looking at things as well (Siegel, 1999; Coppola & Cassibba, 2010)). By externalizing these experiences, it's easier for individuals who have been through trauma to get a sense of how they've changed, and sometimes to discover strengths or values that, prior to the experience, they weren't aware of having. It also locates the trauma and/or depression as "outside" of the individual or family, and thus something that can be worked with; this, as opposed to its existing as an overwhelming, internal "force." I've found that this kind of work can have profound effects with clients, endowing them with the freedom to make their own meaning out of what happened. It's very inspiring work, and has noticeable, measurable effects within the family system.

For one, partnerships can easily be tarnished when each parent experiences trauma in a different way. As I said before, many times men don't show signs or symptoms of PTSD until well after their baby is born. However, they have a very similar rate of PTSD (some studies place the numbers at 23%) as moms do (Shaw et al., 2009; Lasiuk et al. 2013). Additionally, men may express trauma symptoms differently. While a mom may experience intrusive thoughts and paranoia regarding the medical safety of her baby, dads may do things like turn to substances in order to cope. Creating a space for couples to relate to each other and develop a deeper understanding of each other's experience can effectively save a marriage that's under fire. Divorce is very common in this experience, which is compounded by the fact that families may also have to cope with the ongoing special developmental or medical needs of their child. No family can truly be prepared for the NICU until they are in the moment. Even though in most cases the hospital stay is not anyone's fault, it's amazing how quickly and easily we can develop guilt and shame regarding a traumatic birth experience. Additionally, the research is starting to show evidence that the importance of a healthy attachment with a NICU baby can have a significant impact on their developmental outcome. Whereas in a full-term baby, attachment quality doesn't have statistical significance in terms of developmental outcomes, in premature babies it is inextricably intertwined (Borghini et al. 2006; Bilgin & Wolke, 2015; Hoffenkamp et al. 2012; Reynolds et al. 2013). Since both depression and PTSD can have the effect of inhibiting a mother or father's ability to attach to their infants, therapy early on can be incredibly important in preventing roadblocks to attachment. Depression and trauma can both inhibit a parent's ability to meet their child where they are, potentially causing "mixed signals", resulting in a less-than-secure attachment (Whittingham et al., 2014; Auslander & Arad, 2003; Brecht et al. 2012).

DD: Yes having an outlet for NICU parents to cope with strong emotions and relationship changes is key. What are some smart

ways for a NICU professional to engage a parent on a mental health concern without that feeling of judgment?

KW: It's my opinion that support options should be distributed to all parents upon discharge from the NICU. Offering parents access to a range of support: from local therapists and psychiatrists who work with this population, to online support groups, to hospital support groups, to books that could be useful to read. A list of signs and symptoms of NICU-related PTSD and/or postpartum depression may be useful as well. Too often NICU parents blame themselves for the problems that they face, if simply because they're unaware that something may be "out of the norm", or due to the fact that they may feel it's their responsibility to remain "strong". Normalizing the need for support after a traumatic event is a powerful intervention for parents (Whittingham et al., 2014; Preyde & Dingwall, 2009). Giving them access to resources that might be difficult to locate once they're at home and taking care of their medically fragile infant is a terrific way to offer them the support they might need, even if they don't need it initially upon discharge.

Because parents are overwhelmed with medical decisions and the day to day of being in the neonatal intensive care unit, it's wise to provide them with resources, but not create an expectation that they seek out help right away. The key here is empowering them to feel in charge of their own outcomes, that reaching out for help doesn't have a negative implication (ie. That they are "mentally ill"), that by making the decision to take care of themselves through whatever means possible they can change their family's outcome for the positive.

It's also important to remember that due to the level of stress any NICU parent may have whilst still in the NICU, that they might not seem to be receptive to the idea of support. Approaching the subject with care and an awareness that parents are facing a very real trauma in that very moment is important as it is not to stigmatize mental health reactions to a challenging circumstance (Whittingham et al., 2014; Auslander & Arad, 2003). Making parents feel more guilty, ashamed, or "responsible" to save the world can have the opposite effect of what one would want. Coming from a space of empathy, care and awareness is crucial in providing meaningful guidance, as other ways may have the effect of alienating them even further.

DD: I agree "normalizing" the need for mental health help is a great idea as is distributing information about support services at discharge time. Thank you, Kara, for such great insight into the mechanisms behind the trauma and grief as well as key ways to help with healing.

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Newborn Capillary Blood Collection: It's More Than Just Sticking the Heel

Bruce Toben, RRT-NPS, CPFT, FAARC

In vitro diagnostic blood testing in newborn infants is a common practice in most countries prior to hospital discharge. Screening for infectious diseases, metabolic syndromes and genetic disorders are typical for asymptomatic full term babies.[1,2] In addition, during the course of supporting premature or post-term infants, those suffering from congenital anomalies or managing newborn sepsis, a myriad of other laboratory tests necessitating a blood specimen are required. These studies may include: chemistry, hematology, coagulation and infectious disease tests.[3,4,5,6]

The most common method to obtain blood for laboratory testing in newborns is by capillary blood collection from the infant's heel. This anatomic location is used for well babies and initially for those newborns requiring more extensive care. A successful heel stick procedure can be defined by obtaining an adequate sample volume for the tests required, ensuring the specimen is free from artifact and performing the collection procedure with the least stress or trauma to the infant.

From the view of an untrained eye, blood sampling from a newborn's heel my not appear to be a delicate or complicated procedure, however a detailed analysis of what is required for successful blood collection can offer a totally different perspective. The optimal newborn capillary blood collection necessitates: choosing the correct device, collecting a quality specimen, following best practice procedures and periodic training to gain confidence and validate proper technique.

Choosing the correct device: Puncture vs. Incision

There are two types of devices designed to sample capillary blood from an infant's heel, those that puncture the skin and those that produce an incision.

A device that punctures the skin, such as a lancet, incorporates a pointed angled blade. These devices are marketed in both manual and automated designs. When making a puncture, downward pressure is applied causing the point to pierce multiple layers of skin at a 90° angle (Figure 1). As the depth of the penetration increases, the blade cuts the capillaries and blood rises to the skin's surface for collection. Although simple in function, a lancet-type device is flawed in its inherent design. In order for the cutting blade to effectively reach the layer of the capillary loops, the pointed tip must simultaneously protrude deeper into the subcutaneous tissue, often into the area abundant with never fibers and potentially to the calcaneus, which is at a depth of 2.4 mm in low birth weight infants[7]. Sticking the heel in this manner causes undue pain and stress that may contribute to short, medium and long range[8] complications to what, should be a relatively benign procedure.

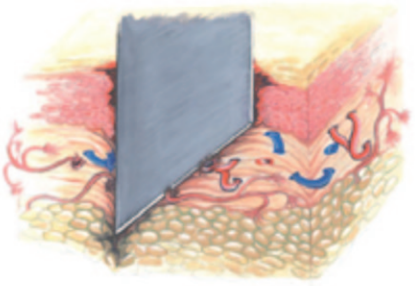

Figure 1. Heel stick performed with a puncture device.

The puncture device pierces the tissue at a 90° angle. As the blade cuts the capillary loops, the tip reaches the depth of nerve endings.

Another device design for capillary collection is an automated system that creates a small skin incision. When the operator activates the trigger mechanism, a spring loaded sterile surgical steel blade swings out from its protective housing and incises the skin in a sweeping arc motion (Figure 2). The cut is made at a pre-engineered depth and then the blade permanently self-retracts back into the device.

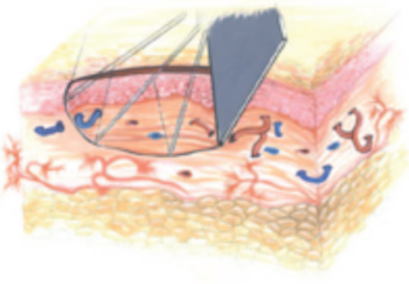

Figure 2: Heel stick performed with an incision device.

The incision device produces a surgical cut in a sweeping arc motion at a precise depth to maximize capillary exposure and minimize stimulation to nerve endings.

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Some incision devices have their trigger mounted on the top surface of the unit. To operate these systems, a downward thrust is needed to activate the blade. Like the lancet-type device, this design is associated with similar adverse consequences, i.e., pushing the blade deeper into the skin than intended or desired. Ergonomically advanced incision devices, such as Tenderfoot® (Accriva Diagnostics, San Diego, CA, USA), have their trigger on the side of the unit. This feature does not create any additional downward motion, thus eliminating any inadvertent increase in blade penetration.

Obtaining a Quality Specimen

A quality capillary sample is a specimen of sufficient blood quantity to satisfy the laboratory's minimal volume requirements and ensures the blood is collected in such a manner as to prevent contamination from artifact that could introduce preanalytical errors to the test results. At the core of this laboratory requisite is a procedure oriented to create a steady blood flow from the capillary bed to the skin surface without applying pressure to the heel. Squeezing or milking the heel can cause hemolysis of the sample or add tissue fluid artifact that may contribute to erroneous test results.[9] Manipulation of the heel by trying to press more blood to the surface of the skin can be another source of pain and cause bruising. The skin's primary blood-supply is located at the junction of the dermis and subcutaneous tissue, 0.35 to 1.6 mm[7] from the surface of the heel. To achieve good blood flow, the heel stick needs to cut an ample portion of these capillary loops. The optimal incision depth is guided by body weight (Table 1), which also limits exposure to the nerve ending and provides a safe marginal distance from the calcaneus to prevent bone trauma.

Table 1. Heel incision depth for capillary blood collection based on body weight.

Body Weight	Incision Depth
<1,000 g	0.65 mm
1,000 – 2,500 g	0.85 mm
2,500 – 9,000 g	1.00 mm
>9,000 g	2.00 mm

Complications associated with the heel stick procedure include: crying,[10] stress,[11] pain[12,13,14] bruising[15] (Figure 3), localized or generalized necrosis[16] and osteochondritis.[17] Although crying, stress and pain may be categorized as an innocuous side effect of the phlebotomy procedure, these untoward conditions can carry significant consequences. Alteration in heart rate and respiratory pattern that accompanies these states can dramatically affect blood gases, cardiac output and systemic, pulmonary and cerebral blood pressures. The recovery back to baseline physiologic status can be prolonged, especially in high acuity infants. Unless the heel stick achieves sufficient blood flow, a second attempt may be needed to collect the desired specimen volume. If this is required, the iatrogenic risks increase and from a facilities perspective, the cost of the procedure doubles.

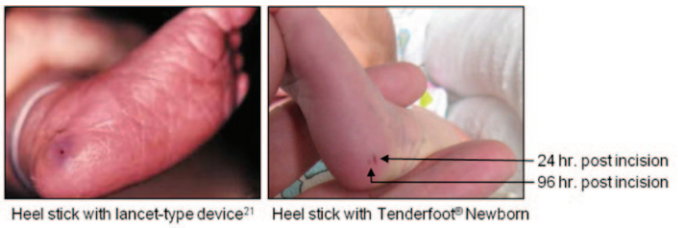

Figure 3: Skin healing post capillary heel collection: puncture vs. Tenderfoot.

Best Practice Procedures[18,19]

Performing a heel stick for capillary blood collection is a minimally invasive procedure and requires Universal Precautions for bloodborne pathogens.

1. The ideal posture for a heel incision is with the baby in a supine position with the knee at the open end of a bassinet. This position allows for the foot to hang lower than the torso, improving blood flow.
2. When the baby is in an acceptable position for this procedure, wipe the heel with an antiseptic swab and allow to air dry. Do not touch the prepared area or permit the heel to come into contact with any non-sterile item or surface.
3. Remove the appropriate incision device from its package taking care not to rest the blade slot end on any non-sterile surface.
4. Remove any safety clip from the trigger. Once the safety clip is removed, DO NOT touch the trigger or the blade slot.
5. The baby's heel should be held with your non-dominant hand, your fingers around the ankle and lower leg, while partly encircling the baby's heel with your thumb. Hold the foot firmly but DO NOT squeeze or extend the foot. Extension may damage the Achilles tendon and cause extreme pain.
6. Raise the foot above the baby's heart level and carefully select the incision site (Figure 4). Avoid any edematous area or a site within 2.0 mm of a prior incision. Use your dominate hand to place the incision device against the heel and press it firmly to the skin. The blade-slot should be flush against the heel so that its center point is vertically aligned with the desired incision site. Ensure that both ends of the device have made light contact with the skin and depress the trigger.
7. After triggering, immediately remove the device from the infant's heel and discard appropriately.
8. Using only a dry sterile gauze pad, gently wipe away the first droplet of blood that appears at the incision site.
9. Take care not to make direct wound contact with the collection container, test card or capillary tube, and fill to the desired specimen volume.
10. Following blood collection, gently press a dry sterile gauze pad to the incision site until bleeding has ceased. This step will help prevent a hematoma from forming. Whether or not to bandage the baby is a controversial issue because of skin sensitivity and the potential for bandage aspiration. However, the incision site should be noted by the primary care nurse to ensure that the heel can be monitored for bleeding and inflammation.

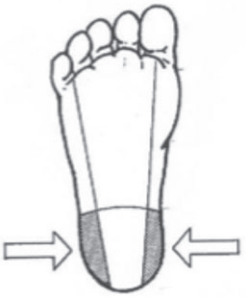

Figure 4: Preferred zone to perform a heel incision for capillary blood collection. The safe sampling area to incise a newborn's heel is illustrated by the shaded zone. The area is marked by a line extending posteriorly from a point between the fourth and fifth toes and running parallel to the lateral aspect of the heel, and a line extending posteriorly from the middle of the great toe running parallel to the medial aspect of the heel. An incision is made with a self-retracting blade at a precise depth, specific to the weight of the newborn, to optimize the exposure to the capillary loops and avoid trauma to nerves and the calcaneus.[20]

Newborn Heel Incision Training

Developing the incision skill set to achieve optimal outcomes can be challenging, as it is rarely permissible or ethical to practice such procedures to gain learning experience with the newborn population. To address this vital training need, Accriva Diagnostics recently released the Tenderfoot Educational Kit (Figure 5). The objects of this new educational tool are to build familiarity with the devices used for the capillary blood collection, to hone proper technique and to validate the performance of healthcare professionals who are responsible for this phlebotomy procedure.

Figure 5: Tenderfoot Educational Kit.

The Tenderfoot Educational Kit includes:

- Sample incision devices for: micro-preeme, preeme, newborn and toddler patients
- Full term infant foam manikin foot for demonstrating product technique. The life-like training aid represents the foot of an approximate 3.5 Kg newborn. The recommended anatomic guidelines are printed on the bottom surface of the heel, similar to Figure 4.
- Instructional Video
- Literature for clinical professionals
- An informational guide for parents

To receive a Tenderfoot Educational Kit, complete the form on www.tenderfootcares.com.

Appropriate and timely medical management of the newborn, in part relies upon the accuracy of diagnostic laboratory tests. Obtaining a quality capillary heel specimen that meets the needs of the laboratory, while not incurring undue stress or pain to the infant, is a factor of the device used and skill set of the healthcare professional performing the procedure. Choosing an incision device that can safely penetrate the skin at a precise optimal depth and following best practice guidelines will ensure a quality specimen with low risks of complications. Finally, practicing the capillary heel collection technique on a manikin-like foot model will build the skill set needed to perform the procedure with confidence.

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The Effects of Antenatal Dietary and Lifestyle Advice for Women Who are Overweight or Obese on Neonatal Health Outcomes: the LIMIT Randomised Trial

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Abstract

Background: Overweight and obesity during pregnancy represents a considerable health burden. While research has focused on interventions to limit gestational weight gain, there is little information describing their impact on neonatal health. Our aim was to investigate the effect on a range of pre-specified secondary neonatal outcomes of providing antenatal dietary and lifestyle advice to women who are overweight or obese.

Methods: We report a range of pre-specified secondary neonatal outcomes from a large randomised trial in which antenatal dietary and lifestyle advice was provided to women who were overweight or obese. Pregnant women were eligible for participation with a body mass index of 25 kg/m^2 or over, and singleton gestation between 10+0 and 20+0 weeks. Outcome measures included gestational age at birth; Apgar score below 7 at 5 minutes of age; need for resuscitation at birth; birth weight above 4.5 kg or below 2.5 kg; birth weight, length and head circumference (and Z-scores); admission to the nursery; respiratory distress syndrome; and postnatal length of stay. Data relating to the primary outcome (large for gestational age infants defined as birth weight above the 90th centile) and birth weight above 4 kg have been reported previously. Analyses used intention-to-treat principles.

Results: In total, 2,142 infants were included in the analyses. Infants born to women following lifestyle advice were significantly less likely to have birth weight above 4.5 kg (2.15% versus 3.69%; adjusted risk ratio (aRR) = 0.59; 95% confidence interval (CI) 0.36 to 0.98; P = 0.04), or respiratory distress syndrome (1.22% versus 2.57%; aRR = 0.47; 95% CI 0.24 to 0.90; P = 0.02), particularly moderate or severe disease, and had a shorter length of postnatal hospital stay (3.94 ± 7.26 days versus 4.41 ± 9.87 days; adjusted ratio of means 0.89; 95% CI 0.82 to 0.97; P = 0.006) compared with infants born to women who received Standard Care. Conclusions: For women who are overweight or obese, antenatal dietary and lifestyle advice has health benefits for infants, without an increase in the risk of harm. Continued follow-up into childhood will be important to assess the longer-term effects of a reduction in high infant birth weight on risk of child obesity.

Background

Globally, it is estimated that 170 million children under the age of 18 years [1], are overweight or obese. Obesity is occurring at an increasingly early age, affecting more than 43 million children aged 0 to 5 years world-wide [2], and 21% of Australian children 2 to 3 years of age [3]. The World Health Organization has described childhood obesity as "one of the most serious public health challenges of the 21st century", [4] with obese children exposed to its consequences, including disease progression and disability, earlier and for longer duration.

The economic costs of childhood obesity are profound [5]. Australian data indicate that children who are overweight or obese at 5 years of age have medical costs within the first 5 years of school that are $9.8 million higher than those of children of normal body mass index (BMI) [6]. Data from the USA indicate that childhood overweight and obesity are associated with an additional cost of $14.1 billion annually, reflecting prescription drugs and emergency and outpatient attendances [7], with a further $238 million annually reflecting inpatient admissions [8]. The direct medical costs, in both childhood and adulthood, directly attributable to high child-hood BMI have been conservatively estimated to be $6.24 billion, with over 2 million quality adjusted life years lost [5].

The intra-uterine environment is recognised as playing a key role in the development of later health and disease [9], representing a crucial period in the subsequent programming of obesity. Both high maternal BMI and excessive gestational weight gain have been consistently associated with adverse pregnancy outcomes [10-13], and are significant predictors of increased adiposity and future child/adult obesity [14-17], with some studies also finding consequent associations with cardiometabolic risk factors, including higher blood pressure [18,19]. The antenatal period therefore represents a unique window in which intervention designed to alter maternal diet

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and weight gain may significantly influence infant adiposity, and modify future risk of both child and adulthood obesity.

Although there is considerable research focused on the effects of dietary and lifestyle interventions to limit gestational weight gain by pregnant women who are overweight or obese, their effect on neonatal outcomes has been poorly reported in the literature to date [20-22]. In the few studies specifically involving women who are overweight or obese where birth outcomes have been reported, the predominant focus has been on infant birth weight, with no reporting of other relevant clinical infant outcomes [20-22]. We report the findings of the LIMIT randomised trial, evaluating the provision of antenatal dietary and lifestyle advice to women who were overweight or obese on a range of pre-specified secondary neonatal health outcomes.

Methods

Ethics

Ethics approval was granted by the Women'sand Children's Local Health Network Human Research and Ethics Committee at the Women'sand Children'sHospital, the Central Northern Adelaide Health Service Ethics of Human Research Committee (Lyell McEwin Hospital) and the Flinders Clinical Research Ethics Committee (Flinders Medical Centre). Approval to conduct the trial was provided by the Human Research and Ethics Committee at each participating centre, and all participants provided written informed consent.

Study design

We conducted a multicentre randomised trial across the three major metropolitan maternity hospitals within Adelaide, South Australia. The methods [23] and primary findings [24] of the LIMIT randomised trial have been reported previously, and the trial has been registered on the Australian and New Zealand Clinical Trials Registry (ACTRN12607000161426). Additional clinical neonatal outcomes were added to the final working protocol, reflecting piloting of data collection processes. These amendments were pre-specified in the final working protocol, early in the conduct of the trial, and prior to any analyses being undertaken.

Inclusion and exclusion criteria

Women with a BMI of 25 kg/m^2 or greater and singleton pregnancy between 10+0 and 20+0 weeks gestation were eligible to participate in the trial. Women with a multiple pregnancy, or type 1 or 2 diabetes diagnosed prior to pregnancy were ineligible.

Trial entry

All women had their height and weight measured and their BMI calculated at their first antenatal appointment, and eligible women were counselled about participation.

Randomisation, masking and group allocation

Randomisation occurred by telephoning the central randomisation service, using a computer-generated schedule, with balanced variable blocks, and stratification for parity (0 versus ≥1), BMI at antenatal booking (25 to 29.9 kg/m^2 versus ≥30 kg/m^2), and collaborating centre. Women were randomised and allocated to either 'Lifestyle Advice' or 'Standard Care'.

Intervention

Lifestyle advice group

Women randomised to receive Lifestyle Advice participated in a comprehensive dietary and lifestyle intervention over the course of their pregnancy, which included a combination of dietary, exercise and behavioural strategies, delivered by a research dietician and trained research assistants [23]. Women were provided with dietary advice consistent with current Australian standards [25]; to maintain a balance of carbohydrates, fat and protein, to reduce intake of foods high in refined carbohydrates and saturated fats, while increasing intake of fibre, and to promote consumption of two servings of fruit, five servings of vegetables, and three servings of dairy each day [25]. Physical activity advice primarily encouraged women to increase their amount of walking and incidental activity [26]. The content and structure of the intervention sessions has been described in detail previously [24].

Standard care group

Women randomised to receive Standard Care continued their pregnancy care according to local hospital guidelines, which did not include routine provision of advice related to diet, exercise or gestational weight gain.

Study outcomes

In clinical practice, there is considerable variation in definitions of 'large for gestational age,'including birth weight at or above the 90th centile for gestational age and infant sex, birth weight above 4 kg, and birth weight above 4.5 kg, which are often used interchangeably. These have been recognised as associated with early childhood obesity [18,27], and were chosen as outcome measures in the LIMIT randomised trial. The incidence of infants born large for gestational age (birth weight ≥90th centile for gestational age and infant sex; primary outcome), and with birth weight above 4 kg have been reported previously [24]. Prespecified secondary neonatal outcomes included gestational age at birth; Apgar score of 7 or above at 5 minutes of age; need for resuscitation at birth; birth weight above 4.5 kg or below 2.5 kg; birth weight (and Z-scores); birth length (and Z-scores); head circumference (and Z-scores); admission to neonatal intensive care unit; admission to special care baby unit; respiratory distress syndrome [28] (with moderate or severe disease defined as mean airway pressure >10 cm H_2O and/or inspired oxygen fraction (FiO_2) >0.80 with ventilation); proven systemic infection requiring treatment; retinopathy of prematurity; necrotising enterocolitis; neonatal encephalopathy [29]; seizures; and postnatal length of stay.

Ponderal Index was calculated using birth weight and length (kg/m^3). Predicted fat free mass was calculated using the following formula:

$$0.507 + 0.646 \times \text{weight (kg)} - 0.089 \times \text{sex} + 0.009 \times \text{length (cm)},$$

where 1 = male and 2 = female [30].

Analysis and reporting of results

Analyses were performed on an intention-to-treat basis, according to the treatment group allocated at randomisation. Multiple imputation was performed separately by treatment group, using chained equations to create 100 complete datasets for analysis. Women who withdrew consent to use their data, or had a miscarriage, termination of pregnancy, or stillbirth, were excluded from the imputation and analysis. Sensitivity analyses were performed using the available data and different imputation models. Binary outcomes were analysed using log binomial regression, with treatment effects expressed as relative risk (RR), or Fisher's exact test with no imputation for rare

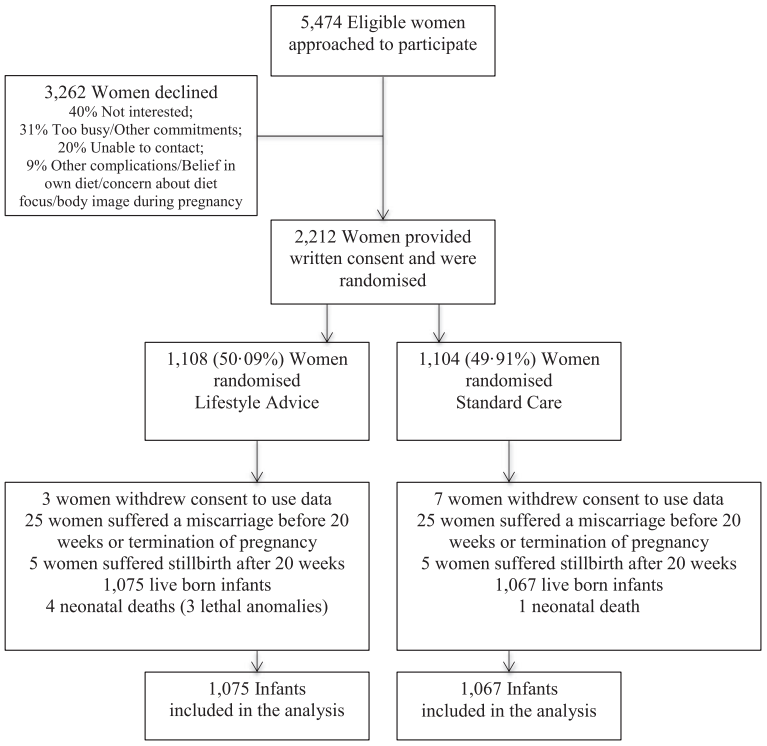

Figure 1. Flow of participants through the trial.

outcomes. Continuous outcomes were analysed using linear regression, with treatment effects expressed as differences in means. Count outcomes were analysed using Poisson regression, or using negative binomial regression where over-dispersion was present, with treatment effects expressed as ratios of means.

Both unadjusted and adjusted analyses were performed, with adjustment for the stratification variables. Outcomes derived from birth weight were additionally adjusted for maternal age, socioeconomic status and maternal smoking. Statistical significance was considered at $P < 0.05$ (two-sided) with no adjustment for multiple comparisons. All analyses followed a pre-specified statistical analysis plan and were performed using SAS software (v9.3; SAS Inc., Cary, NC, USA).

Sample size

Our predetermined sample size of 2,180 women was based on our primary trial outcome, the incidence of large for gestational age infants [24].

Results

Between June 2008 and December 2011, we recruited and randomised 2,212 women, with 1,108 allocated to receive Lifestyle Advice, and 1,104 Standard Care (Figure 1). There was a total of 2,142 live-born infants included in the analyses (1,075 Lifestyle Advice; 1,067 Standard Care). The characteristics of women at the time of randomisation were similar between treatment groups (Table 1).

There were no statistically significant differences identified between the two treatment groups with regards to gestational age at birth (Lifestyle Advice 39.29 ± 1.74 weeks versus Standard Care 39.23 ± 2.07 weeks; adjusted difference in means 0.07; 95% confidence interval (CI) 0.10 to 0.23; P = 0.42) (Table 2). However, infants born to women allocated to Lifestyle Advice were less likely to weigh above 4.5 kg (Lifestyle Advice 2.15% versus Standard Care 3.69%; adjusted risk ratio (aRR) = 0.59; 95% CI 0.36 to 0.98; number needed to treat (NNT) = 66; 95% CI 34 to 950; P = 0.04), compared with infants born to women allocated to Standard Care. This finding is consistent with our previous report of a significant 18% RR reduction in birth weight above 4 kg [24]. Furthermore, infants born to women allocated to Lifestyle Advice were shorter (birth length z-score –0,26 ± 0,76 versus –0,18 ± 0,80; adjusted difference in means –0,07; 95% CI –0,14 to –0,01; P = 0,04) than infants born to women allocated to Standard Care.

There was no statistically significant difference in infant admission to neonatal intensive care (Lifestyle Advice 1.12% versus Standard Care 2.18%; aRR = 0.51; 95% CI 0.26 to 1.02; P = 0.06). However, infants born to women following Lifestyle Advice were less likely to have respiratory distress syndrome (Lifestyle Advice 1.22% versus Standard Care 2.57%; aRR = 0.47; 95% CI 0.24 to 0.90; NNT = 75; 95% CI 40 to 532; P = 0.02), particularly moderate or severe respiratory disease (Lifestyle Advice 0.09% versus Standard Care 1.42%; P < 0.001), compared with infants born to women allocated to Standard Care (Table 2). Infants born to women in the Lifestyle Advice group also had a shorter postnatal length of hospital stay (3.94 ± 7.26 days versus 4.41 ± 9.87 days; adjusted difference in means 0.89; 95% CI 0.82 to 0.97; P = 0.006). There were no other statistically significant differences in infant outcomes identified between the groups.

Sensitivity analyses produced similar results, and did not alter the conclusions regarding the effectiveness of treatment in either the unadjusted or adjusted analysis for any outcome (data not shown).

Discussion

Our findings indicate that provision of lifestyle advice to women who are overweight or obese during pregnancy is associated with a significant reduction in the risk of birth weight above 4.5

Table 1 Demographic and clinical characteristics at trial entry (baseline)

Characteristic	Lifestyle advice (n = 1105[a])	Standard care (n = 1097[a])	Total (n = 2202[a])
Maternal age, years[b]	29.3 ± 5.4	29.6 ± 5.6	29.4 ± 5.5
Gestational age at entry, weeks[c]	14.0 (11.9 to 17.0)	14.1 (11.9 to 17.0)	14.1 (11.9 to 17.0)
Body mass index, kg/m^2[c]	31.0 (28.1 to 35.9)	31.1 (27.7 to 35.6)	31.1 (27.9 to 35.8)
Body mass index category[d]			
25.0 to 29.9	458 (41.4)	468 (42.7)	926 (42.1)
30.0 to 34.9	326 (29.5)	318 (29.0)	644 (29.2)
35.0 to 39.9	202 (18.3)	183 (16.7)	385 (17.5)
≥40.0	119 (10.8)	128 (11.7)	247 (11.2)
Public patient[c]	1081 (97.8)	1067 (97.3)	2148 (97.5)
Weight, kg[b]	88.6 ± 17.3	88.2 ± 17.6	88.4 ± 17.4
Height, cm[b]	164.9 ± 16.6	164.8 ± 16.5	164.8 ± 16.6
Race[c]			
Caucasian	995 (90.0)	998 (91.0)	1993 (90.5)
Asian	26 (2.4)	34 (3.1)	60 (2.7)
Indian	40 (3.6)	35 (3.2)	75 (3.4)
Other	44 (4.0)	30 (2.7)	74 (3.4)
Smoker[c]	154 (13.9)	126 (11.5)	280 (12.7)
Nulliparous[c]	457 (41.4)	441 (40.2)	898 (40.8)
Previous preterm birth[c]	57 (5.2)	59 (5.4)	116 (5.3)
Previous pre-eclampsia[c]	46 (4.2)	51 (4.6)	97 (4.4)
Previous stillbirth[c]	13 (1.2)	6 (0.5)	19 (0.9)
Previous neonatal death[c]	11 (1.0)	7 (0.6)	18 (0.8)
Previous caesarean section[c]	197 (17.8)	214 (19.5)	411 (18.7)
Family history of diabetes[c]	288 (26.1)	290 (26.4)	578 (26.2)
Family history of hypertension[c]	389 (35.2)	369 (33.6)	758 (34.4)
Family history of heart disease[c]	187 (16.9)	179 (16.3)	366 (16.6)
Index of socio-economic disadvantage[e]			
Unknown	2 (0.2)	1 (0.1)	3 (0.1)
Quintile 1, (most disadvantaged)	340 (30.8)	321 (29.3)	661 (30.0)
Quintile 2	271 (24.5)	264 (24.1)	535 (24.3)
Quintile 3	173 (15.7)	174 (15.9)	347 (15.8)
Quintile 4	150 (13.6)	178 (16.2)	328 (14.9)
Quintile 5, (least disadvantaged)	169 (15.3)	159 (14.5)	328 (14.9)

[a]Includes all women randomised who did not withdraw consent to use their data.
[b]Mean ± standard deviation.
[c]Median (interquartile range).
[d]n (%).
[e]Socioeconomic index as measured by SEIFA (socioeconomic indexes for areas [31]).

kg, in addition to a significant reduction in risk of respiratory distress syndrome, particularly moderate or severe disease, and a shorter postnatal hospital length of stay. Importantly, we did not identify any increase in the risk of harm, including low infant birth weight.

Our randomised trial has a number of strengths, including being the largest to date to evaluate the effect on clinically relevant neonatal outcomes of an antenatal lifestyle intervention for overweight or obese women. We utilised robust methodology, including blinding of outcome assessors and central randomisation, and achieved a high rate of infant follow-up and available birth outcome data.

Our trial is not without limitations. As highlighted previously [24], a potential limitation is the generalisability of our findings, with 60% of eligible women declining to participate (Figure 1). However, the demographic characteristics of women participating in the LIMIT trial are similar to the characteristics of the broader South Australian birthing population [32], providing reassurance that our findings are applicable in a wider clinical setting. It is also important to acknowledge that we report a number of secondary neonatal health outcomes. Although all were pre-specified, the study was not powered to identify differences in many of the secondary outcomes occurring relatively infrequently, and interpretation should therefore be with an element of caution.

Table 2 Infant outcomes by treatment group

Outcome	Lifestyle advice (n = 1075[a])	Standard care (n = 1067[a])	Unadjusted		Adjusted	
			Treatment effect (95% CI)	*P*-value	Treatment effect (95% CI)	*P*-value
GA at birth, weeks[b]	39.29 ± 1.74	39.23 ± 2.07	0.06 (−0.10 to 0.23)	0.44	0.07 (−0.10 to 0.23)	0.42
Apgar score <7 at 5 minutes	22 (2.07)	22 (2.09)	0.99 (0.55 to 1.78)	0.98	0.99 (0.55 to 1.77)	0.97
Resuscitation required at birth	196 (18.23)	191 (17.89)	1.02 (0.85 to 1.22)	0.84	1.01 (0.85 to 1.21)	0.88
Birth weight, g[b]	3481 ± 554	3492 ± 613	−11.55 (−61.13 to 38.03)	0.65	−6.90 (−55.47 to 41.67)	0.78
Birth weight Z-score[b]	0.37 ± 1.03	0.43 ± 1.09	−0.06 (−0.15 to 0.03)	0.18	−0.05 (−0.14 to 0.03)	0.23
Birth length, cm[b]	49.84 ± 2.42	49.92 ± 2.84	−0.08 (−0.31 to 0.14)	0.48	−0.08 (−0.30 to 0.15)	0.51
Birth length Z-score[b]	−0.26 ± 0.76	−0.18 ± 0.80	−0.07 (−0.14 to −0.01)	0.03	−0.07 (−0.14 to −0.01)	0.04
Birth head circumference, cm[b]	34.77 ± 1.60	34.77 ± 1.90	0.00 (−0.15 to 0.15)	0.96	0.01 (−0.14 to 0.16)	0.92
Birth head circumference Z-score[b]	0.21 ± 1.03	0.26 ± 1.09	−0.05 (−0.14 to 0.04)	0.31	−0.05 (−0.14 to 0.04)	0.32
Birth weight ≥4.5 kg	23 (2.15)	39 (3.69)	0.58 (0.35, 0.97)	0·04	0·59 (0·36, 0·98)	0·04
Birth weight ≤2.5 kg	43 (4.03)	56 (5.29)	0.76 (0.51 to 1.13)	0.18	0.74 (0.50 to 1.09)	0.13
Ponderal index, kg/m^3[b]	27.95 ± 2.85	27.82 ± 2.91	0.12 (−0.12 to 0.37)	0.33	0.12 (−0.12 to 0.36)	0.34
Predicted fat free mass, kg[b]	3.07 ± 0.38	3.08 ± 0.42	−0.01 (−0.04 to 0.02)	0.59	−0.01 (−0.04 to 0.03)	0.73
Admission to NICU ≥4 days	12 (1.12)	23 (2.18)	0.52 (0.26 to 1.03)	0.06	0.51 (0.26 to 1.02)	0.06
Admission to SCBU	388 (36.12)	382 (35.77)	1.01 (0.90 to 1.13)	0.87	1.00 (0.90 to 1.12)	1.00
Respiratory distress syndrome	13 (1.22)	27 (2.57)	0.47 (0.25 to 0.91)	0.03	0.47 (0.24 to 0.90)	0.02
Respiratory support	65 (6.09)	77 (7.20)	0.84 (0.61 to 1.16)	0.30	0.84 (0.61 to 1.15)	0.27
Moderate/severe respiratory disease	1 (0.09)	15 (1.42)	N/A	<0.001[d]	N/A	N/A
Discharged home on oxygen	1 (0.09)	3 (0.28)	N/A	0.37[d]	N/A	N/A
Patent ductus arteriosus	2 (0.19)	5 (0.47)	N/A	0.29[d]	N/A	N/A
Proven systemic infection	0 (0.00)	2 (0.19)	N/A	0.25[d]	N/A	N/A
Retinopathy of prematurity	1 (0.09)	4 (0.38)	N/A	0.22[d]	N/A	N/A
Necrotising enterocolitis	3 (0.28)	1 (0.09)	N/A	0.62[d]	N/A	N/A
Neonatal encephalopathy	0 (0.00)	0 (0.00)	N/A	N/A	N/A	N/A
Neonatal seizures	1 (0.09)	3 (0.28)	N/A	0.37[d]	N/A	N/A
Postnatal length of stay infant, days[e]	3.94 ± 7.26	4.41 ± 9.87	0.89 (0.82 to 0.97)	0.007	0.89 (0.82 to 0.97)	0.006

NICU, neonatal intensive care unit; SCBU, special care baby unit.
[a]Includes all live-born infants.
[b]Values are mean ± SD, and treatment effects are differences in means based on imputed data.
[c]Values are n(%), and treatment effects are relative risks based on imputed data.
[e]Values are mean ± SD, and treatment effects are ratios of means based on imputed data.
[d]*P*-value derived Fisher's exact test based on available data.

The findings of a significant 41% RR reduction in birth weight above 4.5 kg among infants born to women following Lifestyle Advice compared with Standard Care is consistent with the 18% RR reduction in birth weight above 4.0 kg reported previously [24]. Immediate birth consequences associated with high infant birth weight are well recognised, and include shoulder dystocia and its sequelae, perinatal asphyxia, neonatal hypoglycaemia, need for nursery admission [33-36], and respiratory distress syndrome [37]. However, meta-analyses of population-based cohort studies indicate a longer-term association between high infant birth weight and an increased risk of both child [38,39] and adulthood overweight and obesity [40,41]. Observational data from 7,738 14-year-old adolescents in the United States Early Childhood Longitudinal Study [42] highlighted a significantly higher prevalence of obesity among children with birth weight above 4 kg. Whereas children of high birth weight represented 12% of the cohort, 36% of individuals who were obese at 14 years of age had birth weights over 4 kg [42]. Antenatal interventions that are successful in reducing the risk of high infant birth weight therefore represent a public health strategy of significant potential in tackling the increasing problem of overweight and obesity, both in the short and longer term [43,44]. The ongoing follow-up of infants born to women who participated in the LIMIT trial is therefore of great importance to evaluate the impact of reducing high infant birth weight on subsequent early childhood obesity.

We observed a 53% RR reduction in neonatal respiratory distress syndrome in infants born to women allocated the lifestyle intervention. This difference in neonatal respiratory distress syndrome was not explained by differences in the use of antenatal corticosteroids, or in differences in gestational age at birth. Some of this difference may reflect the observed 26% reduction in preterm birth and the 53% reduction in preterm pre-labour ruptured membranes (PPROM) among women in the intervention group [24], although these differences did not reach statistical significance. Although some authors have

identified an increased risk of preterm birth in obese women [45], others indicate that this reflects iatrogenic prematurity rather than spontaneous labour [10]. In an analysis of the Danish National Birth Cohort, Nohr and colleagues identified an increased risk of preterm birth in obese women due to an increase in PPROM, which was postulated to reflect an increased risk of chorioamnionitis [46], although specific description of neonatal respiratory morbidity was not presented. Although we observed a significant reduction in risk of respiratory distress syndrome in infants born to women allocated to the lifestyle intervention, our findings do not suggest an aetiology related specifically to differences in risk of PPROM, chorioamnionitis or infectious causes [24].

Increasingly, there is recognition that although the consequences of preterm birth and prematurity can occur in a setting of clinical chorioamnionitis, effects are also evident following subclinical or histological inflammation [47]. However, the pathways affected and precise mechanisms remain to be determined, with evidence of an imbalance in the production of pro-inflammatory and anti-inflammatory cytokines [48]. There is increasing recognition that adipose tissue is far from an inert storage organ, being responsible for the active secretion of a number of metabolically active adipocytokines [49], and there is a well-described association in non-pregnant individuals between obesity and a low-grade inflammatory state [50,51], which, while speculative, may share similarities with subclinical chorioamnionitis.

Conclusions

To our knowledge, our findings are the first to describe a significant reduction in neonatal respiratory morbidity among infants born to women who are overweight or obese following an antenatal dietary and lifestyle intervention.

Furthermore, we postulate that this may be mediated by the significant improvements in maternal diet and physical activity following antenatal intervention, which we have reported previously [52]. It will be important to further consider specific dietary components and physical activity, and the impact these factors may have on maternal markers of inflammation, which are currently being evaluated through our prospectively established bio-bank.

Evidence to date about the effect of antenatal dietary and lifestyle interventions for women who are overweight or obese has focused on gestational weight gain, to the detriment of robust data describing both maternal and infant health outcomes [53]. Our randomised trial addresses this gap in the literature. Our findings indicate that providing an antenatal dietary and lifestyle intervention for women who are overweight or obese has health benefits for the infant, without increasing the risk of harm. Continued follow-up of participants, and ongoing interrogation of our bio-bank will be important to identify potential mechanistic pathways whereby changes to maternal diet and physical activity impact on clinical outcomes.

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Attitudes Among the General Austrian Population Towards Neonatal Euthanasia: a Survey

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Abstract

Background: The Groningen Protocol aims at providing guidance in end-of-life decision-making for severely impaired newborns. Since its publication in 2005 many bioethicists and health care professionals have written articles in response. However, only very little is known about the opinion among the general population on this subject. The aim of this study was to present the general attitude towards neonatal euthanasia(NE) among the Austrian population and the factors associated with the respondents' opinion.

Methods: A cross-sectional study was conducted among the general Austrian population. Computer-assisted telephone interviews were performed with 1,000 interviewees aged 16 years and older. Binary logistic regression was performed in order to determine factors that are independently associated with the respondents' opinion about neonatal euthanasia.

Results: While 63.6% of the participants rejected the idea of neonatal euthanasia for severely impaired newborns, 36.4% opted either in favor or were undecided. Regression analysis has shown the respondents' educational level ($p = 0.005$) and experience in the care of terminally ill persons ($p = 0.001$) to be factors that are positively associated with the rejection of neonatal euthanasia, whereas a higher age was associated with a lower degree of rejection ($p = 0.021$).

Conclusions: We found that the majority of the Austrian population rejects the idea of neonatal euthanasia for severely impaired newborns. However, given the increasing levels of rejection of NE among the younger generations and among people with a higher educational level, it cannot be precluded that the rejection rate might in future increase even further, rather than decrease.

Background

Voluntary active euthanasia (VAE) is a highly discussed topic throughout Europe. In the Netherlands VAE was legalized in 2002 for competent adults and minors from the age of 12 upwards [1]. This legislation, however, requires specific conditions to be fulfilled before a patient's life can be ended: the request for euthanasia must be voluntary and carefully considered, the suffering must be unbearable, there must not be any other reasonable alternatives, an independent physician must have been consulted, and the request must be properly reported. In the case of minors, parental consent is additionally required. Only when all the above conditions are met are physicians exempted from criminal liability. Since the law makes no mention of newborns, neonatal euthanasia (NE) is still illegal. Nevertheless NE has been known to take place in the Netherlands [2-4].

After many years of open discussion, Verhagen and Sauer published the Groningen Protocol in 2005. It was developed at the University Medical Center of Groningen based on legal precedents and explicitly supported NE [5]. One of the main goals of the Groningen Protocol was to enable a more transparent end-of-life decision-making for newborns and to provide guidance on how to properly report these decisions. Neonates, for whom this protocol was intended, can be categorized into three groups. Group one consists of infants without any chance of survival despite receiving optimal medical treatment. This group comprises infants with a severe underlying disease, such as lung or kidney hypoplasia. The second group includes newborns who can only survive with intensive treatment and who will die shortly after the withdrawal of intensive care; for example infants with severe brain abnormalities or extensive organ damage caused by extreme hypoxemia. Lastly, there is the third and most controversial group, consisting of neonates who might survive in the long run but whose suffering is considered to be unbearable and impossible to alleviate. A highly typical example is a child with the most serious form of spina bifida [5,6].

Furthermore, the Groningen Protocol lists several conditions that have to be fulfilled before a physician may attempt to end a newborn life. First of all, the doctor must be absolutely certain about both the diagnosis and prognosis for the newborn, and unbearable suffering must be present. Second, due to the lack of any decisional capacity, neonates are incapable of giving their consent. Therefore, the informed consent of both parents is required. Another requirement is that the diagnosis, prognosis, and unbearable suffering must be confirmed by at least one independent physician. Lastly, the procedure must be performed according to the accepted medical standard [5,7]. Cases of NE are reviewed and where the tight guidelines are met, prosecutors will not bring a charge against the physician who carried out NE.

Since the publication of the Groningen Protocol, many bioethicists and health care professionals involved in the treatment of severely ill newborns have written in response and

Table 1 Univariate analyses – attitudes toward neonatal euthanasia in per cent, by socio-demographic characteristics

	Cases	Rejection	Approval	Chi^2-test
	N	%	%	P-value
Total sample:	1000	**63.6**	**36.4**	-
Sex:				
Male	473	62.8	37.2	0.630
Female	527	64.3	35.7	
Age group:				
16-25 yrs.	124	**76.0**	**24.0**	**<0.001**
25-34 yrs.	170	**70.6**	**29.4**	
35-44 yrs.	189	**70.4**	**29.6**	
45-59 yrs.	244	**57.4**	**42.6**	
60-74 yrs.	216	**58.8**	**41.2**	
75 years or older	57	**38.6**	**61.4**	
Level of education:				
Compulsory school	159	**48.4**	**51.6**	**<0.001**
Apprentice/vocational degree	543	**61.6**	**38.4**	
High school diploma	163	**72.4**	**27.6**	
University	127	**80.3**	**19.7**	
Income:				
1.quintile	208	66.8	33.2	0.690
2.quintile	185	64.3	35.7	
3.quintile	193	63.7	36.3	
4.quintile	203	59.8	40.2	
5.quintile	184	63.8	36.2	
Socio-cultural ideology:				
Conservative	314	63.1	36.9	0.653
Liberal	600	64.6	35.4	
Political orientation:				
Left-wing	222	**67.7**	**32.3**	**0.032**
Centre	521	**66.0**	**34.0**	
Right-wing	144	**55.2**	**44.8**	
Experience with caring for the severely ill:				
Ves	435	64.5	35.5	0.555
No	563	62.7	37.3	
End-of-life care experience:				
Yes	446	**67.6**	**32.4**	**0.020**
No	552	**60.5**	**39.5**	
Marital status:				
Single	219	**71.7**	**28.3**	**<0.001**
Married	529	**64.3**	**35.7**	
Extra-marital cohabitation	123	**67.5**	**32.5**	
Divorced/seperated/widowed	126	**42.9**	**57.1**	
Persons in household:				
Living alone	172	**53.5**	**46.5**	**<0.001**
2 persons	288	**58.7**	**41.3**	
3 or more persons	540	**69.4**	**30.6**	
Number of children:				
No children	708	**60.7**	**39.3**	**0.011**
1 child	137	**67.2**	**32.8**	
2 or more children	155	**72.9**	**27.1**	
Self-rated health:				
Very good	343	67.3	32.7	0.090
Good	445	64.0	36.0	
Moderate-very poor	205	58.0	42.0	

questioned its justification [8-14]. Supporters of NE argue that there are neonates whose suffering cannot be relieved, even when withdrawing the life-sustaining treatment, and for whom there is no hope of improvement. Their central argument is based on the judgment of the neonate's quality of life, arguing that in such cases death would be more humane than a continued life. According to this reasoning, life-ending measures can be acceptable in such cases of unbearable suffering, if conducted under very strict conditions [5].

In Austria, active euthanasia is illegal for anyone, including newborn children. In recent years, we find a recurring public debate supporting either the liberalization of euthanasia for adults or the protection of the legal status quo. During the Nazi period, involuntary euthanasia programs were installed in Austria, directed at both mentally and physically disabled adults but also children [15]. Due to the historical burden, active euthanasia for neonates is a delicate subject in Austria that is neither discussed in public nor by the scientific medical community. Studies investigating the attitude toward NE among health professionals or lay people in Austria are lacking. Admittedly, only a small number of investigations on this topic can be found in international scientific literature. The EURONIC project is an important study conducted among the staff of neonatal intensive care units in several European countries. It presents the opinions of neonatologists and nurses on the diverse legal regulations and their self-reported practices for end-of-life decision-making in 10 different European countries [2,16]. A French group investigating the attitude towards end-oflife decision making for newborns addressed which method of ending a newborn life is more acceptable among the French [17,18]. They came to the conclusion that euthanasia was less accepted than withdrawing or withholding care. They suggested that acceptability was a function of the circumstances.

Very little is known about the general public attitude towards NE; only the two studies presented by Teisseyre et al. [17,18] addressed the public, however, they were not based on representative samples. Therefore, the aim of this paper was to present the prevailing attitude towards NE as well as the factors associated with the respondents' opinionamong arepresentativesampleofthe Austrian population.

Methods

Study design, participants and data collection

The cross-sectional survey about attitudes toward euthanasia was conducted among inhabitants of Austria aged 16 years and older in December 2009. Participants were contacted via computer-assisted telephone interviews (CATI), a telephone surveying technique in which the interviewer is guided by a script provided through a software application. Telephone numbers were sampled from the current electronic telephone directory of Austria using the random-last-digits procedure (RLD). This allowed the inclusion of private and secret telephone numbers as well as of mobile phone numbers that are not listed in publicly available telephone directories. A randomized

Table 2 Results of binary logistic regression analyses: rejection of neonatal euthanasia, by independent variables (n = 805)

	Rejection of neonatal euthanasia			
	Odds ratio	95% CI		P-value
		Lower	Upper	
Sex: male (ref = female)	0.77	0.55	1.06	0.104
Age group (ref = 16–25 years)				**0.021**
25-34 years	**0.49**	**0.25**	**0.98**	**0.044**
35-44 years	0.53	0.26	1.11	0.092
45-59 years	**0.30**	**0.14**	**0.63**	**0.001**
60-74 years	**0.35**	**0.16**	**0.77**	**0.009**
75 years or older	**0.23**	**0.08**	**0.66**	**0.006**
Level of education (ref = compulsory school)				**0.005**
Apprentice training/intermediate vocational degree	**1.64**	**1.03**	**2.62**	**0.036**
High school diploma	**1.86**	**1.05**	**3.31**	**0.034**
University	**3.29**	**1.71**	**6.34**	**<0.001**
End-of-life care experiences (ref = no)	**1.75**	**1.26**	**2.41**	**0.001**
Marital status (ref = single)				**0.048**
Married	0.96	0.54	1.70	0.876
Extra-marital cohabitation	0.70	0.38	1.30	0.254
Divorced/separated/widowed	**0.45**	**0.23**	**0.90**	**0.024**
Persons in household (ref = living alone)				0.087
2 persons	1.08	0.59	1.99	0.793
3 or more persons	1.57	0.88	2.80	0.127
Constant	2.23			0.056
Nagelkerkes R^2		13.9 %		

Variables excluded by backward procedure: income, socio-cultural ideology, political orientation, experience in care of severely ill, number of children in household and self-rated health.

selection and screening procedure based on age, sex, and educational level was used to select interviewees from within contacted households. In order to complete a representative sample of 1,000 interviews 2,413 persons had to be contacted (response rate = 41.4%). This surveywas conductedbythe Institute of Empirical Social Research (IFES, Vienna) on behalf of the Institute of Social Medicine and Epidemiology (Graz).Toensure representativeness of the final sample, IFES constructed a weighting variable based on representative values of the basic socio-demographic characteristics of the Austria population. Persons unable to communicate in German were excluded before starting the interview.

After calling a selected person, verbal informed consent was obtained from all individuals that were able and willing to participate in the study, otherwise calls were discontinued by the interviewer. All information that was entered into the survey was anonymous. Identification based on the provided data was impossible at any time. The Ethics Committee of the Medical University of Graz waived the necessity for ethical approval.

Variables

Age was categorized into 6 different groups: 16–24, 25–34, 35–44, 45–59, 60–74, and 75 years and older. Educational level was divided into the following categories: 'compulsory school' (9 yrs of education), 'apprenticeship/vocational school' (10to12yrs), 'high school diploma' (12to13yrs) and 'university diploma' (15 yrs or more). Moreover, the interview included questions about the respondents' socio-cultural ideology ('conservative', 'liberal')and political orientation ('left-wing', 'center' and 'right-wing'). Additionally, interviewees were asked whether they had any experience in the care of severely ill ('yes', 'no')orany end-of-life care experience ('yes', 'no') and how they would self-rate their health ('very good', 'good', 'moderate', 'poor', 'very poor'). Data on marital status as well as the number of persons and the number of children in the household were also collected.

The problem formulation specifically addressed the highly controversial group of infants included in the Groningen Protocol (with response categories 'in favor', 'against', 'undecided' and 'don't know'). The question about the attitude towards NE was preceded by items concerning attitudes toward euthanasia for terminally ill adults. The wording of the NE item was:

> "And now for another medical situation that refers to the beginning rather than to the end of life: Anew-born child is diagnosed with a serious illness or severe disability, leading to a life expectancy of only a few years in poor quality of life. In this case, are you personally in favor or against the administration of a lethal drug injection at child birth to spare the infant further suffering?"

Answer categories were 'approve', 'disapprove', 'undecided' and 'don't know'. The categories 'undecided' and 'don't know' were both interpreted as 'depending on the circumstances' and were therefore allocated to 'approve' in order to dichotomize the answer categories. To evaluate the attitude towards NE, we classified the answer categories into either 'approve' or 'disapprove, with 'disapprovers being the actual target group of our analysis. A similar approach was taken by Moulton et al. [19] and in a previous analysis performed with data of this survey [20].

Data analysis

Univariate analyses were performed by cross-tabulating attitudes by determinants. Associations were tested using Chi2-tests for independence. Stepwise binary logistic regression was performed in order to determine factors independently associated with the respondents' opinion on NE for severely impaired newborns. All analyses were adjusted for sex and age. Variables with $p > 0.1$ were excluded by backward procedure. We used a threshold value of 0.1 as exclusion criteria, which resulted in maintaining near-significant variables showing p-values between 0.05 and 0.1 in the model. Statistical analysis was carried out using IBM¨ SPSS Statistics 19.0 software for MS Windows¨ and statistical significance was defined as $p \leq 0.05$.

Results

Univariate correlates of attitudes

The final sample of 1,000 persons (aged 16 to 90 years, mean age 46.3 years) comprised 473 men (47.3%) and 527 women (52.7%). 63.6% of all interviewees rejected NE while the other 36.4% ('approvers' by definition) included persons who opted in favor, were undecided, or didn't answer the item (Table 1). No significant difference was found between men and women regarding their rejection rates.

A strong link between the attitude towards NE and age group was observed: the older the interviewee, the higher the approval rates. In addition, the oldest age group (75 years and older) displayed the highest overall percentage of approval (38.6%).

There is also a strong association between the level of education and the attitude towards NE. Rejection rates increased with the level of education, ascending to over 80% among university graduates.

The variable political orientation showed higher rejection rates among politically left-(67.7%) and center-oriented (66%) interviewees than in politically right-wing oriented interviewees (55.2%). By contrast, no association between socio-cultural ideology and attitude towards NE was detected.

Moreover, respondents with end-of-life care experience were more likely to reject NE than those without. In case of experience with the care of severely ill and self-rated health no significant association was found.

An increased number of persons in the household, however, showed to have a significant effect on the opinion about euthanasia. The higher the number of persons in the household, the more likely was a rejection of the practice. This was also observed for the variable number of children, albeit to a lesser extent.

Independent predictors of attitudes

The logistic regression model explained 13.9% of the variance based on the examined variables (Table 2). In regression analysis, the variable age group showed a significant association with the rejection of NE. A lower tendency to reject was observed with increasing age (OR = 0.23, p = 0.006, 75 years and older vs. 16–25 years old). However, no significant gender effect was shown. Much like in univariate analysis, educational level here also turned out to have a great effect on respondents' attitude towards NE. Euthanasia was more frequently rejected by people with a higher educational status (OR = 3.29, $p < 0.001$, university vs. compulsory school). The other socio-economic variable family income was, however, not associated with the rejection of NE. Regression analysis revealed that out of the two variables regarding care experience, end-of-life care experience had a significant association with the attitude towards NE. People with experience in the care of terminally ill were more likely to reject NE than those without this experience (OR = 1.75, p = 0.001). By contrast, experience with the care of severely ill had no independent effect on the rejection of NE and was therefore excluded from the model. The variable marital status only showed a significant effect when comparing single with divorced (OR = 0.45, p = 0.024), thus indicating that divorced or separated persons show lower rejection rates.

Discussion

Overall, 63.6% of the study population rejected the idea of NE for severely impaired newborns while 36.4% opted in favor or were undecided. This percentage stands in sharp contrast with approximately 30% of competent adults who do not agree with VAE, a relationship that we found in a previous analysis of the same survey data [20]. In general, there are two main arguments supporting VAE. First of all, there is the right of patient autonomy and freedom of choice. This right suggests that an autonomous adult with decisional capacity has the right to freely decide about his/her own life or death. The second argument in support of VAE is that of beneficence and individual well-being. If a patient suffers unbearably despite optimal medical care, then one may decide that the burdens outweigh the benefits of living. In the case of NE, however, the first of the two main arguments is not applicable and the second one is controversial. Neonates obviously have no decisional capacity and are unable to express their wishes. Therefore, parents and the staff of neonatal intensive care units must rely on clinical clues and interpret an infant's behaviour in order to assess the severity of their suffering. Moreover, even with apparent suffering is the extent of the infant's suffering, and whether or not it is unbearable, a matter of subjective evaluation [10,21-23]. Our data and the analysis of the same sample by Stronegger et al. [20] show different determinants for the attitudes towards VAE and NE, respectively. Therefore, it can be suggested that the respective attitude might be based on different motivations and considerations.

Furthermore, in the case of VAE it was suggested that cognitive convictions—such as the ideological positioning—might be strong determinants influencing the interviewees' opinion [20]. However, this variable did not have any effect on the interviewees' attitude towards NE, thus hinting to a more emotional reasoning concerning end-of-life decision-making for newborns.

Our analysis confirmed a strongly positive association between a higher educational level and a higher rejection rate of NE among the Austrian population whereas several American [19,24,25] and European [26,27] studies concerning VAE observed a different trend: in these studies a higher educational level was associated with a lower rejection rate. This inverse trend in Austria had already been observed in prior studies [20,28]. We should, however, bear in mind that these studies were focusing on VAE and that it is therefore debatable whether the available data are comparable to our study. A possible approach to explain this relationship might be that persons with a higher educational level are considered to have a better health awareness and a better knowledge of prenatal care. They might, therefore, be more familiar with the early detection of high-risk pregnancies and genetic testing and thus consider NE to be highly avoidable by a more widespread use of prenatal prevention.

One of the factors that consistently correlated with the attitude towards NE was age. The only available cohort study investigating the effect of the age and birth cohort on the attitude towards VAE suggests that people mostly stick to their opinion over life [29]. Thus it can be supposed that age effects observed in cross-sectional studies concerning end-of-life attitudes are primarily birth cohort effects. Our study, however, observed a severe shift in the attitudes of the different age groups. The rejection rate among the youngest age group was twice as high as the rate observed in the oldest age group. This might be due, among other reasons, to the growing emotional value and role children play for their parents today and to the ever-decreasing number of children per family [30].

Some bioethicists have argued that parents could use the Groningen Protocol as a means to escape from the unwanted burden of caring for an impaired child [12]. Our data suggest that end-of-life care experience is positively associated with the rejection of NE. This could be an indication that both an increased willingness to give care and an open mind towards suffering would lead to an increased rejection of NE.

In recent years, the question of legalizing neonatal euthanasia along the lines indicated by the Groningen protocol has been very controversially discussed in the medical ethics literature. Approval and disapproval seem to be almost balanced when referring to the number of expressed opinions. Concerning the general public in Austria, a clear reluctance to accept legalization seems to prevail and it may increase even further. Therefore, if physicians involved in neonatal care would intend to introduce regulations such as the Groningen Protocol, strong and comprehensible arguments would be needed in a first step to gain wider public acceptance.

Conclusion

The present study examined whether the idea of applying euthanasia to severely impaired infants is acceptable among a representative sample of the general Austrian population. The majority judged NE (i.e. the administration of a drug with the purpose of ending a patient's life) as being unacceptable. Our results have shown that age (resp. birth cohort), educational level, and end-of-life care experience are strongly associated with a higher tendency to reject NE. However, given the increasing levels of rejection of NE among the younger generations and among people with a higher educational level, it cannot be precluded that the rejection rate might in future increase even further, rather than decrease.

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Validation Study of the RightSpot Infant pH Indicator for Verification of Feeding Tube Placement in the Neonatal Intensive Care Unit

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Abstract

Background: Improper feeding tube placement in infants is a cause of increased cost and morbidity.[1] The RightSpot infant pH indicator is a device that measures the pH of aspirates from feeding tubes to help determine proper placement. Previous studies have shown that a low pH reading would indicate proper placement of the NG tube in the stomach.[2] A study was necessary to ensure the accuracy and validity of the RightSpot pH indicator.

Objectives: The aim of the study was to validate the accuracy of the RightSpot indicator's pH measurement of gastric aspirates by comparing the results with a standard pH monitor for neonates at different ages and gestations.

Methods: This prospective observational study enrolled 31 subjects from September 2014 to January 2015. Up to eight samples were obtained per subject totaling 240 samples. Infants with congenital anomalies were excluded. Infants who were not feeding, receiving an acidified liquid human milk fortification or medications known to alter the pH of gastric contents were also excluded. Gastric samples were aspirated through the Right Spot indicator and applied to the pH meter prior to the infant's feeding. Readings from the two devices were recorded and compared. Data was collected on gestational age, day of life, length of feeds, residual amount and the type of feeding. Descriptive statistics are provided.

Results: The RightSpot indicator was accurate 100% of the time within a pH of ± 0.5 on 236 samples when compared to the measurements of the same sample taken with the Scientific Instruments pH meter I-12. A pH below 5.9 was noted in all of the 240 samples. In 189 samples a pH below 4.5 was noted. The pH ranged from 0.9 to 5.9 without correlation to age, corrected gestational age, weight, residuals and the time of the last feeding.

Background

Improper feeding tube placement in infants is a cause of increased cost and morbidity in the Neonatal Intensive Care Unit (NICU).[1] Ellett and Beckstrand's study report the rates of feeding tube misplacement in children range from 21.8% to 43.5%.[2] The improper placement of a feeding tube in the respiratory tract can be lethal. In 2005, the Joint Commission in the United States classified the placement of a feeding tube in the trachea or bronchus as a Sentinel Event.[3] Although radiologic methods are considered the gold standard for determining feeding tube placement, the use of radiologic methods can cause harm when used repeatedly in the neonatal population.[1] An assessment device that could decrease the necessity of radiologic methods was needed to help verify correct gastric placement of feeding tubes. Routinely, NICUs require that nasogastric (NG) tube placement is confirmed using both radiologic and non-radiological methods including auscultation, aspiration, and tube measurement. Unfortunately, clinicians remain uncertain about the reliability of bedside methods.[4]

At the study center, Banner - University Medical Center Phoenix, NICU guidelines require NG tube placement is confirmed after initial tube insertion, before every feed, before medication administration and any time tube placement is questioned. Methods of confirming feeding tube placement include auscultation, aspiration, and measurement of the depth of the feeding tube. Auscultation involves instilling a small amount of air in the feeding tube while listening through a stethoscope placed over the stomach. If a "whoosh" is heard, the feeding tube is considered to be placed correctly. Unfortunately this technique is not always reliable as an infant's thin abdominal wall allows sounds to be transmitted to the stomach regardless of whether the feeding tube is placed in the respiratory tract, lung, esophagus, stomach, or intestine.[5,6] A second method of placement confirmation involves the aspiration of a small amount of gastric contents. Misinterpretation can occur as the pulmonary aspirates can be similar to gastric aspirates in coloration. Although The National Patient Safety Agency excluded neonates from their Reducing the Harm Caused by Misplaced Nasogastric Feeding Tube Guidelines, they recommend that observation of the appearance of the aspirate should not be used in infants to verify correct placement of feeding tubes.[7] A third method of tube placement confirmation is the measurement of the depth of the feeding tube. This is accomplished by measuring the distance from the ear to nose to xiphoid process and making note of where the feeding tube lies at the nostril.[8] This process of confirmatory assessment occurs multiple times throughout the day.

Right BioMetrics, has developed the RightSpot infant pH indicator, a device that rapidly verifies gastric pH as the caregiver aspirates contents from a nasogastric (NG) or orogastric (OG) tube. The device has the ability to report pH measurements

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within a 0.5 pH unit with a range of 4.5-7.0. A corresponding color change occurs within the device allowing the caregiver to confirm initial tube placement in the stomach as well as subsequent necessary confirmations. A study was needed to ensure the accuracy and validity of the RightSpot pH indicator in the clinical setting.

Primary Objective

To validate the accuracy of the RightSpot indicator's pH measurement of gastric aspirates by comparing the results with a standard pH monitor for neonates at different ages and gestation.

Secondary Objective

To describe pH values for neonates.

Methods

Eligible patients were identified based on the study's inclusion/exclusion criteria. The objectives and requirements of the study were explained to the parents or legally authorized representatives of the infants. Ample time was given to review and discuss the informed consent. The criteria for enrollment were as follows:

1. Inclusion Criteria
   - Infants in the Newborn Intensive Care Unit with an NG tube in place
2. Exclusion Criteria
   - Infants with congenital or genetic abnormalities
   - Infants with gastroschisis
   - Infants with upper airway abnormalities: Choanal atresia, cleft palate, or tracheal-esophageal fistula
   - Infants receiving any supplement or medication known to alter the pH of gastric contents
   - Infants receiving Enfamil liquid human milk fortification
   - Infants who were NPO status

Prior to the NG tube feedings, gastric aspiration was performed to verify feeding tube placement. The research nurse would place the RightSpot pH indicator device in the opening of the NG tube and aspirate approximately 1 ml of gastric contents. Up to 8 samples were obtained at different scheduled feedings for each subject enrolled. The pH value displayed by the RightSpot pH indicator was visualized and recorded. A sample of the same aspirate was then applied to the clinically approved pH monitor and these results were recorded. Readings from the Right Spot infant pH indicators were compared to the readings from the Scientific Instruments pH meter I-120. The pH meter was calibrated prior to each sample collection.

Permission for usage of the device was received from the FDA as a waiver under the Clinical Laboratory Improvement Amendment (CLIA) of 1988. The study received Institutional Review Board oversight from Banner Health.

Statistics

The data was analyzed to determine the agreement and accuracy of two modes of gastric pH measurement by comparing the readings from a pH indicator to a standard clinically approved monitor. Agreement by intraclass correlation co-efficient (ICC) was obtained to compare the pH readings from the RightSpot indicator and the pH readings from the clinically approved pH monitor. The ICC estimates are presented with 95% confidence intervals (CI). The bias and precision of measurement by the test indicator in comparison to the clinically approved monitor was assessed by the Bland-Altman method. Accuracy was determined by estimating the root mean square of differences.

The data, clustered on the subject, were evaluated per subject to identify variability or demonstrate homogeneity. In the presence of homogeneity, only the first measurement was used. In absence of homogeneity, the data was analyzed with data clustered at the subject level.

Results

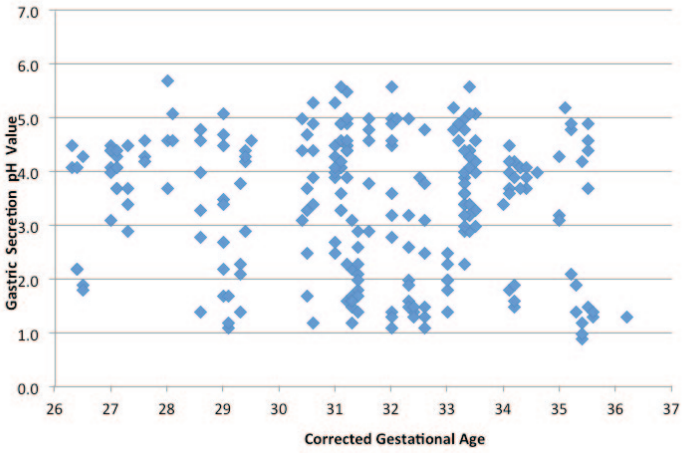
In this prospective observational study 31 subjects were enrolled from September 2014 to January 2015. A total of 240 samples were obtained with 3-8 samples per subject. Mean values for data collection are present in Table 1. The infant's weights were between 705 and 2260 grams with an average weight of 1410 grams at the time of sample collection. The gestational age of the study subjects was between 24 6/7 weeks gestation and 34 0/7 weeks gestation. The adjusted gestational age at the time of sampling was between 26 3/7 days and 36 2/7 days. Samples were obtained from day of life 2 through day of life 67. The average amount time since the last feeding finished prior to obtaining the sample was 2 hours and 15 minutes. Six of the 31 subjects were on liquid protein fortifiers and eight were receiving Neosure powder as a supplement. The mean residual at the time of sample collection was 1.4 ml. NG feeding tubes sizes were 4 and 6 Fr.

The RightSpot Indicator system and the pH meter reported the same gastric pH ± 0.5 on 236 of the samples tested. A pH below 5.9 was noted in all of the 240 samples tested with both methodologies. In 189/240 samples, a pH ≤4.5 was noted by both systems. The ICC between the two testing systems was 0.9714 with a variance of 0.1. Proton pump inhibitors were not administered in the study population. The mean gastric pH obtained from this population was 3.4 with a standard deviation of 1.3 and median of 3.5 using the pH meter. The pH ranged from 0.9 to 5.9 without correlation to age, adjusted gestational age, weight, residuals and the time of the last feeding. Table 2 depicts the pH gastric secretions and the lack of correlation to corrected gestational age.

Table 1. Description of Findings.

# Subjects	31
# of Samples	240
Mean weight at time of sample collection (g)	1410
Mean gestational age at birth in completed weeks	29
Mean adjusted gestational age in completed weeks at time of sample	32
Mean day of life at time of sample	18
Mean residual at time of sample collection (ml)	1.4
Mean time from last feeding to sample collection	2h 15min
Mean gastric pH using pH meter	3.4 ± 1.3
Median gastric pH using pH meter	3.7
Mean gastric pH using RightSpot Indicator	4.6 ± 0.2
Median gastric pH using RightSpot Indicator	4.5
Correlation and Variance	0.9714 and 0.108

Table 2. Adjusted gestational age at time of sample collection in conjunction with gastric secretion pH value.



Discussion

Acidification of the infant's stomach does not appear to be related to age, gestation, corrected gestation, residuals, weight or timing of the last feeding. The RightSpot pH indicator system is a reliable method of determining gastric pH from an indwelling feeding tube and may be used as a reliable component of the process to confirm placement of NG feeding tubes. This device is non-invasive, disposable, non-radiographic and allows for accurate confirmation of feeding tube placement by nursing. The utilization of pH to confirm feeding tube placement can decrease the need for radiologic methods and the use of ancillary hospital professionals. The RightSpot pH indicator may ultimately decrease costs and the delay of infant feeding. The RightSpot device may increase patient safety by preventing prevent mal-positioned feeding tubes and aspiration events.

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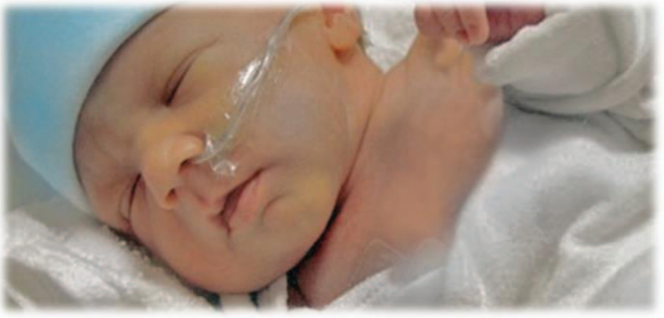

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