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Editorial Advisory Board

Human milk makes all the difference

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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News

Mercury Medical Expands Team

Mercury Enterprises has announced that John Gargaro MD has joined the Corporate Board of Directors and Douglas Smith has joined the company as Vice President of Sales and Marketing. Dr. Gargaro is currently a board certified orthopedic surgeon and graduate of Harvard University and the University of Michigan Medical School. He is currently Chief of the Department of Orthopedic Surgery at Kaiser Permanente Colorado, former Chairman of the Department of Orthopedic Surgery and former Treasurer of the Medical staff at St Joseph Hospital, Denver CO. Industry experience includes consulting positions with Wright Medical and Johnson & Johnson/DePuy, as well as clinical research and speaker panel positions for Sanofi-Synthelabo Inc. and Organon Labs.

Douglas Smith's background includes 20+ years of sales and marketing experience with GE Healthcare, Dräger, Maquet Medical Systems USA and Siemens Medical Solutions USA, Inc. Mercury Medical, a veteran-owned medical products manufacturing and marketing organization, focused on airway management and anesthesia, is recognized by the industry as a leading provider of innovative airway management devices.

Neonatal Resuscitation Protocols

The Helping Babies Breathe neonatal resuscitation protocol significantly reduces early neonatal deaths, according to a study from Nepal. The quality improvement approach includes identifying the barriers for health workers to adhere to neonatal resuscitation, developing an improvement plan to address the barriers as well as formation of quality improvement teams. Over a million babies worldwide die every year within a day of life, the vast majority due to birth-related complications. Resuscitation initiated within the first "golden" minute reduces deaths by 30%, the researchers explain in their paper. To improve neonatal outcomes, the simplified resuscitation protocol has been in place in many resource-poor settings. This involves keeping the baby warm, suctioning the airways, and bag and mask ventilation within the first minute, if required. Despite this, over a third of neonatal deaths in Nepal were due to intrapartum causes, casting doubts about appropriate use of the protocol. Their prospective cohort study evaluated the impact of a quality improvement cycle (QIC) at the tertiary care Paropakar Maternity and Women's Hospital with over 22,000 babies delivered every year. The QIC was designed and planned from July to December 2012 and implemented from January to September 2013. Perinatal mortality, antepartum and intrapartum stillbirths, and first-day neonatal deaths during the two periods were compared. The QIC included a two-day training of all involved, daily bag-and-mask practice on mannequins, self-evaluation after each delivery, peer reviews after every resuscitation and refresher courses. The hospital recorded 9,588 and 15,520 deliveries during the baseline and intervention periods, respectively. Prior to the intervention, the perinatal mortality, intrapartum stillbirths, and first-day neonatal deaths were 30.9, 9.0, and 5.2 per 1,000 births, respectively. The corresponding figures during the intervention period declined to 23.3, 3.2, and 1.9, respectively (p<0.001), the researchers report. In their multiple regression analysis, the risk of intrapartum stillbirths and first-day neonatal deaths declined by 54% and 49% (odds ratio 0.46 and 0.51, respectively) following the intervention. Antepartum stillbirths were unaffected.

Preemies Suffer in Adulthood

By early adulthood, adults who were born prematurely at low birth weights are less likely to be employed and to have children, and more likely to have lower incomes, be single and have chronic health conditions than those born at a healthy weight, according to a new study. The new study continues to follow the first generation of extremely low birth weight babies who survived in the early era of advanced neonatal care. The authors reported their outcomes a decade ago at 24 years of age and at that time they were comparable to (full-term) children, despite the fact that 28 percent had disabilities. Employment and educational parameters were similar. But after the transition to adulthood, there are differences between the groups. The

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Early Inhaled Nitric Oxide and Progression of Hypoxic Respiratory Failure (HRF)

View the webinar on-demand at
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Created by practitioners, for practitioners.
Review various elements of HRF treatment, including:

- Acute HRF in newborns
- The pathophysiology of HRF
- Optimizing oxygenation in HRF
- Evidence for the earlier use of inhaled nitric oxide in the treatment of HRF

Satyan Lakshminrusimha, MD
Chief, Division of Neonatology
Women and Children's
Hospital of Buffalo
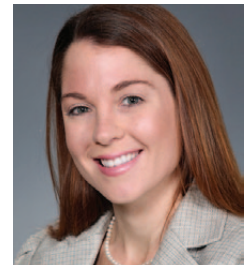
Ashley Darcy Mahoney, PhD, NNP-BC
Neonatal Nurse Practitioner,
South Dade Neonatology
Assistant Professor,
Emory University School of Nursing

Indication

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

Important Safety Information

- INOMAX is contraindicated in the treatment of neonates dependent on right-to-left shunting of blood.
- Abrupt discontinuation of INOMAX may lead to increasing pulmonary artery pressure and worsening oxygenation.
- 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, inspired NO_2, and methemoglobin during INOMAX administration.
- INOMAX must be administered using a calibrated INOmax DS_{IR}® Nitric Oxide Delivery System operated by trained personnel. Only validated ventilator systems should be used in conjunction with INOMAX.

Please see Brief Summary of Prescribing Information on adjacent page.

Mallinckrodt Pharmaceuticals

INOmax® (nitric oxide) GAS, FOR INHALATION

INOmax® (nitric oxide gas)
Brief Summary of Prescribing Information

INDICATIONS AND USAGE

Treatment of Hypoxic Respiratory Failure

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

CONTRAINDICATIONS

INOmax is contraindicated in neonates 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 there is an unexpected change in NO_2 concentration, or if the NO_2 concentration reaches 3 ppm 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.

Worsening 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.

DRUG INTERACTIONS

Nitric Oxide Donor Agents

Nitric oxide donor agents such as prilocaine, sodium nitroprusside and nitroglycerine may increase the risk of developing methemoglobinemia.

OVERDOSAGE

Overdosage with INOmax is 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.

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researchers studied 189 adults born between 1977 and 1982. One hundred had been born prematurely, weighing less than 1 kg, while the other 89 had weighed more than 2.5 kg. All participants completed standardized questionnaires on health, education, employment, social integration, sexuality and reproduction. More than half of each group were women. One in five of those born premature had neurologic impairments. In their mid-20s, the two groups had similar life circumstances and achievement, and at ages 29 to 36, educational achievement and family and partner relationships were still similar - but fewer premature adults were employed or employed full time. On average, the premature group was making $20,000 less per year than the term group. Half of the premature group was never married or single, compared to about a third of the full-term group, and 20 percent had never experienced sexual intercourse compared to 2 percent of the term group. More adults in the premature group also reported being homosexual or bisexual than in the term group, although it's not clear why that would be and the sample of people in this study was relatively small.

Life-saving Treatment Not Given to All Moms

A steroid injection that prevents disability and even death in premature babies is only being administered to half of the mothers who give birth prematurely in hospital. The World Health Organization conducted a study that has been published in The Lancet, from May 2010 to December 2011. It examined the use of antenatal corticosteroids, which cost less than one US dollar each, and reduce the risk of respiratory distress syndrome in premature babies. The use of tocolytic drugs to slow down labour and allow the antenatal corticosteroids to work was also studied. Using data from a WHO Multicountry Survey, 29 countries and over 300,000 births in 359 hospitals were studied. It showed that only 52 percent of women who gave birth at 26-34 weeks' gestation and were eligible for the injection actually received the treatment while in labour. The rate varied between countries as the majority studied were of low-and-middle income. More so, only 18 per cent of women who could receive both the antenatal corticosteroids and tocolytic drugs were actually given them.

Drug Treatment Reduced for Neonates

Use of a stringent protocol to treat neonatal narcotic abstinence syndrome (NAS) reduces the duration of opioid exposure as well as the length of hospital stay, according to a new study. The benefits of a stringent protocol are significant, regardless of the opioid used for treatment. NAS is increasing in prevalence in the US, and yet there is currently no consensus with regard to the best treatment drug or best taper strategy for NAS management. The study advances medical understanding of the "best practice" for NAS management. Eric S. Hall, PhD, from the Prenatal Institute at Cincinnati Children's Hospital in Ohio, and colleagues present the results of their cohort analysis in July 28 article in Pediatrics. The multicenter cohort includes charted data from 547 pharmacologically treated infants and is larger than any other previously published study or meta-analysis. "Our study identified key differences in NAS management strategies that translated into shorter opioid exposures and reduced length of hospital stay. Results indicate that the use of a stringent weaning protocol, rather than the particular opioid chosen for treatment, was the most important predictor of length of hospital stay and duration of opioid treatment," the authors write. "Consistent with previous literature describing improvements in pediatric outcomes through standardization of care, study results suggest that the greatest impact on outcomes is achieved through implementation and adherence to a formalized NAS treatment protocol with agreed-upon starting doses, explicit instruction about dose escalation, and strict weaning parameters," the authors explain. The study included only infants who required opioid therapy (417 managed with an established weaning protocol and 130 managed without an established weaning protocol). After the researchers accounted for hospital variation, infants who received protocol-based weans had a significantly shorter duration of opioid treatment (17.7 vs 32.1 days; $P < .0001$) and shorter hospital stay (22.7 vs 32.1 days; $P = .004$). Among those who received protocol-based weaning, the duration of opioid treatment and length of stay were no different in infants treated with morphine compared with those treated with methadone. When the authors analyzed the data from patients who were treated with phenobarbital, they found a longer duration of phenobarbital administration in patients treated with morphine compared with those treated with methadone ($P \leq .002$).

The protocol-driven wean described in the current study has the advantage of reducing the length of drug treatment.

Neonatal Jaundice and Brain Damage
Early detection of jaundice and immediate treatment can ensure neonatal damage to a baby's brain won't happen. The condition is the result of a yellow substance, bilirubin, which breaks down in the liver and is usually removed from the body via stools. While the fetus grows in the womb, it is fed by the mother's placenta, which is also responsible for removing this bilirubin. Bilirubin is created when the body replenishes the old red blood cells. After birth, the newborn's liver must independently start casting this substance out, a process which can take some time to develop adequately. While there is a high level of bilirubin in the baby's blood, it causes the skin and whites of the baby's eyes to appear yellow. Breastfeeding jaundice is another type of neonatal jaundice commonly seen in the first week of life among breastfed babies. It occurs when the baby does not nurse well, or the mother's milk supply is low. If there are any signs which appear after the newborn goes home, the bilirubin levels should be measured right away. Besides a simple blood test, hospitals today use probes that estimate the bilirubin level by merely touching the baby's skin. A baby with neonatal jaundice must be kept well-hydrated, either with breast milk or formula food. A regular feeding schedule encourages bowel movements, which will help remove bilirubin through the stool. Some newborns diagnosed with jaundice may need to be treated in the hospital for one to two days. Sometimes, the infant will be placed under special blue lights for a treatment called phototherapy. The light helps break down bilirubin in the baby's skin. It is a rare occurrence that a baby has severe neonatal jaundice. This may

occur if there is a phenomenal advancement in the number of red blood cells the body needs to replace. This is a chronic symptom in small-for-gestational-age babies, and sometimes in twins. It may also occur if there is a mismatch in the blood type between the mother and the baby. Very high levels of bilirubin can be toxic to the brain and can lead to complications associated with neonatal jaundice. When the bilirubin gets into the central nervous system, it can lead to a condition called kernicterus. Kernicterus may have begun to develop if the infant begins to exhibit extreme lethargy, changes in muscle tone, and a high-pitched cry. Information in this article was compiled by Nilofar Neemuchwala.

Obese Women Need Medical Help Too
Personal biases and concerns about professional liability are leading some obstetricians to avoid obese patients, putting babies and the moms at greater risk of complications. Dr Sigal Klipstein, chairwoman of the committee on ethics of the American College of Obstetricians and Gynecologists, says it is time for doctors to push aside prejudice and fear. They must take more positive steps to treat obese women who are pregnant or want to become pregnant. Obesity affects 36 percent of women of childbearing age and is linked to a host of difficulties during pregnancy, labor and delivery, including gestational diabetes, hypertension and pre-eclampsia to miscarriage, premature birth, emergency cesarean delivery and stillbirth. The infants of obese women are more likely to have congenital defects, and they are at greater risk of dying at or soon after birth. Babies who survive are more likely to develop hypertension and obesity as adults. A published analysis of 38 studies found that even modest increases in a woman's pre-pregnancy weight raised the risks of fetal death, stillbirth and infant death. Dr Klipstein and her colleagues recently issued a report on ethical issues in caring for obese women. Obesity is commonly viewed as a personal failing that can be prevented or reversed through motivation and willpower. But the facts suggest otherwise. Although some people manage to shed as much as 100 pounds and keep them off without surgery, many obese patients say they've tried everything, and nothing has worked. "Most obese women are not intentionally overeating or eating the wrong foods," Dr Klipstein said. "Obstetricians should address the problem, not abandon patients because they think they're doing something wrong." The committee report emphasizes that "obese patients should not be viewed differently from other patient populations that require additional care or who have increased risks of adverse medical outcomes." Obese patients should be cared for "in a nonjudgmental manner," it says, adding that it is unethical for doctors to refuse care within the scope of their expertise "solely because the patient is obese." Obstetricians should discuss the medical risks associated with obesity with their patients and "avoid blaming the patient for her increased weight," the committee says. Any doctor who feels unable to provide effective care for an obese patient should seek a consultation or refer the woman to another doctor. Obesity rates are highest among women "of lower socioeconomic status," the report notes, and many obese women lack "access to healthy food choices and opportunities for regular exercise that would help them maintain a normal weight."

High-volume Units See Better Results
A new study says that treating preemies in high-volume neonatal hospital units increases survival rates. The British study included babies born before 33 weeks of pregnancy who were admitted for extra care. Full term is considered 39 to 40 weeks. The

analysis confirms results of a 2010 US study led by Dr Judith Chung. For the new study, the researchers analyzed data from 20,554 very premature infants delivered at 165 hospitals with neonatal units across the UK. About 4.5 percent of them died in the hospital. Infants were 32 percent less likely to die if they were admitted to high-volume neonatal units compared to low-volume units, the researchers found. The earliest preemies, those born before 27 weeks of pregnancy, benefited the most from high-volume units. Those babies had half the odds of dying when they were treated in neonatal units that handle a high number of premature births, compared to low-volume units, the study published in BMJ Open found.

Hospital Banks on Donor Milk

The Children's Hospital of Philadelphia (CHOP) announced it will develop a non-profit milk bank to provide donor human milk for hospitalized infants at the Hospital's Main Campus, with the goal of opening in late summer of 2015. CHOP will develop the bank in cooperation with the Human Milk Banking Association of North America, a professional organization that sets the standards and guidelines for non-profit donor milk banking in North America. Once open, it will be one of the only non-profit milk banks located inside a freestanding children's hospital in the United States. At CHOP, more than four out of five infants discharged from the Hospital's intensive care units are receiving human milk. The Hospital has used donor human milk since 2006 for at-risk infants to supplement a mother's own milk supply if it is insufficient or if the mother is unable to provide milk for her infant. This milk is ordered from an HMBANA-certified milk bank, where it is processed and pasteurized in accordance with stringent safety guidelines, and then shipped to CHOP. There

are 17 association milk banks throughout the US and Canada. At CHOP, many mothers choose to become human milk donors and CHOP facilitates the donation process in partnership with a HMBANA milk bank. In order to become a HMBANA donor, the mother must meet strict donor criteria to ensure that she is healthy and the milk is safe. Donors must complete a medical history and lifestyle questionnaire and obtain the approval of their healthcare provider prior to donating milk, as well as have a blood test to screen for diseases including HIV, hepatitis B and syphilis. HMBANA-approved donors are volunteers and are uncompensated. These same guidelines will be followed in the future; however, the process will be completed at CHOP and the donated milk will be pasteurized and processed for CHOP's inpatient infant population.

Optimal Oxygen Levels Unclear

It remains uncertain whether to use lower or higher oxygen levels for resuscitating infants born at or before 28 weeks of gestation, according to a recent meta-analysis. Researchers say they found no apparent differences in the overall risk of death or other common preterm morbidities in infants randomized to either 0.3 or less or 0.6 or more fraction of inspired oxygen (FiO2). However, Dr Ju Lee Oei of the Royal Hospital for Women in Randwick, Australia, and colleagues caution that the mixed study designs and analyses used in the selected studies "emphasize the need for more data" before definitive recommendations can be made. "Pure (100%) oxygen has been an integral component of newborn resuscitation for decades, but air (21% oxygen) is now used to resuscitate full-term or near-term babies due to a risk of oxidative injury and stress with 100% oxygen," Dr Oei said. "Very preterm babies, however, are physiologically very different to full-term babies. Many have immature lungs and will continue to need some amount of supplemental oxygen after birth," she explained. In the absence of guidelines, "clinicians now overwhelmingly favor using less (under 30%) oxygen, even air, to resuscitate preterm babies." For their analysis, the researchers reviewed information on randomized controlled trials reported in multiple databases and meeting abstracts over the past 25 years. They included 504 infants from eight randomized studies (low oxygen=251, high oxygen=253) conducted between 2005 and 2014. The team found no significant differences between the groups in the relative risk of bronchopulmonary dysplasia (0.88), intraventricular hemorrhage (0.81), retinopathy of prematurity (0.82), patent ductus arteriosus (0.95), necrotizing enterocolitis (1.61), and overall mortality (0.99). However, they noted that "the overall estimates of effect have wide confidence intervals, which are consistent with substantial benefit or harm."

Placentas Get a Bad Rap

Scientists at the UCSF Medical Center in San Francisco are studying placentas in an effort to unlock more potential benefits. The placenta is a disk of tissue attached to the uterine lining on one side and to the umbilical cord on the other, which grows from the embryo's cells, not the mother's. It is sometimes called the afterbirth: It comes out after the baby is born, usually weighing about a pound, or a sixth of the baby's weight. It provides oxygen, nourishment and waste disposal, doing the job of the lungs, liver, kidneys and other organs until the fetal ones kick in. Dr Susan Fisher, a professor of obstetrics, gynecology and reproductive sciences, and other researchers have studied the placenta for decades, but she said: "Compared to what we should know, we know almost nothing. It's a place where I think we could make real medical breakthroughs that I think would be

of enormous importance to women and children and families." The National Institute of Child Health and Human Development the placenta "the least understood human organ and arguably one of the more important, not only for the health of a woman and her fetus during pregnancy, but also for the lifelong health of both." In May, the institute gathered about 70 scientists at its first conference devoted to the placenta, in hopes of starting a human placenta project, with the goal of finding ways to detect abnormalities in the organ earlier, and treat or prevent them.

Baseline renal parameters may useful in predicting the risk for preeclampsia among pregnant women, according to a study. The findings suggest that a creatinine of 0.75 mg/dL or greater and a urine protein-to-creatinine ratio [UPCR] 0.12 or greater are associated with adverse pregnancy outcomes in women with chronic hypertension, much lower cutoffs than previously used. The researchers retrospectively evaluated data from pregnant women (singleton gestation) seen for prenatal care from January 1, 2000, to June 1, 2014. Included women had a history of chronic hypertension, received prenatal care before 20 weeks of gestation, and had a baseline UPCR and serum creatinine measurement before 20 completed weeks of gestation. The primary outcome was the development of preeclampsia at less than 34 weeks' gestation; secondary outcomes evaluated were the development of severe preeclampsia at any gestational age, any preeclampsia, small for gestational age, preterm birth at less than 35 weeks' gestation, and composite perinatal outcome including perinatal death, neonatal seizures, assisted ventilation, arterial cord pH lower than 7, and 5-minute Apgar score of 3 or lower. The researchers included data on 755 women and set the cutoffs for severe preeclampsia at 0.12 or higher for

UPCR and 0.75 mg/dL or higher for serum creatinine, noting that these thresholds are much lower than typically considered abnormal. Using these cutoffs, the researchers found that the area under the receiver operating characteristic curve for severe preeclampsia at less than 34 weeks was 0.74 (95% confidence interval [CI], 0.7 - 0.8) for the UPCR and 0.67 (95% CI, 0.6 - 0.8) for serum creatinine. Overall, with respect to proteinuria, the study authors found that a UPCR of 0.12 or higher translated to a sevenfold increase in the risk for severe preeclampsia at less than 34 weeks' gestation compared with in women with normal UPCR values (16.4% vs 2.6%; adjusted odds ratio [OR], 7.5; 95% CI, 3.9 - 14.6). In addition, the researchers note that women with a serum creatinine level of 0.75 mg/dL or higher were three times more likely to develop severe preeclampsia at less than 34 weeks' gestation compared with women with serum creatinine values within the normal reference range (15.7% vs 4.6%, respectively; adjusted OR, 3.5; 95% CI, 1.9 - 6.3). Of note, severe preeclampsia at less than 34 weeks' gestation was only found in 1.6% of patients when both baseline renal function tests were below the cutoffs. Secondary outcomes such as the development of mild preeclampsia and severe preeclampsia at any gestational age were also increased among women with UPCR and serum creatinine levels above the threshold. A baseline UPCR above the cutoff was also associated with an increased risk for preterm birth at less than 35 weeks' of gestation (31.8% vs 16.4%; adjusted OR, 2.4; 95% CI, 1.6 - 3.5). The results for neonatal composite and small for gestational age, in contrast, were not significantly different between groups. The study authors suggest that the utility of baseline renal values in pregnant women with chronic hypertension has been questioned because reference ranges used to assess renal impairment have been based on data from

healthy, nonpregnant women, in whom these cutoffs would still be considered within the normal reference range.

Untreated Depression and Pregnancy

Untreated depression during pregnancy is associated with an increased risk for preterm birth and low birth weight — two of the leading causes of mortality and morbidity in infants — results of a new meta-analysis suggest. "Although this does not mean that treating depression with antidepressants will reduce these risks, this is an important piece of information for clinicians and women to take into account in the decision-making process around management of depression," said lead author Alexander Jarde, PhD, postdoctoral fellow, Department of Obstetrics and Gynecology, McMaster University, Hamilton, Ontario, Canada. The analysis showed that the odds of preterm birth reported in studies by authors receiving support from pharmaceutical companies were significantly higher than the odds reported in studies by authors who did not receive such support. Researchers performed an exhaustive literature search for randomized and nonrandomized studies reporting adverse neonatal outcomes in pregnant women with untreated depression in comparison with pregnant women without depression. Studies assessed depression using either a clinical interview/diagnosis or a screening tool or scale.

NANN PREVIEW

Accriva Diagnostics

Booth 112

What products do you plan to exhibit at NANN?

Accriva Diagnostics will be featuring our Tenderfoot line of infant heel incision devices ranging from Micro-Preemie to Toddler sizes. For over 25 years, the Tenderfoot has been the gold standard in the industry and is the only heel incision device made in America. We take pride in our quality systems that are overseen by a team of highly skilled engineers to ensure that we provide a premium product.

What's new this year? Tell us about your latest products or future plans.

None compare to the Tenderfoot's patented Softsweep™ technology. As the originator of heel incision devices, many have tried to replicate our proprietary technology, but cannot achieve the same results. When used as intended, the 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 when compared with traditional lancet devices.

Why should our readers stop by your display?

At this year's NANN we will be introducing the Tenderfoot Educational Kit that can be ordered to help train and educate your neonatal nursing team. Kits can be ordered by visiting www.TenderfootCares.com or by stopping by our NANN booth.

The Tenderfoot Educational Kits will include:
- Sample devices for hands-on training
- Newborn-sized foam foot
- Instructional video
- White paper on proper newborn blood collection

Accriva Diagnostics manufactures a range of products to help support our Neonatal Caregivers. Visit us to learn about our Hemochron line of products for ECMO centers, and our Avoximeter 4000 instrument for monitoring MetHb in infants.

CODAN

Booth 220

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.
- Preassembled Systems Save Precious Setup Time
- 0.2 and 1.2 Micron Air Eliminating Filters
- Needlefree Adapters
- 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, call (800) 332-6326 or visit www.codanuscorp.com.

Draeger

Booth 404

What products do you plan to exhibit at NANN?

Jaundice management, incubators.

What's new this year? Tell us about your latest products or future plans.

Dräger will redefine neonatal care with the launch of its new technology for optimal thermoregulation and developmental care for neonates.

Why should our readers stop by your display?

Visitors will be able to experience hands on the latest innovation in thermoregulation technology in more than 10 years.

NeoMagic®

A family of Neo Medical Inc.

MST Introducer Kits

At Neo Medical, we know that vascular access starts with the right introducer. To compliment our catheters, we now offer a series of introducers designed just for small patients. The Neo Magic MST Introducer Kit has eliminated the need for multiple restarts and multiple introducers in more than 7200 cases. Allowing for placement of 1.9/2.0 Fr catheters in preemie and even a micro-preemie of 520grams on the first attempt. This proven technology can nearly eliminate the need to consider using less than optimum sized micro PICC lines (1.2Fr or 1.1Fr)

CALL (888)450-3334   www.NeoMedicalinc.com

NeoMed

Booth 335

What products do you plan to exhibit at NANN?
NeoMed will display our complete NeoConnect family of ENFit enteral and pharmacy products, as well as our legacy Enteral Safety products. NeoMed is known for innovative designs that support the specialized feeding and medication dosing needs of the low birth weight, neonatal and pediatric patient. Our innovative ENFit syringe designs, including our low dose syringe tip, have received FDA 510(k) clearance for both enteral and oral administration. We are committed to improve patient outcomes through product designs that meet safety, clinical, and regulatory guidelines while supporting cost containment objectives and minimizing process disruption.

What's new this year? Tell us about your latest products or future plans.
Design, development, and launch of our ENFit products have dominated NeoMed's new product portfolio this year. Our new NeoConnect pharmacy and enteral products support best clinical practices as outlined by leading organizations such as GEDSA, ISMP and ASPEN. In fact, NeoMed offers solutions that allow facilities to adhere to the GEDSA Position Statements, ISMP Medication Safety Alerts, The Joint Commission Sentinel Alert (August 2014), cleanability concerns raised by ASPEN, and medication dosing accuracy concerns raised by various Children's Hospitals. Innovative features include open hub designs to help eliminate fluid accumulation while allowing easy cleaning with our NeoConnect Cleaning Tool, and plugged closures that help reduce bacterial accumulation. The NeoConnect Low Dose Tip syringes provide accurate dosing of both enteral and oral medications, pharmacy adapter caps are designed for rapid-fill, and our NeoSecure "click to close" self-righting tip caps support aseptic technique. In addition, we have released a family of EBM collection products and trophic/colostrum feeding kits.

What educational or training materials will be available?
NeoMed continues our tradition of sponsored clinical education for NANN Attendees. Our online ENFit training modules, complete with competency quizzes, will support education and training initiatives emphasizing the clinical considerations and protocol impacts associated with ENFit transition.

Why should our readers stop by your display?
Stop by Booth 335 to see how NeoMed products and our Customer Loyalty Program can support your transition to ENFit.

Owen Mumford

Booth 316

What products do you plan to exhibit at NANN?
- Unistik TinyTouch Heelstick – Preemie .85mmx1.75mm
- Unistik TinyTouch Heelstick – Full Term 1.00mmx2.50mm
- Unistik TinyTouch Individually Packaged Heelsticks – Preemie .85mmx1.75mm
- Unistik TinyTouch Individually Packaged Heelsticks – Full Term 1.00mmx2.50mm
- Unistik TinyTouch Safety Lancets – Low Flow Glucose Testing 18G
- Unistik 3 Safety Lancets – Gentle 30G

- Unistik 3 Safety Lancets – Comfort 28G
- Unistik 3 Safety Lancets – Normal 23G
- Unistik 3 Safety Lancets – Extra 21G
- Unistik 3 Safety Lancets – Dual 18G
- Unistik Touch – Contact Activated Safety Lancets – 30Gx1.5mm, Lowest Flow
- Unistik Touch – Contact Activated Safety Lancets – 28Gx1.8mm, Low Flow
- Unistik Touch – Contact Activated Safety Lancets – 23Gx2.0mm, Medium Flow
- Unistik Touch – Contact Activated Safety Lancets – 21Gx2.0mm, High Flow

What's new the year? Tell us about your latest products or future plans.
Unistik TinyTouch 18G single-use safety lancets for low flow glucose testing launched this year. This product features Comfort Zone Technology®, comprised of eight raised pressure points, which work to send a signal of comfort to the brain, helping to eliminate the pain associated with the blood sampling. New individually packaged Unistik TinyTouch devices feature lot and expiry information with each device, providing the ultimate traceability. These are available in 25 count quantities.

What educational or training material will be available?
Sell sheets, IFU's, brochures, free product samples.

Tell us about any speakers or in-booth promotions?
Visit our booth for a free water bottle! Come learn about our free cost savings analysis or how to set-up product trials and evaluations.

Why should our readers stop by your display?
When it comes to capillary sampling, Unistik products combine enhanced quality of care with significant cost savings opportunities versus other national brands. Supporting the needs of healthcare professionals and patients is what Owen Mumford is all about—making a world of difference to a world of people.

Prolacta Bioscience Inc.

Booth 414

What products do you plan to exhibit at NANN?
Prolacta Bioscience® is the first and only company to offer hospitals a complete line of neonatal nutritional products made exclusively from donor breast milk to meet the nutritional needs of the most fragile, critically ill infants in the NICU:
- **Nutritional & Caloric Human Milk Fortifiers**
  Prolact+ H²MF® Human Milk Fortifier the first and only nutritional fortifier made from 100 percent donor breast milk instead of cow milk. It is designed to help meet the nutritional needs of extremely preterm infants. It is available in 24, 26, 28, and 30 Cal/fl oz.

  Prolact CR® is the first and only Human Milk Caloric Fortifier. It is a pasteurized formulation of human milk cream derived from donor milk that increases the caloric content of mom's or donor to achieve a 20 Cal/fl oz solution.

- **Premature Infant Formula**
  Prolact RTF™ is the first and only Human Milk-Based Premature Infant Formula. When mom's or donor milk is unavailable, it delivers standardized caloric content of 24,

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1.9 Fr Extended Dwell PIV
Extended Dwell Peripheral
Intravenous Catheter (PIV)

The Extended Dwell PIV is offered in a 6-8 cm lenth catheter.

Allowed for use up to 29 days it is designed to eliminate the use of PIV's in the neonatal setting and improve the outcomes of many therapies where a PICC line is not necessary. It is the perfect alternative to traditional peripheral intravenous catheters for neonatal and pediatric patients.

The length and softness of the catheter material contribute to its use for greater dwell times in patients with fragile veins/skin, or difficult peripheral access.

The catheter is inserted using the appropriate introducer of your choice. Choose from an OTN introducer or MST introduction method.

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26, or 28 Cal/fl oz. It is the first preemie infant formula made from human milk as opposed to cow milk.

- **Donor human milk**
  Prolact HM® is the first and only protein- and calorie-standardized Donor Human Milk product. When mother's own milk is unavailable, it delivers a standardized minimum of 20 Cal/fl oz. and an average of 1.1 grams of protein per 100ml, so neonatologists can ensure the nutritional content of each feeding.

  PremieLact® is calorie-standardized Donor Human Milk for trophic feeds.

What's new this year? Tell us about your latest products or future plans.

Prolacta Bioscience is dedicated to Advancing the Science of Human Milk® and continues to make significant investments in research and development, clinical studies and world-class manufacturing facilities for its Neonatal Nutritional Products to bring the healing power of breast milk to the most fragile preemies.

What educational or training materials will be available?

At the request of many hospitals, Prolacta provides a series of brochures to assist hospitals with their educational initiatives on the importance of human milk nutrition for babies in the NICU. The series of brochures, which are also available in Spanish, facilitates the hospital education programs on topics such as, Premature Babies. What to Expect in the NICU; Nutrition for Premature Babies; 100% Human Milk Nutrition. The Best Nutrition; What is Necrotizing Enterocolitis?

Tell us about any speakers or in-booth promotions.

Prolacta Bioscience will be sponsoring a breakfast symposium on Sunday, October 29th on "Compelling Evidence for Nursing Advocates for and Exclusive Human Milk Diet (EHMD) in the NICU". This symposium will cover:

Immunological Benefits of Human Milk. The beneficial role of human milk in neonatal immune system development will be discussed in detail. Speaker: Neonatal Nurse Practitioner

Preterm Nutrition. Recommendations for optimal human milk-based human milk fortification will be discussed in detail. Speaker: NICU RD

Clinical and economic outcomes in the use of an EHMD for ≤1250 g birthweight infants will be reviewed and discussed. Speaker: Neonatologist

Dual perspective on the importance of human milk nutrition in the NICU and the importance of advocacy. Speaker Neonatal Nurse and Parent of Preemie

Why should our readers stop by our display?

PeekabooICU will be at the Prolacta booth to showcase their new iPhone NICU Preemie Parent app. This new informative and engaging application provides comprehensive, customizable features designed to empower parents throughout the NICU journey. PeekabooICU acknowledges the support of Prolacta Bioscience for this unique new resource. PeekabooICU is perhaps best known to date for their unique NICU Journey Bead program, in which parents collect developmental milestone

beads symbolic of their baby's unique story in a tangible, therapeutic way.

There is mounting clinical evidence supporting the improved outcomes of an exclusive human milk diet for extremely premature infants. Visit the booth to obtain copies of the many published studies on human milk nutrition.

As the pioneer in human milk-based nutritional products, Prolacta has built the only state-of-the-art, pharmaceutical-grade manufacturing facility for human breast milk products. Visit the booth to learn more and to find out how you can sign-up for an in-person facility tour in California.

Standards and Practices for Human Milk Products

In this feature, Neonatal Intensive Care interviews clinicians and healthcare providers about the actual application of specific products and therapies. This interview is with Terry S Johnson, APN, NNP-BC, MN.

Neonatal Intensive Care: What are the current practices in preparing and mixing human milk products for use in the NICU?
Terry S Johnson: The American Academy of Pediatrics (AAP) in its 2012 Policy on Breastfeeding and Use of Human Milk recommendation said that the benefits of human milk "are such that all preterm infants should receive human milk" and that "the potent benefits of human milk, mother's own milk, fresh or frozen, should be the primary diet." If a mother's own milk is "unavailable despite significant lactation support, pasteurized donor milk should be used." The AAP "supports the use of banked human milk as the 'first alternative' to mother's milk."

(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)

The profound nutritional needs for growth and development of the premature infant require the fortification of mother's own milk or donor human milk. The AAP recommends human milk "should be fortified appropriately for the infant born weighing less than 1.5 kg."

(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)

Current practice is often different from current recommendations. Many NICU's are "playing catchup" to the AAPs recommendations for human milk feeding. This is most frequently because of a lack of physical space and personnel. This can result in potential risk of bacterial contamination, human milk loss or wastage, and safety issues with misconnections.

Variation in clinical practice is also due to the rapidly evolving human milk usage in this population. Prolacta Bioscience is committed to advancing the science of human milk and its clinical usage in the NICU patient. This commitment extends beyond the quality taken in human milk product development, manufacturing, and safety to tools to facilitate best practices by clinicians using human milk.

NIC: Is there any standardization of practice that you observe?
TJ: I have observed incredible efforts on the part of NICU's

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and nursing and dietary staff to adhere to the "Guidelines for Infant Feedings: Guidelines for Preparation of Human Milk and Formula in Health Care Facilities, second edition. American Dietetic Association, 2011." This publication provides current criteria to ensure both the safe administration of human milk and human milk split-products and to preserve the integrity and nutritional and immunologic value of human milk.

NIC: Are there new practices being introduced to enhance patient safety?
TJ: Patient safety is the number one priority when your patient population weighs less than 1500 grams and may be only 24 weeks gestational age. As NICU clinicians, we must be diligent in utilizing best practices with this vulnerable population. There are three important areas to ensure patient and product safety in the use of human milk in the NICU. The first has to do with the safety, quality, and integrity with which a mother's own milk and donor human milk are collected, maintained, screened, and handled prior to feeding. The second is in regards to tubing misconnections (see below). The third is the recent undertaking by the Academy of Nutrition and Dietetics (AND) to initiate an update of the "Guidelines for Infant Feedings: Guidelines for Preparation of Human Milk and Formula in Health Care Facilities." This is currently underway.

NIC: Can you tell me about some of the concerns with the current practices in mixing and administration of human milk products in the NICU?
TJ: The clinical concerns with current practices is more related to the dramatic increased use of human milk in the NICU and a mismatch in space and personnel. Human milk utilization requires space, specialized equipment, and specific training of personnel to ensure its safe usage. Many NICU's do not have the availability of a "designated milk room or lab or preparation area." This necessitates the handling and mixing of human milk at the bedside and this is problematic. The NICU bedside is a high-traffic zone with multiple personnel and equipment moving through it continuously. In NICU's it is not uncommon that the bedside nurse will be trying to thaw, fortify, aliquot, and set up delivery of the milk in this limited space. Even with best of intents the risk for less than ideal aseptic handling of this milk, which is also a biologic fluid, can be compromised. Human milk is subjected to freezing, thawing, mixing, refrigeration and delivery times which increase the risk of bacterial growth. We are looking forward to innovations that have the potential to lessen the risk of introduction of environmental bacteria into the milk.

NIC: We hear that Prolacta Bioscience is introducing a transfer lid in the near future that may address concerns about the risk of introduction of environmental bacterial into milk. Can you tell us about it?

TJ: Yes, Prolacta is currently conducting research and testing on an ancillary device for use specifically with its human milk products. The project evolved out of Prolacta Bioscience's concern and commitment to patient safety. Beginning in 2006, JCAHO identified safety concerns regarding tubing issues, including misconnections. This led to the International Organization for Standardization (ISO) release of ISO 80369-1:2010 in 2010, small bore connectors for liquids and gases in healthcare applications. ISO specified the intent for general requirements for small-bore connectors which were "used in medical devices or accessories intended for use with a patient" out of concern for real or potential risk of patient injury to death. Following on the ISO, in 2013 the Global Enteral Device Manufacturer Organization (GEDSA) was formed in 2010 to help introduce enteral feeding ISO standards and enhance patient safety. The formation of GEDSA was timely as The Joint Commission (JCAHO) released Sentinel Event Alert 53, Managing Risk During Transition to New ISO Tubing Connector Standards, in 2014. A sentinel event is an "unexpected occurrence that involves death or serious injury to patients". It is forwarded to all health care facilities, published in The Joint Commission newsletter, website, and materials, and is released to public media. A sentinel event requires immediate investigation, response from health care systems and is assessed on site visits to health care facilities.

NIC: How would a NICU and/or a NICU healthcare professional find value in using a transfer lid?

TJ: The transfer lid is a starting point of the evolving process in managing safe and aseptic enteral feeding administration. Overburdened nurses and milk techs in the NICU already manage multiple priorities. Limited numbers of NICUs have a separate milk processing/handling area for human milk storage and preparation. In most units, human milk is handled at the local bedside or in a common, multi-use area. Knowing that this is the state of practice, the use of transfer lids promotes aseptic maintenance of bottles and containers that are used in these multiple use areas. Using the transfer lid eliminates the practice of inserting multiple syringes into the bottle of human milk which can lead to the increased risk of contamination. The sterile and ready to use transfer lid reduces product exposure to the environment, especially due to the number of times the bottle is opened and accessed for dosing the human milk.

NIC: What impact do you see this having on feeds in the NICU?

TJ: First, and foremost is the reduction in risk of environmental contamination of human milk from limited contact from multiple syringe insertions or touch contamination from syringes sitting on a counter then being inserted in the milk. Secondly, the requirement of a feeding system that eliminates the potential for a misconnection between an enteral feeding line and another line such as an IV or vascular access or monitoring line is set for the state of California this year.

Terry's clinical experience has included the NICU, Special Care and Normal Newborn Nursery, as well as Developmental Followup Services.

A nationally known speaker and educator, Terry was the 2009 recipient of the Braden E. Griffin M.D. Memorial Lectureship Award from the University of Massachusetts Medical School. She was a 2007 fellow in the Patient Safety Leadership Fellowship Program through the Health Research and Educational Trust and the American Hospital Association. Terry was the 2006 recipient of the National Association of Neonatal Nurses SIG (Special Interest Group) Leadership Award. She also served on AWHONN's Advisory Committee for Care of the Late Preterm Infant.

How to Incorporate a New Safe Sleep Program in the NICU

In this feature, Neonatal Intensive Care interviews clinicians and healthcare providers about the actual application of specific products and therapies. This interview is with Debra Lewis, BSN, RNC-NIC, Staff Nurse, NICU, Baptist Health Lexington (KY).

Neonatal Intensive Care: When did you introduce the HALO® Safer Way to Sleep program in the NICU?
Debra Lewis: We have been using this program for about three years in the NICU.

NIC: What inspired you to incorporate a new safe sleep program?
DL: I attended a national neonatal nursing conference where safe sleep practices were addressed. I also met the HALO representative and learned about the tools they make available to hospitals at no cost. This information inspired me to re-examine the safe sleep practices in our own hospital's NICU. In addition, my colleague who helped me spearhead the program lost her own baby to SIDS, so safe sleep is a topic that is very important and, of course, personal to us.

NIC: How did you go about evaluating your current safe sleep practices?
DL: Working with the support of our neonatologists, the nurse researcher and our Institutional Review Board (IRB), we did an assessment of our nurses' safe sleep behaviors to compare to the recommended practices. As we know well that what nurses do in the hospital is often modeled or imitated by the parents. It is critically important that the way our nurses handle the preemies meets the highest standards of safe sleep. Our research revealed that the nurses were not always putting the babies in cribs as the American Academy of Pediatrics recommended, particularly when we used blankets for swaddling.

NIC: How did you re-educate your staff?
DL: We created a self-learning module for all the NICU and Mother Baby nurses to ensure their safe sleep knowledge was up-to-date. Unbeknownst to the nurses, we continued our assessment at the one-month, three-month and six-month marks to ensure that everyone was maintaining the highest level of safe sleep practices, and we were thrilled to have positive results every time. After discovering our biggest area of concern was the bundling of infants, we began using HALO® SleepSack® Swaddles in the NICU, an initiative supported by administration and the medical staff.

NIC: What kind of support did you have from the neonatologists on staff?
DL: The doctors in the NICU were very much in favor of the research, and after seeing our data they supported the

introduction of the Safer Way to Sleep program as a way for the nurses to practice and teach safe sleep. As a matter of fact, the neonatologists personally covered the shipping costs for the HALO SleepSack Swaddles (which are free to all hospitals).

NIC: What has been the response from parents?
DL: Parents are very interested in learning about safe sleep for their baby, and we make a point of reviewing this with them before discharge. Since many of the parents of preemies have their baby shower after the baby is born, we suggest that they add wearable blankets to their registry. Our hospital also added the HALO SleepSack Swaddle to the gift shop to facilitate this as well.

NIC: Do you ever interact with grandparents on safe sleep?
DL: Since our babies may be in the NICU for an extended period

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we welcome grandparent visits if supported by the parents. Our staff reviews safe sleep with them as well as well as the parents as they may provide childcare services at some point for the baby. Even an occasional sleepover at the grandparents' home requires safe sleep practices.

NIC: How do you feel personally about this new program?

DL: After a career of more than 40 years, I can honestly say that doing the research and initiating the HALO® Safer Way to Sleep program has been an inspiration. The support of the hospital for research that leads us to be better in our profession and have a positive effect on the patient experience and safety is always a win-win for all.

The Benefits of a Laryngeal Mask Airway Over Endotracheal Intubation for Surfactant Delivery

Chris Campbell

When it comes to any type of treatment—every step should be taken to ensure the cure doesn't do more harm than good. Some treatments are effective in achieving the goal intended, but are so hard on the human body that they can cause long-term damage. Case in point—surfactant therapy, an effective treatment to increase the ability of the lung to inflate. But the way surfactant is delivered can have a negative impact on a patient, especially when it comes to the most fragile patients a hospital can treat—neonates. According to a study by the Department of Pediatrics at the Albany Medical College, the risks of "chronic lung disease" are increased for neonates if mechanical ventilation is required during the administration of surfactant due to "protracted respiratory depression."

So the AMC team of Pinheiro et al set out to study two methods of delivering surfactant—the standard approach of intubation-surfactant-rapid extubation, or INSURE, via endotracheal tube (ETT) versus the laryngeal mask airway (LMA).

The goal was to "evaluate whether surfactant therapy delivered through an LMA in moderately preterm neonates with mild-to-moderate respiratory distress syndrome (RDS) can effectively replace an INSURE approach while decreasing the need for subsequent mechanical ventilation."

Surfactant Delivery

While surfactant improves oxygenation and reduces the need for mechanical ventilation, the AMC study describes the tricky situation in delivering the therapy to neonates: "Tracheal intubation with positive pressure ventilation (PPV) is the approved method of surfactant delivery…However, intubation induces pain and physiological instability in neonates, leading to hypoxemia and bradycardia while increasing systemic and intracranial pressures.[4-6] Premedication to minimize pain and stress of neonatal intubation is recommended by the American Academy of Pediatrics and Canadian Paediatric Society,[7,8] as available evidence suggests that it may increase procedural effectiveness and safety relative to unmedicated intubations.[9-12] Premedication with morphine and atropine was used routinely in the Albany Medical Center neonatal intensive-care unit (NICU) for elective intubations, including those performed for rescue surfactant. However, protracted respiratory depression may necessitate mechanical ventilation, which increases the risk of chronic lung disease.[1,2] Indeed, administering surfactant while minimizing exposure to invasive ventilation is the rationale

underlying the INSURE (intubation-surfactant-rapid extubation) approach to surfactant therapy."[13,14]

However, the authors added that the INSURE strategy can "reduce the need for intubation and mechanical ventilation,[13] but it still requires laryngoscopy and transient tracheal intubation, using either an ETT,[13,30,31] a feeding catheter[32] or a vascular catheter."[33,34]

The authors warned that the use of an ETT "may have immediate and persistent adverse effects." The LMA approach is a "supraglottic, minimally invasive device that can support short-term ventilation in adults, children or neonates,[15] avoiding some undesirable effects of endotracheal intubation. LMAs are easily inserted with minimal training, resulting in less misplacement and failure of ventilation than intubation.[16] The LMA is an effective airway for neonatal resuscitation,[3] but it has also been used to administer surfactant. Recent studies including case-reports and pilot trials on preterm neonates[15,17-20] and data from a piglet model of RDS[21] suggest that the LMA might be useful for minimally invasive surfactant administration, although its effectiveness relative to tracheal intubation remains unknown."[22]

Designing The Study

The AMC team put these two approaches to the test between 2010 and 2012 at the Albany Medical Center NICU. Over 32 months of enrollment, 146 patients were assessed for eligibility, and 61 were randomized. The study authors noted that this is the "first to directly compare surfactant delivery via an LMA to traditional administration through an ETT, demonstrating that both methods produce similar acute physiologic improvement."

The study is also unique "addressing the practical question of whether surfactant delivered via LMA produces similar effects to a contemporary INSURE strategy on both FiO2 and short-term clinical outcomes."

According to the study authors, "moderately preterm infants diagnosed with RDS, receiving nasal continuous positive airway pressure with FiO2 0.30 to 0.60, were randomized to two groups at age 3 to 48 h. Those in the ETT group were intubated following premedication with atropine and morphine, whereas the LMA group received only atropine. Both groups received calfactant before a planned reinstitution of nasal continuous positive airway pressure, and had equivalent pre-specified criteria for subsequent mechanical ventilation and surfactant retreatment. The primary outcome was failure of

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Chris Campbell is the Senior Editor of Neonatal Intensive Care.

surfactant treatment strategy to avoid mechanical ventilation; we differentiated early from late failures to assess the contribution of potential mechanisms such as respiratory depression versus less-effective surfactant delivery. Secondary outcomes addressed efficacy and safety end points."

Results

It was noted in the study that "with accruing evidence that the LMA is easier to use than an ETT,[15,16] causes less pain, trauma and neurocirculatory disturbances than endotracheal intubation,[24-27] and can be used for surfactant delivery,[15,17,18] we envisioned a potentially advantageous alternative to INSURE."

The results of the study backed up what the authors "envisioned" as out of the patients who were studied, the "failure rate was 77% in the ETT group and 30% in the LMA group (Po0.001). The difference was related to early failure, as late failure rates did not differ between groups. FiO2 decrease after surfactant and rates of adverse events were similar between groups."

The study authors expanded on these results, saying that "we found a substantially higher rate of failure to avoid mechanical ventilation in the ETT group, which was accounted for by early failures, suggesting that respiratory depression due to morphine premedication was principally responsible for the apparent superiority of the LMA strategy."

The study included one note about how the LMA approach could also benefit certain types of health care providers that might be lacking resources: "As our study targeted neonates ≥29 weeks, the results may not apply to more immature populations. There is only one reported neonate weighing 1000 g who received surfactant through an LMA,[18] as a size 1 LMA (the smallest available) is relatively large for such patients. Still, the LMA may be an important alternative to intubation for surfactant administration in settings with low resources[20,28] or limited staff expertise in intubation."[29]

In conclusion, the study authors wrote that "rescue surfactant through an LMA in newborns with mild-to-moderate RDS produces physiological and short-term clinical outcomes similar to a morphine-based INSURE approach while obviating the need for laryngoscopy, tracheal intubation and analgesia. As morphine likely increased post-intubation ventilatory requirements, optimal premedication strategies for INSURE should avoid morphine and minimize the duration of respiratory depression—which might be achievable with a rapid-onset, short-acting agent such as remifentanil. Larger studies could then evaluate whether less-invasive surfactant delivery via LMA produces respiratory outcomes equivalent to those of an optimized INSURE approach."

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Utilizing Inhaled Nitric Oxide Noninvasively Following Extubation

Laura Lerch, BS, RRT-NPS; Michael A Porte, MD

Inhaled Nitric Oxide for the use of Meconium Aspiration Syndrome with pulmonary hypertension (PPHN) is clinically indicated and practiced nationally. Clinical objectives for ventilating infants noninvasively are to reduce ventilator induced lung injury (VILI), to reduce ventilator associated infections, and to reduce sedation. We present a case of severe Meconium Aspiration Syndrome, in a term infant who continued to require inhaled nitric oxide, based on echocardiogram evidence of persistent pulmonary hypertension (PPHN), after extubation. The patient received iNO through a RAM cannula.

Introduction

Meconium is present in amniotic fluid in 10-15% of all deliveries. Aspiration occurs in 2-6% of those.[1] The more depressed the baby as reflected by Apgar scores and arterial cord blood metabolic acidosis, the greater the likelihood of aspiration syndrome (MAS). Of those with MAS, 30-60% require mechanical ventilation and 2-7% will die.[2] Furthermore, greater than 20% of infants with meconium aspiration syndrome have PPHN. Management of MAS needs to be thoroughly investigated to help understand what the optimal management should be.[2]

Case Report

This is a case report about a 3.150 kg infant male, born at 40 and 4/7 weeks gestation. He is born via normal, spontaneous vaginal delivery with an uncomplicated maternal history at an out-born hospital. Delivery was complicated by thick meconium stained amniotic fluid and a nuchal cord was present. Resuscitation was preformed following Neonatal Resuscitation Program guidelines. Intubation for meconium was completed twice. Chest compressions were required for thirty seconds. Apgars were 3 (at one minute of life), 5 (at 5 minutes of life), and 7 (at ten minutes of life). The infant remained intubated with endotracheal tube CPAP (continuous positive airway pressure) until the neonatal transport team arrived from our Level Three facility.

Upon arrival of the Transport Team, the infant was placed on conventional ventilation with ventilator mode SIMV (synchronized intermitted mandatory ventilation), a PIP (Peak inspiratory pressure) of 20 cmH2O, PEEP (positive end expiratory pressure) of 5 cmH2O, respiratory rate of 45 breaths

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per minute, inspiratory time .35 seconds, and 0.90 FiO2 (fraction of inspired oxygen). Initial capillary blood gas revealed a respiratory acidosis 7.19/pCO2 78 mmHg/ HCO3 29.7 mmol/L/-1.0 (base excess). Ventilator settings were increased to a peak pressure of 22 cmH2O with a respiratory rate of 60. Transport stabilization was completed, and infant was transported to a Level Three NICU. Hypoglycemia was treated with boluses of D10W.

On admission to the NICU, venous blood gases showed worsening respiratory acidosis: 7.13/pCO2 84 mmHg/HCO3 26.7 mmol/L/-4.9 (base excess), despite increased ventilator settings. Oxygen requirement was at 80%. Surfactant was given once. Follow up VBG improved: 7.30/pCO2 49 mmHg/ HCO3 23.3 mmol/L/-3.2 (base excess). Oxygen requirements remained at 70% to 80% to keep oxygen saturation greater than 94%. The infant had persistent tachypnea despite ventilator change from SIMV to A/C (assist control) and the addition of IV Morphine for sedation. A UVC was placed. A peripheral arterial line was eventually inserted. An EEG started due to perinatal cardiorespiratory depression and clinical observation of 'twitches'.

DOL 1: High endotracheal tube terminating at the thoracic inlet. Recommend advancement by 5 mm. Findings compatible with meconium aspiration. Probable tiny bilateral pleural effusions.

Table 1. Summary of Blood Gas in conjunction with Interventions.

	cbg	abg	Abg	Abg	Abg	Abg	Abg	cbg	cbg	cbg
Age	0 hrs	12 hrs	DOL 2	DOL 3	DOL6	DOL 7	DOL 9	DOL 12	DOL 18	DOL 31
pH	7.19/	7.30	7.25	7.26	7.41	7.39	7.387	7.387	7.369	7.34
PCO2 (mmHg)	78	42	57	59	50	48	55	52	60	51
pO2 (mmHG)	57	118	66	52	92	70	62	57	48	58
Bicarb	29.7	20.0	23.5	26.0	30.8	28.2	32	31	34	27
Base Excess	-1.0	-5.7	-3.8	-1.8	5.4	3.0	6	4.8	6.9	1.2
Intervention:		iNO started	Switch to HFOV	Max settings HFOV Steroids Started	Weaning iNO	Conv. Vent	Post ext	iNO Off	Ncpap	RA

Echocardiogram was completed at 12 hours of life and summary showed evidence of PPHN with bidirectional shunting through the PDA, right ventricular hypertrophy with right ventricular dilation flattened ventricular septum, and tricuspid regurgitation with estimated mean PA pressure at 65 mmHg. Systemic Blood Pressure was 63/48 mmHg with a mean of 53.

OI is +25. After a discussion with pediatric cardiology to discuss the echo findings, inhaled nitric oxide was started in line with the conventional ventilator, at 20 ppm. Difference between pre and post ductal oximeters was 3% prior to intiating inhaled nitric oxide. Infant also presents with relative hypotension requiring two boluses of normal saline and a Dopamine drip.

Seven hours after starting iNO, the PaO2 climbed to 118 on ABG (7.30/pCO2 42 mmHg /PaO2 118 mmHg /20.0 mmol/L/-5.7 (base excess)). The Oxygen Index improved to 11.5 with ventilator settings: PIP: 28 cmH2O, PEEP: 7 cmH2O, inspiratory time: 0.35 seconds, 50 breaths per minute, pressure support: 10 cmH2O, but FiO2 remained around 0.80.

At 24 hours of life, despite iNO and increased ventilator settings, FiO2 requirements was greater than 0.80. Nebulizers were started in line with the ventilator for secretion management. (Aerogen was placed on the inlet to the heater chamber, below the injector module; the sample line filter was changed every four hours to protect the iNO system monitor from aerosol contamination). Albuterol (2.5MG/3ML) was ordered at a dose of 1.25 mg every 12 hours. The Albuterol was mixed with hypertonic with Sodium Chloride 7% at a dose of 1.1 ml (we added 0.4 ml sterile water + 3% NaCl neb with 1.25 mg albuterol). Due to worsening secretions nebulizer frequency was increased to every 6 hour.

Over the next 24 hours the FiO2 was weaned to 0.57. However, ventilator settings remained high. The highest conventional settings recorded were: Assist Control Mode, 50 breaths per minute, PIP: 30 cmH2O, PEEP: 7 cmH2O, Inspiratory time 0.32 seconds. Despite these significant settings the PaCO$_2$ remained in the mid-50s mmHg. Physician's goal was to achieve PaCO$_2$ around 40 mmHg. OI ranged from 12-15.6.

At two days of age, the infant had an episode requiring manual ventilation using high peak airway pressures. SpO2 dropped into the low 40s. Recovery was very slow. Following this event an ABG showed PaCO2 increasing to 57mmHg PaO2 66 mmHg, pH 7.25, 23.5 mmol/L, -3.8 (base excess). iNO was continued at 20 ppm and the infant was switched to high frequency oscillatory ventilation (HFOV). Nebulizers were held while on HFOV. Initial HFOV settings were: MAP (mean airway pressure) 17 cmH2O, Amplitude 40, Hz 10, Inspiratory time 33%, Bias Flow 15 Lpm.
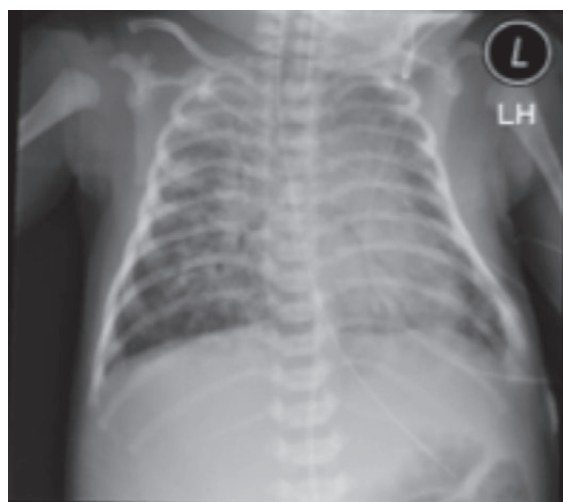
DOL 2: Slightly worsened bilateral predominantly central patchy opacities, which may represent a combination of superimposed worsened atelectasis and central vascular congestion.

Echocardiogram was repeated at two days of age. There was evidence of severe pulmonary artery hypertension, no PDA, patent foramen ovale, mainly left to right with normal pulmonary venous return, dilated hypertrophied right ventricle, and with mildly decrease LV systolic function.

Over the next 12 hours HFOV settings continuously increased reaching a maximum of: Mean Airway Pressure 20 cmH2O, Amplitude 52, Hertz 9, Bias flow 20 Lpm, and FiO2 of 1.00. OI is greatly elevated at 38.5. ABG showed 7.26/pCO2 59 mmHg /PaO2 52 mmHg /26.0 mmol/L/-1.8 (base excess). The baby remained on Dopamine. Total fluids were increased due to concern for intravascular volume depletion with high HFOV limiting venous return.

At this time there was a family conference to discuss two possible options: a transfer to an ECMO center including the risk associated with transporting the infant and the actual risks of ECMO, or starting systemic steroids which have their own risks. The family and hospital team chose to start the glucocorticoid dexamethasone due to ventilator failure, severe secretions, and bradycardia/desaturation events.

At three days of age, dexamethasone was started at 0.1 mg/kg IV, Q6 hours, to reduce lung inflammation.

After dexamethasone was given for one day, an ECHO on showed: improved mild to moderate right sided chamber dilation, and normal right ventricular systolic function, ongoing.

The child had significant pulmonary improvement with dexamethasone. The dexamthasone was weaned by 0.1 mg/kg/ per day from 0.4 to 0.1 mg/kg/ per day over three days. At six days of age HFOV settings were: (MAP: 15 cmH2O, Amplitude: 34, Hz: 9, Flow: 20 Lpm, Inspiratory time 33% and FiO2 0.34). The iNO was weaned from 20 ppm to 18 ppm while PaO2 remained greater than 90 mmHg. The goal was to keep PaO2 60 to 100 mmHg, as the child was very labile.

Repeat echocardiogram was done after the iNO was initially weaned. This showed improvement in pulmonary arterial pressures. Pulmonary artery pressure improved and right sided chamber dilatation decreased.

At seven days of age, the infant transitioned back to conventional ventilation (SIMV mode, respiratory rate of 45 breaths per minute, PIP: 25 cmH2O, PEEP: 7 cmH2O, I time: 0.38 seconds, 10 cmH2O of pressure support and FiO2 0.35). Nebulizers via the aerogen was restarted every six hours. Pulmicort SVN as added in BID 0.5 mg. Nitric Oxide was then weaned by 5ppm every six hours until reaching a dose of 5 ppm.

At eight days of age, the infant met the NICU's extubation guideline: FiO2 ≤35%, rate ≤ 25 bpm, PIP ≤ 18 cmH2O; pH ≥ 7.20, PCO2 ≤ 55 mmHg; No paralytic or excessive sedation; Caffeine if GA ≤30 wks; Post extubation support for 72 hrs.
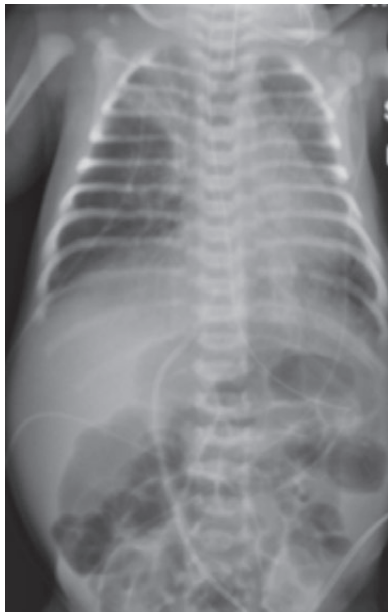
DOL 9: Pre extubation: Stable position of ETT and UVC. Persistent pulmonary hyperinflation. Persistent subsegmental atelectasis in the right upper lobe. Persistent streaky interstitial opacities consistent with history of meconium aspiration. Relative increased lucency in the right lateral chest, which may be secondary to projection however underlying pneumothorax cannot be definitively excluded.

The infant was extubated from SIMV 20 bpm, PIP: 18 cmH2O, PEEP: 6 cmH2O, 0.38 seconds I time, pressure support of 10 cmH2O and 0.30 FiO2 to Nasal SIMV rate of 40, PIP 22 cmH2O, PEEP 6 cmH2O, I time- 0.5 seconds, and 0.40 FiO2 and 4 ppm iNO. Nasal SIMV was provided via the RAM cannula.

iNO had been weaned to 4 ppm remained at 4 ppm despite an increase in oxygen requirement. pCO2 on serial cbg's showed a compensated respiratory acidosis at 57 to 55 mmHg post extubation.

DOL 9: Post Extubation: Persistent mild pulmonary hyperinflation. Persistent coarse interstitial opacities throughout the lungs with subsegmental atelectasis in the right upper lobe and left lower lobe, consistent with known history of meconium aspiration.

Nasal SIMV settings were increased to a pressure of 24 cmH2O and PEEP of 7 cmH2O due to a FiO2 requirement. However, chest X-ray findings showed over-inflation and subsegmental atelectatis bilaterally.

From 9 to 12 days of age, the iNO was weaned by 1 ppm every day. The child remained on nasal SIMV settingds around 0.40 FiO2 and cbg showed: 7.387/pCO2 52 mmHg/31 mmol/L/4.8 base excess).

The infant transitioned to nasal CPAP. (CBG: 7.369/pCO2 60 mmHg/34 mmol/L/6.9 base excess).
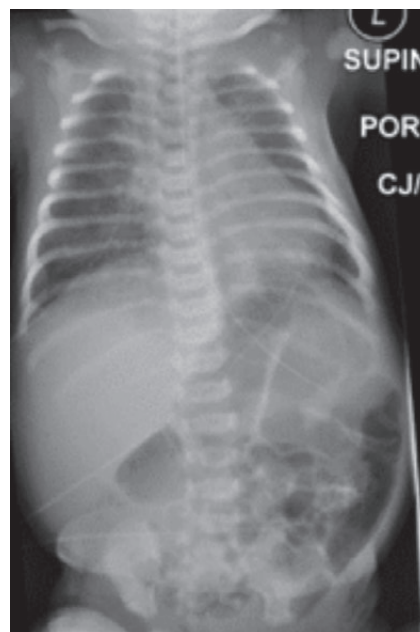
DOL 23: No significant change in course central opacities, likely atelectasis.

On day of life 23, the infant transitioned to 1/8 Lpm of 100% oxygen via nasal cannula. All nebulizers were discontinued. At 31 days of age, the infant transitioned to room air. Capillary blood gas showed: 7.344/pCO2 51 mmHg/27 mmol/L. Echocardiogram was normal, with resolution of PPHN and normal contractility.

Discussion

A 40 4/7 week infant was admitted for meconium aspiration syndrome with severe pulmonary hypertension, which has at discharge. The infant's hospital course was complicated by eight days on endotracheal tube ventilation, 15 days of NIPPV, 5 days of NCPAP, and 8 days of straight flow nasal cannula. The hild had 11 days of iNO, and one week of systemic steroids. He had a course of IV antibiotics for MAS and required IV sedation. Off of the sedation the infant experienced fussiness and went home on acetamiophen. Prior to discharge, the infant was able to be weaned to room air, tolerated all feeding orally, and had good weight gain.

The parents elected not to have brain MRI because the vEEG was normal. Head ultrasound did reveal bilateral grade 1 IVH.

In review of this case, the child tolerated iNO delivered by RAM cannula. However, following extubation the oxygen requirement increased from 0.30 to 0.40. Although the chest X-ray revealed areas of hyperinflation, the SIMV had to be increased. It may have been beneficial to increase the iNO dose at the time of extubation.

Furthermore, did increasing positive pressure via a RAM cannula could cause more irritation, and increased effort for exhalation.

Meconium will inactivate a newborn's endogenous surfactant and decrease levels of surfactant proteins A and B.[1] Causing a severe inflammatory response. MAS impacts alveolar circulation. This was a severe case of both inflammation and circulation impairment.[3]

Nair,[4] et al reported a case PPHN with mild respiratory distress responding to nasasl cannula iNO. Our case represents severe MAS with severe PPHN, with on going iNO requirement after extubation. The child tolerated iNO by RAM cannula.

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Measuring the Differences Between 4 Bubble CPAP Systems

Chris Campbell

While medical professionals who work in hospital settings won't be surprised, some parents might be a little shocked to learn that in facilities with million-dollar equipment, many use a "homemade" version of a device designed to help infants with respiratory distress to breathe spontaneously.[1]

The device is called a bubble CPAP, and it's an affordable type of CPAP that specifically supports infants. Many hospitals employ "off-label" bubble CPAP devices concocted out of items found in their facilities.[4]

But use of the "homemade" devices is changing after medical device makers were granted FDA clearance to market bubble CPAP devices far more sophisticated than those created in-house at hospitals.

A group of researchers with the Center for Developmental Therapeutics, Seattle Children's Hospital Research Institute, were curious about how homemade devices and those manufactured by medical device companies would compare when tested against each other.

Poli et al had a theory about these devices: "We hypothesized that there are no differences in the magnitude of oscillations in lung volume in a preterm neonatal lung model when different bubble CPAP systems are used."

After putting four devices through their paces, however, the researchers concluded something completely different — leading them to call for more study to learn about the existence of possible physiologic benefits between different devices.

The Devices
When an infant is suffering with respiratory distress syndrome (RDS), bubble CPAP is an invaluable device, according to the study authors: "Unlike CPAP provided by a mechanical ventilator, bubble CPAP transmits small-amplitude, high frequency pressure oscillations around the mean airway pressure.[2] These pressure oscillations are created by gases bubbling through the air-water interface of the submerged expiratory tube. Lee et al[3] first observed the chest walls of infants supported by bubble CPAP oscillating at a frequency similar to high-frequency oscillatory ventilation. Furthermore, Pillow et al[2] demonstrated that mechanical pressure oscillations created by bubble CPAP may be more beneficial than ventilator

CPAP to aid in lung recruitment and to improve gas exchange in premature lambs, claiming that oscillations augment ventilation."

Four different models of bubble CPAP were tested: a "homemade system that has been described by several investigators[4,6,7] and three FDA-cleared systems: bubble CPAP system (Fisher & Paykel Healthcare, Auckland, New Zealand), Babi.Plus bubble positive airway pressure valve with an n CPAP nasal kit (A Plus Medical, Carlsbad, California), and WaterPAP (Airways Development, Kenilworth, New Jersey)."

The four systems were tested on an anatomically realistic replica with either appropriate or proprietary prongs attached, according to the authors: "Nasal resistance in the newborn accounts for nearly half of the total airway resistance.[8] As such, we designed a realistic replica of the nasal airway modeled from a computed tomography scan of an infant at 28 weeks of gestation." The replica was attached to a Silastic test lung sealed within a calibrated plethysmograph.

The authors described the homemade device as "a water-filled bottle with a corrugated tube submerged within it. The expiratory limb was stabilized in the water column using a 10-mL syringe plunger; the CPAP level was determined by the length of the tube submerged in the water, indicated by tick marks at 1-cm intervals written on the limb.[7]"

To measure pressure oscillations: "The nasal prongs were inserted into a Tygon tubing adapter that was affixed to the nasal airway model. The adapter formed a tight seal (no leak) between the nasal model and prongs. All bubble CPAP systems had the expiratory limb set to a depth of 6 cm."

The Results
The study authors are upfront in saying that after testing the four devices, they had to "reject our hypothesis," going on to say that "the major finding of this study is that the bubble CPAP systems provided quantifiable oscillations in DV that may prove to be clinically meaningful and that the different bubble CPAP systems studied exhibited differences in the magnitude and frequency of volume oscillations delivered to a preterm infant lung model."

The study authors found many deep flaws in the homemade device: "Although the homemade device is the most cost-effective form of bubble CPAP, it possesses more variability in its frequency output than the other devices. If employed in the clinical setting, patients on the homemade device will experience

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a different waveform at different flows. The variability may be attributed to the tube submerged inside the homemade system and the increase in swaying motion observed as flow increases… The homemade system secures its depth with a syringe plunger, which may not be the most reliable method of maintaining CPAP. Furthermore, the homemade system does not possess a pressure relief mechanism."

By contrast, the authors wrote, "as price increases, performance consistency, fullproofing the CPAP level, and safety against drastic pressure increases are included. Although the magnitude of oscillations may not be reflected in the cost of the systems or the hierarchy of designs, the clinical application of the systems benefits from the refined ergonomic utility with regard to performance and safety."

One conclusion the authors found as that "the Fisher & Paykel Healthcare bubble CPAP system provided greater DV than any of the other devices at all of the respective bias flows (P < .05). The Fisher & Paykel Healthcare and Babi.Plus systems generally provided DV at lower frequencies than the other bubble CPAP systems. The magnitude of DV increased at bias flows of > 4 L/min in the Fisher & Paykel Healthcare, Airways Development, and homemade systems, but appeared to decrease as bias flow increased with the Babi.Plus system."

"Based on cost, the more expensive devices, such as the Fisher & Paykel Healthcare and Babi.Plus devices, have less variability than their cheaper counterparts. Knowing the exact pressure waveform being delivered to a patient is useful for a hospital standardizing care. Furthermore, with regard to ergonomics and safety, the FDA-approved systems have the most reliable designs…The Fisher & Paykel Healthcare system utilizes indents on the expiratory limb to secure the CPAP level and possesses an intricate mechanism for maintaining consistent water level not found on the Babi.Plus system."

In conclusion, the authors found that "with regard to clinical practice, the best device would depend on the type of therapy a clinician wants to employ. If ventilator-like CPAP is best for the patient, then the Babi.Plus system would be the closest option, but if oscillatory therapy is desired for infants with low lung compliance, then the Fisher & Paykel Healthcare system would result in the largest fluctuations in DV. Although each system uses a similar means to deliver bubble CPAP, the resulting therapy delivered to the patient may be different depending on which system is used."

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Umbilical Cord Knot Leading To Fetal Demise

Maria Monica Ossa*, Tarik Zahouani, Tony Abdelmaseeh, Sara Lillo, Benamanahalli Rajegowda

Introduction

Umbilical cord accidents (UCA) represent 10% to 15% of stillbirths.[1] They are thought to be caused by cord compression with cessation of blood flow to the fetus in the setting of a cord prolapse, nuchal cord or true knot in the umbilical cord. True umbilical cord knot is a common complication that occurs in 0.3 to 2.1% of all pregnancies.[2] Predisposing factors include advanced maternal age, multiparity, obesity, chronic hypertension, gestational diabetes, previous spontaneous abortion, male fetuses, small fetuses, long umbilical cord, polyhydramnios, and genetic amniocentesis.[3] True knots of the umbilical cord are associated with a four-fold increased risk of antepartum fetal death and they are present in about 3-5% of all stillbirths.[4] We are reporting a case of intrauterine fetal demise (IUFD) secondary to tightened true knot of the umbilical cord.

Case Presentation

A 36 year-old woman, multigravida (7 pregnancies, 2 voluntary terminations of pregnancy, 1 spontaneous abortion) at 32 weeks of gestation presented to the emergency room (ER) complaining of no fetal movements. Her medical history was remarkable for chronic hypertension and obesity. Her previous pregnancies were complicated with severe preeclampsia. She had regular prenatal care during current pregnancy. At 15 weeks of gestation, due to advanced maternal age, she underwent an amniocentesis which confirmed a normal male karyotype with elevated alpha-fetoprotein (AFP). Fluorescence in-situ hybridization did not show numerical chromosomal abnormalities. At 19 weeks of gestation, transabdominal ultrasonography (US) depicted a single intrauterine gestation with detectable heartbeat and posterior placenta; no gross abnormalities were detected and umbilical cord was not visual. At 32 weeks of gestation, the patient did not feel any fetal movements for 12 hours, which prompted her to go the ER. During the bedside sonogram, no fetal heart rate was detected and IUFD was diagnosed. The patient underwent induction of labor. A deceased baby boy was delivered with Apgar scores of 0 and 0, at 1st and 5th minute respectively. His weight was 1960 grams. On initial examination, the baby had a tight one-loop cord around his neck with a tight knot of the cord interrupting blood supply (Figures A and B). An examination of the umbilical cord showed vascular congestion in the umbilical vein with possible long umbilical cord. There were no gross fetal abnormalities. The placenta was delivered

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spontaneously and noted to be intact. The placental pathology showed a 1.5 cm in diameter umbilical cord containing 3 mildly distended blood vessels but otherwise unremarkable.

Discussion

Umbilical cord lengths vary from 5 to 175 cm with an average length of approximately 55 cm. After 28 weeks of gestation, the cord does not significantly lengthen.[2] The Umbilical cord is helical in nature, with as many as 380 helices. Umbilical cord complications or accidents have been reported in 10-15% of stillbirths.[1] They are thought to be caused by cord compression with cessation of blood flow to the fetus in the setting of a cord prolapse, nuchal cord or true knot in the umbilical cord. The reported frequency of cord prolapse of the umbilical cord varies between 0.2 and 0.6% of births. In most series of cord prolapse, the perinatal mortality is approximately 15%. Among term infants and among all infants delivered by Cesarean within 10 minutes of cord prolapse, mortality is <5%. Cord entanglement in the form of nuchal cords occurs in about 30% of uncomplicated pregnancies, including multiple nuchal cords which occurs in 3.7% of deliveries. There is no evidence that nuchal cords cause fetal death or significant fetal compromise. Although nuchal cords are at times diagnosed by ultrasound, the excellent outcome of these infants demonstrates that no alteration in management is indicated unless the fetus develop distress during labor.[2]

True knots are knots in the umbilical cord where the cord is encircling the extension of the fetal axis rather than the fetus itself, they arise from fetal movements and are more likely to develop during early pregnancy between 9th and 12th week of gestation, when relatively more amniotic fluid is present and greater fetal movement occurs.[3] True knots represent about 4% of all cord complications.[5] The reported frequency of true knots ranges from 0.3 to 2.1% of all pregnancies[2] and 3-5% of all stillbirths are accounted for by the presence of umbilical cord knots.[4]

Maternal reproductive risk factors associated with true knots include advanced maternal age, multiparity, obesity, chronic hypertension, gestational diabetes and previous spontaneous abortion, in addition to obstetric variables such as male gender, long umbilical cord, polyhydramnios and genetic amniocentesis.[3,5,6] The pathophysiology and timing of formation of a true umbilical cord knot can be hypothesized by analyzing specific risk factors such as polyhydramnios, gestational diabetes and multiparity, as they contribute to a large uterine
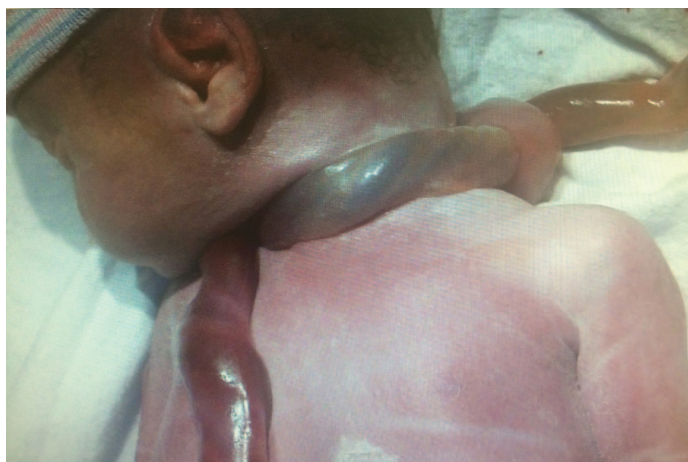
Figure A. Umbilical cord showed clotted blood in the proximal portion.

Figure B. Tight one loop cord around the neck with a tight knot of the cord of the cord interrupting blood supply.

volume predisposing to free and exaggerated fetal movements ultimately leading to the entanglement of the umbilical cord with or without true umbilical cord knot. Patients undergoing amniocentesis may have a higher rate of fetal movements and uterine contractions during the procedure leading to a true knot.[3] The higher occurrence of umbilical cord knot among male fetuses might be explained by their significantly greater umbilical cord length compared to female fetuses.[6] The reason why patients with previous spontaneous abortions are prone to fatal knots is currently unknown. These risk factors were applicable to our case as she was 36 years old, grand multipara, with chronic hypertension and history of spontaneous abortion, underwent an amniocentesis and delivered a male baby who had a long umbilical cord.

Umbilical cord knots are significantly associated with increased risk of several adverse perinatal and early neonatal outcomes such as non-reassuring fetal heart rate, increased occurrence of cesarean section, meconium stained amniotic fluid, cord prolapse, nuchal cord, low Apgar scores at 1 minute and fourfold increased risk of antepartum fetal death.[3,5,6] The clinical significance of low Apgar score is likely to be minor because fetal venous pH values were not affected by umbilical cord knot.[6] The exact mechanism by which the knots produce fetal demise is unknown, but could be secondary to cord vessel compression when the knot tightens. Earlier studies have not shown significant association between umbilical cord knot and fetal growth.[3,5] However, Räisänen et al found a 3.2-fold higher risk of being born small for gestational age , indicating a risk of chronic uteroplacental insufficiency in infants affected by an umbilical cord knot although the mean birth weight did not differ between the study and the control group. They explained this result by the higher occurrence of obesity and diabetes among affected pregnancies that may have masked the negative effect of umbilical cord knot on fetal growth.[6]

Prenatal sonographic diagnoses of cases of a true knot of the umbilical cord have been reported infrequently.[7] Prenatal fetal surveillance, including targeted sonographic examination and Doppler studies, may be challenging as the whole length of the umbilical cord is not routinely seen. Therefore, defining a high risk group of patients that are predisposed to the formation of a true knot of the umbilical cord is important in order to increase perinatal diagnosis. A detailed US examination of the umbilical cord can reveal the hanging noose sign. Four-dimensional and color Doppler ultrasounds allow a precise diagnosis by providing a panoramic view of the umbilical cord and showing the status of

the knot with regard to tension and resistance. Four-dimensional US also enable the observation of instantaneous tension exerted on the umbilical cord that, if sudden and strong, could lead to perinatal complications.[8]

Conclusion

Umbilical cord accidents are an important cause of stillbirth, however, not all true knots will cause fetal mortality unless it ends up in a tight knot causing uteroplacental insufficiency as an acute event. Therefore a careful evaluation of maternal history for fetal activity, fetal wellbeing is much more sensitive than the diagnostic ultrasound for the umbilical cord accidents including knots. Ultrasound studies of the umbilical cord, including insertion, composition, coiling, knotting and prolapse, should be completed. Although the frequency, predisposing factors, and potential outcomes of true knots of the umbilical cord have all been reported, the prenatal diagnosis and clinical management remains challenging, therefore, determining patients susceptible to develop this condition is important in order to increase its detection and provide the best chance of a good outcome. Ultrasound monitoring allows for early recognition of potential complications and ascertainment of fetal maturity.

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Neonatal Brain Injuries and Outcomes: It is Time to Re-Think Assumptions

Deb Discenza

As a parent of a premature baby that had numerous developmental challenges and as one that supports over 28,000 parents of premature babies around the world on the Preemie Inspire network (www.inspire.com/groups/preemie), I find that families are consistently given the most gruesome prognoses for their brain injured infant. The conversation often revolves around an expectation of significant physical, and intellectual disabilities. Some parents are even told that the baby is better off being pulled from support.

Interestingly enough, over time, I found that a large number of these babies on the forum end up doing way better than expected. So imagine my great interest when I happened upon Karen Pape, MD, a neonatologist from Canada who had a strong background in Neonatal Follow-Up. With her forthcoming book, *The Boy Who Could Run But Not Walk: Understanding Neuroplasticity in the Child's Brain*, I realized that I had in my midst a person who could finally provide concrete answers about babies brains, neonatal brain injury and how to achieve the best outcomes possible.

Deb Discenza: Dr. Pape, please tell me about your background and how you came to write this book.
Karen Pape: As a neonatologist and clinical neuroscientist, I have been teaching parents and medical professionals for over 30 years about baby brain neuroplasticity. I think differently from most of my colleagues about this topic, largely because of my training that started off in neuropsychology at McGill University. Donald Hebb, the chairman of the department taught us about the complexity of our human brains and how we learn. At the time, his ideas were completely at odds with the dominant theory that our brains were really more like supercomputers than anything else. If part of our supercomputer brain was damaged, it was commonly assumed that the function was lost for life. In contrast, Hebb taught us that there were well-documented adult humans who had somehow managed to completely recover from devastating injuries. I left McGill knowing that even adult human brains could occasionally recover. At this point in my life, I just assumed that a growing baby brain would recover even better.

You can only imagine my surprise when I hit medical school and was told the exact opposite. Animal brains could recover, but

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human brains were far too complex. If your brain was damaged, you were damaged for life.

So I kept my mouth shut in medical school and throughout my training in pediatrics and neonatology, but I kept reading the neuroscience literature. By the 1980s and 90s, pioneers in human neuroplasticity were challenging the standard medical way of thinking, with clear evidence that all brains, from rats to monkeys and even some adult humans, had neuroplasticity.

I use the word neuroplasticity to describe many different mechanisms by which the brain can recover after an injury. It can grow new brain cells, it can repair areas of damage, it can rewire around areas of injury and it can even co-opt different areas of the brain to take over lost function.

DD: In your book you use the term "recovery" for an infant brain injury akin to an adult stroke patient that receives therapy to recover from brain injury. Please explain.
KP: Thanks to the pioneers in neuroscience and popular writers like Norman Doidge, author of *The Brain That Changes Itself*, most people know that an adult with a first-time, mild stroke has an excellent chance of a complete recovery.[1] Over the past 10 to 20 years, improvements in early diagnosis and treatment as well as vastly improved early rehabilitation therapy has changed the outlook for an adult with a stroke from a relatively hopeless expectation of permanent impairment to a system wide active intervention policy. But unfortunately, the expectation of full recovery for a baby with a similar mild brain injury is that they will at best recover, but they will have cerebral palsy for life. This does not make sense. The neuroscience research tells us that animal brains from rats to monkeys can recover. Baby animals recover faster and more completely. We now know that adult humans can recover from many brain injuries. It is not logical to continue to believe that there is no hope of recovery in our NICU babies with a wide variety of early brain damage.
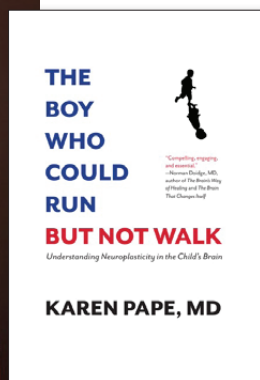
DD: Why is it that neonatologists continue to think of brain injury as not recoverable?
KP: There are several reasons that contribute to create this problem and I discuss them in some detail in my book. Each of them plays an important part.

Knowledge Overload – This is one of the biggest problems. New research knowledge is being produced at an unbelievably fast rate. Busy NICU professionals are hard-pressed just to keep up

Karen Pape, MD, author of the book *The Boy Who Could Run But Not Walk: Understanding Neuroplasticity in the Child's Brain*. www.karenpapemd.com

with information that bears directly on the intensive care of their babies.

Siloes of Knowledge – All branches of medicine are becoming increasingly soloed into narrower and narrower areas of interest. I describe in my book the reality that pediatric neurosurgeons often know far more about the potential of neuroplasticity in children than many neonatologists. Each specialty communicates largely through their own journals and there are more and more of them every year.

Silos of Care – Many neonatologists never see their graduates in Follow-Up and miss the chance to see the babies that do better than expected. Even those in Follow-up rarely are able to see them long enough to accurately document the amount of recovery. NICU Follow-Up is rarely funded to see the post-NICU baby for more than 2 to 3 years and at that age, the baby brain is still in the process of recovery. I often think the NICU nurses have a better concept of recovery as in my experience many of them maintain longer-term interactions with their patient families.

DD: So how have they responded to your speeches on this subject?
KP: I was invited to speak Hot Topics in Neonatology in 2013 and it was a turning point for me that helped me decide to write this book. I talked about baby brain neuroplasticity and presented case studies with videos of children who managed to do better than anybody had ever expected. Probably the most dramatic case was a young girl who had had half a brain removed in a heroic attempt to stop her one-sided seizures. The seizures stopped and she recovered fully apart from mild tightness on one side and a small defect in her visual field. Children who have early hemispherectomies, like this child, are one of the reasons that neurosurgeons know that baby brains can recover.

During my talk I made the point that every neonatologist has seen at least one baby who did surprisingly well in spite of bad brain scan. Then I asked them to put up their hand if they had had this experience. At first there were only a few hesitant hands but as everyone looked around the room, more and more hands were raised. Within a couple of minutes 80 to 90% of the neonatologists had a hand up! The reason they were initially

hesitant and the probable reason that parents are still not given much hope, is that the research data has not yet caught up with clinical care. Knowledge overload, silos of knowledge and siloes of care to just the neonatal period are to blame. This talk and the positive reaction of my peers was one of the deciding factors that got me to finally sit down and write this book. It is written for the parent of an *at risk of* or diagnosed child with cerebral palsy and provides them and the professionals who care for them with a current summary of what we know about the outcomes after early brain damage. It is also important for everyone to understand that there are many innovative treatments now available that are both evidence-based and best practice.[2]

DD: So how did you come to this conclusion regarding recovery?
KP: Early in my career, I was fortunate to be trained by two excellent neonatologists, Paul Swyer and Pam Fitzhardinge, who believed the quality of survival was of importance. They helped me do further training in neonatal pathology that led to co-authoring a book on hemorrhagic and ischemic lesions in the perinatal brain.[3] A further research year led to the first published use of cranial ultrasounds to diagnose bleeding into the brain of premature babies.[4] For the first time we could do sequential scans, in the NICU, without sedation or radiation.

As I worked with CUS and CT scans, we diagnosed more brain problems, but we could also watch as some babies recovered and in Follow-Up Clinic we found many happy surprises.

DD: What would you like for parents to know about this type of recovery?
KP: The type and severity of brain damage in the NICU varies with the age at the time of injury. Spontaneous brain recovery at least takes 3-4 years. We know that some babies recover well. In a recent study, over 80% of babies with a Grade III and close to 50% of those with a Grade IV bleed were cognitively age appropriate and free of any sign of cerebral palsy at 2 years.[5] The results for term-asphyxiated infants, treated with modern care are also improving rapidly. This data is discussed is detail in my book.

DD: What should NICU professionals revamp in their treatment plans to help with this recovery?
KP: As a start, I would suggest that the medical and nursing staff do some in-service updates about what we now know of the current outcome data after bleeds, PVL and HIE. The major adverse outcomes are cognitive impairment and cerebral palsy. It is important that everyone is on the same page when talking with parents about these significant events. Up to 60% of children with CP will walk independently and a further 20% will do it with a cane or a crutch.[6] Significant speech and cognitive delays are more common in babies with the most severe forms of CP and overall it is found in less than 20-25%.

Children at risk can be identified early and there are some studies that suggest we should be offering help as soon as the baby is stable.[7] I believe Follow-up starts in the nursery. As soon as a child is diagnosed with CP, massage and gentle stretching are recommended. Why not start earlier? The NICU studies have been done, all we need to do is follow the data.[8]

All change, particularly big change, starts with the recognition that change is necessary. I hope my book will start the conversation of how we can maximize neuroplasticity and minimize maladaptive habits in the early years. Small changes

can result in us all offering real hope to parents dealing with a sick baby and most importantly give them ways to help. NICU professionals should also celebrate how far the profession has come, measured by current outcome stats.

DD: Thank you, Dr. Pape.

Dr. Pape's book and website provide profound evidence that challenges the conventional opinion about brain injuries in infants. Watch her TED X talk *Baby Brains DO Recover, but Habit Hides* it at http://bit.ly/295N3kU. It is my hope that we can come together to re-think previous assumptions and even better, to change the tide and make sure all of these at-risk children can get the help they need in order to attain the best possible outcome. Doing so will directly impact these lives and those around them, not to mention society as a whole.

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What Mattered Most: From NICU Pump Dependency To Exclusive Breastfeeding

Katherine (Katie) McGee RN, BSN, IBCLC

For the newly-delivered NICU mother, the transition to motherhood is often shrouded with feelings of loss and lack of control. The unexpected end of pregnancy by an urgent or emergent delivery and the chaotic early postpartum days are not what she planned. Dreams of blissful hours with the newborn are replaced with the reality of constant worry. Separation of any length from the little someone who means everything to her is often unbearable. If not given accurate information, timely assistance, and frequent follow up, her lactation goals may soon be included among her losses.

I am not just a nurse lactation consultant. Long before I entered the professional field of lactation, I was a new NICU mom. I grieved the end of my pregnancy when my first babies, twins, suddenly arrived at 30 weeks. I longed for the four kicking feet inside that were now swaddled in separate isolettes. Both baby equipment and maternity items brought me to tears as I felt trapped in a state of motherhood limbo, unable to care for them on the inside or outside of my body. My babies were stable and there was seemingly much to celebrate. Yet, we were not a unit anymore and everything felt wrong. In my dazed hours after the emergency C-section, I wondered if all hope of providing my milk to them was also lost. The odds of lactation success felt stacked against us. I knew I wanted to exclusively breastfeed but thought, "How am I going to do this?"

I count it as a great accomplishment that I was able to achieve my goal. I am often asked how I was able to provide 100% of my milk during their 6 week NICU stay and transition to breastfeed them without ever needing formula. I know it was not just sheer determination that led to my success. There were people and factors that kept me on the right path toward my goal. Just as I was transformed from NICU mom to breastfeeding mom, I want to lead other mothers on the same avenue toward success. Looking back, there were key interactions and research proven tools that acted as my bridge and carried me from NICU pump dependency to breastfeeding mother. These were the elements that mattered most and were ultimately able to allow me to become an exclusively breastfeeding mom of twins despite my babies arriving 10 weeks early.

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What mattered most on day one? Initiation of milk supply

As the neonatologist provided an update on my tiny twins only hours old, I interjected, "I do not want them to receive a single drop of formula." She replied, "We have got to get you pumping!" It seemed like moments later that Paula Meier entered my room, to help me get started with a hospital grade breast pump and to fit me into the proper sized breast shields. She was so reassuring and kind and included my husband and mother in the discussion. She stayed with me and explained what my colostrum would do for my babies. She held up the 1ml syringe full of my first colostrum and told me she was bringing it to the NICU and would be sure that half went to my son and half to my daughter. She explained that it would bring about the cascade of positive changes that were meant to happen so many weeks from now. It was the most emotionally healing and empowering interaction. There was something I could do…something so important to them that only I could provide. My inner voice turned from," How can I possibly do this?" to "I am doing this. They are going to receive my milk and then they are going to nurse."

What mattered most during the NICU stay? Maintaining my supply

I received frequent, in person follow up from Paula during the NICU stay. Little did I know at the time I was receiving it, that Dr. Paula Meier is a world-renowned expert on human milk. The NICU set up was as ideal as possible. I was allowed to visit anytime and was able to sit between my two babies and eventually hold them skin to skin or in my arms while pumping. This proximity and ability to stare at them mattered to me. I didn't have to exit the room to pump, but stayed right where I wanted and needed to be. At home, I set up a pumping station with the same style of hospital grade pump. I had a cooler bag to transport my milk in its freshest state right to the babies' caregivers. Labeling my own milk made me confident it was done correctly. The milk expression logs I was using gave me focus. I felt excited each time the 24 hour total increased toward full volume and was reassured by proof that I was making enough to feed two babies. Paula was able to review my milk expression logs to easily provide feedback and adjustments to my pumping plan.

The babies were only about 10 days old when I first asked my son's nurse about non-nutritive nursing. Her initial response was that we should let him rest. Then, she made an about face and replied, 'You know what, yes, he needs it, and so do you." I proceeded to pump and then place my little 3-lb son to my

Table 1. Summary: What Matters Most.

Day One	Approach mother to discuss her lactation goals; provide timely and accurate information about outcomes for mothers and babies who receive mothers own milk and mothers who provide their milk to their babies.	When possible, the use of breastfeeding peer counselors for day one interaction with the new NICU mother is ideal. Those who have personal experience providing milk for hospitalized infants may be important to increasing the rates of human milk feedings and breastfeeding in other NICU settings. (Rossman 2010) Mothers often change the decision (about providing milk) when hearing about the health outcomes for them or their infant. (Miracle 2004)
	Stay with mother throughout the first pumping session to assist with set up, proper usage, assessment of proper breast shield sizing, provide careful assistance to teach milk collection techniques, demonstrate care and cleaning of breast pump parts, provide milk expression records with instructions for use.	Properly fitted breast shields maximize pumping efficiency. (Meier 2000)
	Provide a hospital-grade (multi-user), double electric breast pump with Initiation Technology™ with instructions for use and care, encourage her to use it freely at her baby's bedside and provide rental for use home.	Breast pumps that mimic the unique sucking patterns used by healthy-term breastfeeding infants during the initiation and maintenance of lactation are more effective, efficient, comfortable and convenient than other breast pump suction patterns. (Meier 2011)
During the NICU stay	Ensure professional "check in" occurs with the NICU mother daily/ nearly daily for the first two weeks.	Frequent contact is needed as NICU mothers often change their feeding goals after birth of a VLBW infant. (Hoban 2015)
	Monitor milk collection and storage. Provide target volumes with routine discussions about volume and pumping intervals.	Ideal target volumes should reach 750-1000 milliliters within the first two weeks post birth. Providing target volumes helps set expectations of the volume of milk toward meeting lactation goals. (Meier 2010).
	Provide a lot of encouragement and comfort measures. Facilitate Kangaroo care and encourage/facilitate non-nutritive feeding at breast.	Nonnutritive sucking can be initiated once the infant is no longer intubated and has demonstrated improvement in the transition to direct breastfeeding and longer breastfeeding rates. (Narayanan 1981)
	Encourage and offer assistance to facilitate nutritive feedings by providing a nipple shield in the proper size with instructions for use and care, effective positioning along with and pre and post test-weights.	Nipple shield use increases milk intake without decreasing total duration of breast feeding for preterm infants. (Meier 2000)
	Observe for appropriate intervention needed in special circumstances, ie, hind milk collection. Provide simple growth charts during hind milk feeding, tour to the deep freezer to view stored milk.	
Transition home	With the mother, plan for a gradual transition from state of pump dependence toward increased breastfeeding with an understanding that continued use of hospital-grade (multi-user) breast pump during this vulnerable period of time along (with scale rental for pre and post weights) will be needed.	Pre and post test weighing provides an accurate estimate of intake during breastfeeding across a large range of infant weights and intake volumes.. (Meier,1994} This information is critical as a mother determines volumes transferred at breast feeding.
	Provide resources for community support such as local La Leche League International chapters to connect with other breastfeeding and pumping mothers in the community.	
	Ensure frequent contact by phone by Breast Feeding Peer Counselor, IBCLC, to answer questions during the final weeks of transition toward meeting lactation goal. Remind that attainment of lactation goals is in sight.	Encouraging words are often the support mothers need.

breast. To my surprise he opened wide, latched on and fell asleep. I was crying with joy and could almost feel the prolactin surge in my body. I'll never forget that. These are the moments that propel NICU mothers onward. There were dozens more of these interactions with both babies. Kangaroo care, pumping, and non-nutritive feedings filled my days and finally, I began to feel like their mom.

Once the babies began showing development in feeding cues, Paula taught me how to use a nipple shield and obtain pre and post weights with their breastfeeding attempts. This was an exciting and busy time. The scale revealed to all the amount of milk transferred which was very useful. The nipple shields were the tool that helped them transfer more milk. They were still tiny and still needing supplements of my pumped milk — but they were breastfeeding. We were part way to my goal of exclusivity.

About 3-4 weeks into their NICU stay their growth began to plateau. Paula ran crematocrits on my milk and taught me how to collect and label my hind milk. She created a simple growth chart on the end of their isolettes and the spikes in both did more than just show evidence of progress. It probably did not take Paula long to create, but I'll never forget the growth charts showing the weight gain that was a direct result of my hind milk pumping. It was because I had maintained an adequate supply for two babies that I was able to obtain hind milk when it was needed.

What mattered most during the busy transition home?

We took them home together after 6 weeks. I have a special place in my heart for NICU moms, but an extra special place for moms who are bringing home NICU multiples. The cycle of nursing, pumping and feeding never quite seemed to end. It is a huge milestone to bring a NICU baby home, and it is perhaps the most important time for frequent contact as it is an overwhelming transition. If not reminded often that the goal is in sight, it may still feel unattainable to a former NICU mother.

At about 44 weeks corrected, I sat nursing my twins, together. Shortly thereafter we weaned from the nipple shields. We would nurse thousands of times after, and breastfeeding quickly became the easiest part of caring for them. This was made possible thanks to all of the elements put into place starting after delivery. With the NICU a distant memory and the pump, shields and scale now unused in the background, I had four eyes gazing into mine. Finally, I was just a new mom breastfeeding her babies, and they were what mattered most.

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Neonatal Vitamin A Supplementation Associated With A Cluster Of Deaths And Poor Early Growth In A Randomised Trial Among Low-Birth-Weight Boys Of Vitamin A Versus Oral Polio Vaccine At Birth

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Abstract

Background: The effect of oral polio vaccine administered already at birth (OPV0) on child survival was not examined before being recommended in 1985. Observational data suggested that OPV0 was harmful for boys, and trials have shown that neonatal vitamin A supplementation (NVAS) at birth may be beneficial for boys. We set out to test this research question in a randomised trial.

Methods: The trial was carried out at the Bandim Health Project, Guinea-Bissau. We planned to enrol 900 low-birth weight (LBW) boys in a randomised trial to investigate whether NVAS instead of OPV0 could lower infant mortality for LBW boys. At birth, the children were randomised to OPV (usual treatment) or VAS (intervention treatment) and followed for 6 months for growth and 12 months for survival. Hazard Ratios (HR) for mortality were calculated using Cox regression. We compared the individual anthropometry measurements to the 2006 WHO growth reference. We compared differences in z-scores by linear regression. Relative risks (RR) of being stunted or underweight were calculated in Poisson regression models with robust standard errors.

Results: In the rainy season we detected a cluster of deaths in the VAS group and the trial was halted immediately with 232 boys enrolled. The VAS group had significantly higher mortality than the OPV0 group in the rainy season (HR: 9.91 (1.23 – 80)). All deaths had had contact with the neonatal nursery; of seven VAS boys enrolled during one week in September, six died within two months of age, whereas only one died among the six boys receiving OPV (p = 0.05). Growth (weight and arm-circumference) in the VAS group was significantly worse until age 3 months.

Conclusion: VAS at birth instead of OPV was not beneficial for the LBW boys in this study. With the premature closure of the trial it was not possible to answer the research question. However, the results of this study call for extra caution when testing the effect of NVAS in the future.

Background

In low income countries a policy of providing neonatal vitamin A supplementation (VAS) is currently under debate. Four randomised trials from Africa and one from Nepal have shown no overall effect on mortality of neonatal VAS [1-5]. Three trials from South East Asia have reported a beneficial effect [6-8]. Several of the trials suggested that while VAS conferred few benefits or even a negative effect for girls, it had a positive effect in boys [1,2,6,8]. From 1985 WHO recommended a dose of oral polio vaccine at birth (OPV0) in addition to the three doses at 6, 10 and 14 weeks of age (OPV1-3). This policy was introduced to improve coverage and immune responses [9-13]. The effect of OPV at birth on overall child mortality was never studied.

The Bandim Health Project (BHP) has worked in Guinea Bissau since 1978 and has examined non-specific and sex-differential effects on mortality of childhood interventions. From 2002–2004 when BHP was conducting a trial of neonatal VAS to normal birth weight children, OPV was lacking for several periods [14] and some of the enrolled children did not get the recommended OPV0. Surprisingly, boys who did not receive OPV0 only had a third of the mortality of boys who got the vaccine. The tendency was slightly opposite in girls, resulting in a highly significant interaction between OPV at birth and sex (p = 0.006). We also studied the effect of OPV0 on the immune response to BCG vaccine; both sexes had a dampened immune response to BCG if they received OPV together with BCG [15].

Based on these results we hypothesised that newborn LBW boys might benefit from receiving VAS at birth instead of OPV0, and we conducted a randomised trial to test that hypothesis. As the previous studies suggested a harmful effect of VAS in girls [2], only boys were randomised to receive VAS or OPV0. Girls were enrolled in another trial. The trial proceeded as planned from February 2008 until November 2008 when the study supervisor noted a bulk of death reports. Seven boys born between 28 August and 16 September 2008 had died before the 2 months visit. Among the seven deaths six had received VAS. This looked like a cluster and the PI decided to halt the trial to examine possible causes and avoid continuing an intervention which potentially had negative effects.

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Table 1 Baseline characteristics of the two randomisation groups

	VAS at birth (N = 116)	OPV at birth (N = 116)
Enrolled in rainy season, n (%)	70 (60)	71 (61)
Enrolled at NH, n (%)	102 (88)	99 (85)
Living inside study area, n (%)	34 (29)	36 (31)
Twin, n (%)	26 (22)	24 (21)
Admission to neonatal nursery, n (%)	29 (25)	30 (26)
Age at inclusion, days (10–90 centiles)	2.5 (1–10)	2 (1–10)
Birth weight, kg (10–90 centiles)	2.21 (1.66-2.45)	2.22 (1.66-2.46)
Ballard score* (10–90 centiles)	36 (27–43)	36 (27–43)
Median maternal age, years (10–90 centiles)	23 (16–29)	22 (17–32)
Maternal schooling, n (%)		
None	40 (34)	38 (33)
<6 years	19 (16)	26 (22)
≥6 years	57 (49)	52 (45)
Electricity available, n (%)		
Yes	27 (23)	35 (30)
No	88 (76)	80 (69)
Unknown	1 (1)	1 (1)
Parity, n (%)		
1	62 (53)	57 (49)
2-3	30 (26)	34 (29)
>3	23 (20)	24 (21)
Unknown	1 (1)	1 (1)
Maternal MUAC, mm (10–90 centiles)	232 (208–276)	238 (208–284)

Abbreviations: NH National hospital; MUAC Mid upper arm circumference.
*Only available for children enrolled at the national hospital.

Methods
Setting
The BHP runs a Health and Demographic Surveillance System (HDSS) in six districts of Bissau, the capital of Guinea-Bissau. Since 2002 the BHP has followed a cohort of LBW children from the whole capital. All newborn children weighing less than 2.5 kg at discharge from the maternity ward of the national hospital (NH) are invited to participate. At the time of the trial, 13% of the children born at the NH were LBW. The children and their mothers are driven home from the hospital. A map is drawn describing the localisation of their houses, GPS coordinates are recorded, and a photo of the house and the mother is taken to ensure that the team will be able to localise the child at subsequent visits. When a child moves, a relative or a neighbour takes the team to the new address. In this way very few children are lost to follow up. LBW children living inside the BHP study area who are born at home are recruited when they come for their first vaccinations at one of the three health centres in the study area. In Guinea-Bissau LBW children do not receive BCG at birth, but are told to come back when they have gained weight, and they typically get BCG together with the DTP and OPV scheduled at 6 weeks of age.

The neonatal nursery offers a very basic care level with possibility of phototherapy and intravenous infusion. Intubation and oxygen therapy was not possible at the time the trial was conducted. Admitted children did often share the available incubators. The service of the neonatal nursery is free, and children of all gestational ages are admitted. There is no possibility of transmission to a higher specialised unit.

Enrolment
The study was initiated 20 February 2008. LBW children identified at the hospital were examined by a doctor or a trained nurse who also assessed maturity using Ballard score [16]. Anthropometric measurements were obtained and the child was examined. Eligible were boys with a weight below 2.5 kg. Exclusion criteria were major malformations, female sex, and weight at enrolment of ≥ 2500 g. Children who had already received BCG and children with clinical signs of vitamin A deficiency were also excluded, as were children that were too sick to be discharged by local standards. These children were referred for treatment. There was no age criterion, as all children weighing less than 2500 g and coming for their first vaccines were eligible. The oldest child enrolled was 64 days old, and the age distribution is described in Table 1. The mothers were informed of the study in the local language, Creole, and got a written explanation of the study in the official language, Portuguese. Oral and written consent was obtained. The mother signed the enrolment form if she could write, if not she put a fingerprint, and an independent observer signed the form. Provided consent, the mother drew a lot from a bag. The lot decided which treatment, VAS or OPV, her son would receive at enrolment. Randomisation was done in blocks of 24. The bags were prepared by the study supervisor; each bag contained 24 stapled lots in separate opaque envelopes. Twins were allocated the same treatment to prevent potential confusion regarding
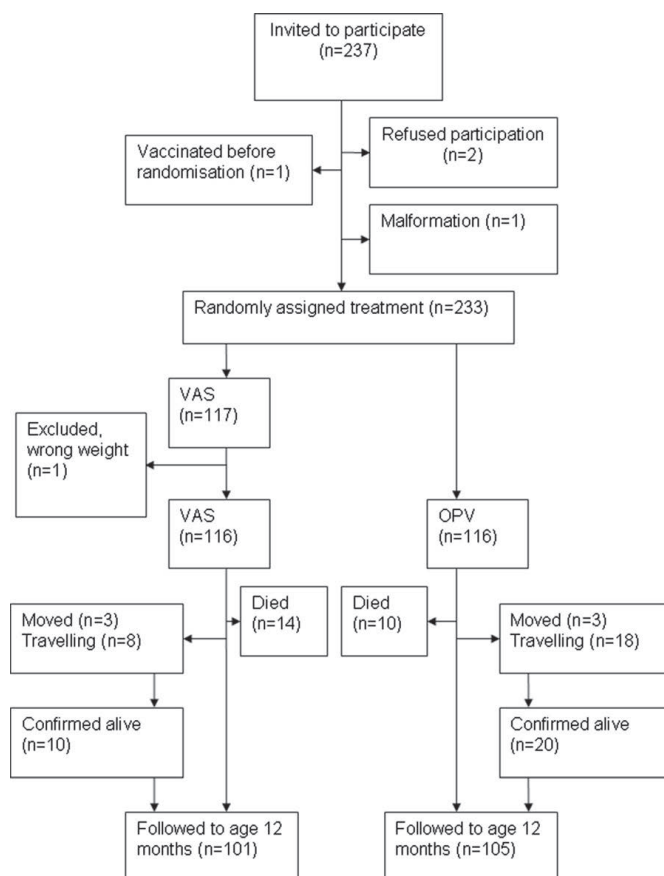
Figure 1 Trial profile.

Table 2 The effect of VAS/OPV at birth on infant mortality overall and by season of enrolment

	Censored at 18 November 2008			With full follow up time		
	VAS MR (Deaths/pyrs)	OPV MR (Deaths/pyrs)	VAS vs. OPV HR (95% CI)	VAS MR (Deaths/pyrs)	OPV MR (Deaths/pyrs)	VAS vs. OPV HR (95% CI)
All	35.1	21.2	1.66 (0.68 – 4.02)	13.6	9.3	1.46 (0.65 - 3.29)
	13/37	8/37		(14/103)	(10/108)	
By season						
Dry	15.8	28.9	0.54 (0.16 - 1.84)	11.9	23.3	0.53 (0.18 - 1.55)
	4/25	7/24		(5/42)	(9/39)	
Rainy	77.1	7.4	10.0 (1.24 – 80.5)	14.9	1.4	9.91 (1.23 - 79.8)
	9/12	1/14		(9/61)	(1/69)	
P for interaction			0.02			0.02

MR per 100 years of follow up.
Abbreviations: Pyrs person years of follow up.

who had been vaccinated and supplemented. All mothers were encouraged to take their child to a health centre at 6 weeks of age to get BCG, OPV, and DTP. At every home visit the assistants checked the children's vaccination cards and pointed out missing vaccines for the mothers to ensure that all children got OPV. Enrolment staff did not take part in the follow-up of the children.

Interventions

Vitamin A was given as a 0.5 ml oral supplement which was slowly released into the mouth of the child with a sterile syringe by a nurse. The supplement came in dark glass bottles that were prepared at Skanderborg Pharmacy, Denmark, and contained 20 doses of 25000 IU vitamin A as retinyl palmitate and 10 IU vitamin E per 0.5 ml oil. The bottles were kept at 2-8°C. Trivalent OPV was supplied through the national immunisation programme and administered orally. There was no blinding.

Outcomes

Primary outcome: infant mortality
The LBW children were visited within the first 3 days after enrolment, and children living inside the study area were visited on day 1–3 after enrolment to check for adverse events. All children who had not died, moved or were travelling were visited at 2, 6, and 12 months of age (Figure 1). The children living inside the BHP study area were furthermore followed by the HDSS. If the child moved outside Bissau or was absent at the visit, relatives or neighbours were asked if the child was still alive and how soon they would be told if the child died. Children travelling at 12 months were visited again at 15–18 months of age. When a death was registered, the assistant asked for the child's health card. A verbal autopsy was conducted around three months after the death by a trained assistant. A local doctor read the autopsy and proposed a diagnosis. The cause of death in broad categories was determined later after reading the verbal autopsy and taking into account the local doctor's diagnosis and possible hospital records.

We collected information on temperature, respiratory frequency, weight gain and a few other variables in the first three days after enrolment to be able to detect possible adverse effects of the intervention (which we did not find); however, we did not collect information on possible specific diagnoses of the surviving children enrolled in the trial.

Secondary outcome: growth
A subgroup of children was visited biweekly for the first 3 months and at 4, 5, and 6 months of age by an anthropometry team measuring weight, length, and arm and head circumference. This sub study was initiated 10 April 2008 and continued enrolling children until the main trial was stopped at 18 November 2008. Measurements were made by two trained field assistants who visited the home of the child. The length of the child was measured supine using a measuring board (Seca Model 416). The weight of the undressed child was measured to the nearest 20 g using an electronic scale (Seca Model 835/336). Middle upper arm circumference (MUAC) and head circumference were measured using a TALC insertion tape. Children who were temporarily absent were visited later the same or the following day, whereas children travelling were only visited at the following round. Children who moved were localised as described above.

Sample size considerations

We expected to enrol 900 boys in three years. With a mortality of 15% between enrolment and 12 months of age, we had 80% power to detect a 40% reduction in mortality for boys with a confidence level of 95%. With a sample size of 300 boys in the growth study, we should be able to detect a weight difference of 150 g in favor of the proposed versus the current policy with a power of 80% and a one-sided alpha of 0.05.

Special investigations initiated after the identification of the cluster

Due to the cluster of deaths described in this paper, one of the authors (NL) supervised the verbal autopsies of the children. In November and December 2008, after the cluster was identified, we took 20 throat swabs from children currently treated at the neonatal nursery to search for viruses. The sample was collected with a cotton swab from the back of the child's throat and placed in an Eppendorff tube containing 1 mL of alcohol. The tubes were stored at room temperature until analysis at Statens Serum Institut, Denmark. The samples were examined for Influenza A and B, Respiratory Syncytial Virus, Human Metapneumovirus, Parainfluenza, Adeno, Corona, Rhino, Entero, and Parecho viruses using PCR on a MagNaPure system. However, when the samples were collected there was no longer a mortality problem at the nursery and nothing was found in the throat swabs.
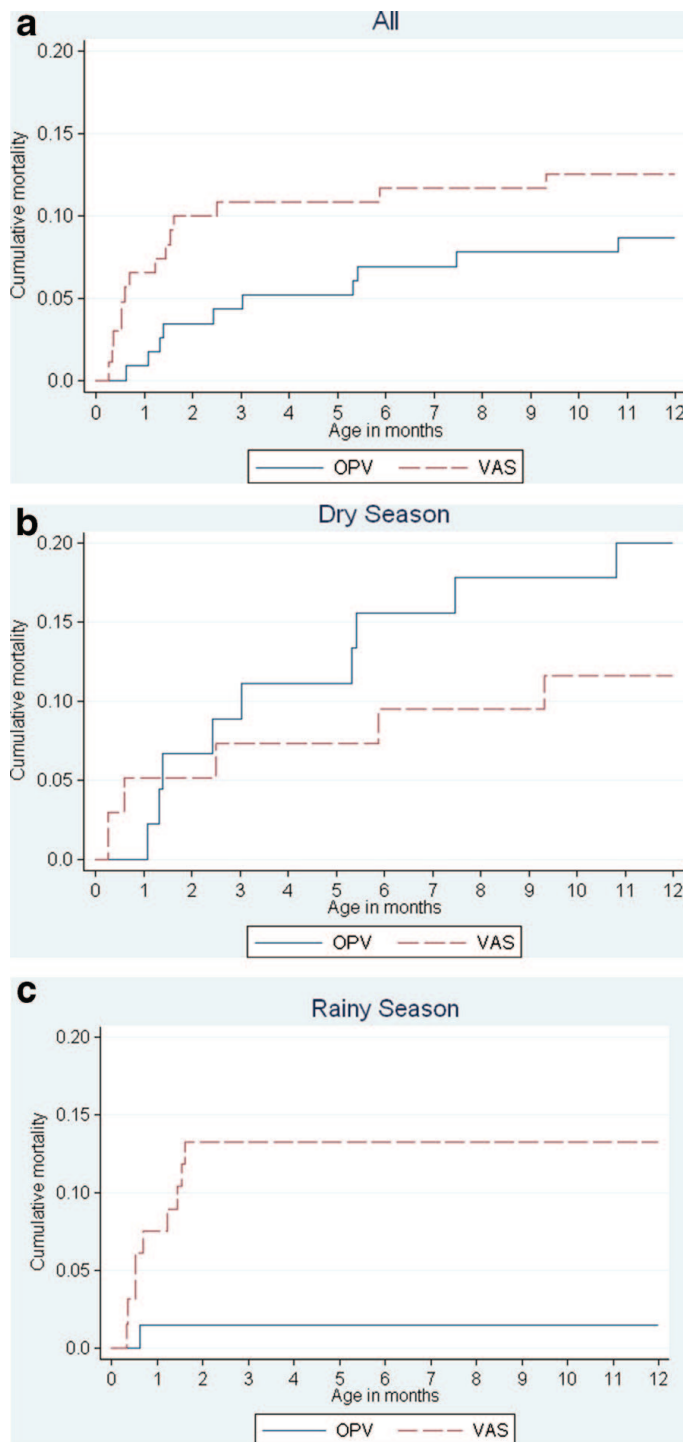
Figure 2. Cumulative mortality curves as a function of receiving VAS or OPV. (a) Overall, (b) Dry season, (c) Rainy season.

Likewise we conducted immunological examinations of cytokine responses among children recruited in October and November. Few children were included and the cluster of deaths had passed. Hence, the results were unrevealing.

Statistical methods

Statistical analysis was performed using Stata 11.2 software (Stata Corporation, College Station, TX). Baseline characteristics of children in the VAS group vs. children in the OPV group were compared using logistic or linear regression.

Table 3 The fraction of dead/enrolled children by place of enrolment, month of enrolment, and randomisation group

| | No. of deaths/enrolled (% dead) | | | |
| | Enrolled at neonatal nursery | | Enrolled at maternity ward or health centres | |
Month of enrolment	VAS	OPV	VAS	OPV
February	0/0 (0)	1/2 (50)	0/4 (0)	1/4 (25)
March	2/3 (67)	0/4 (0)	0/11 (0)	1/10 (10)
April	2/6 (33)	1/4 (25)	0/8 (0)	1/10 (10)
May	0/5 (0)	3/4 (75)	1/9 (11)	1/7 (14)
Total, dry season	4/14 (29)	5/14 (36)	1/32 (3)	4/31 (13)
June	0/2 (0)	0/4 (0)	0/5 (0)	0/6 (0)
July	1/3 (33)	0/1 (0)	1/6 (17)	0/8 (0)
August	1/2 (50)	0/2 (0)	0/8 (0)	0/5 (0)
September	5/6 (83)	1/6 (17)	1/9 (11)	0/9 (0)
October	0/4 (0)	0/0 (0)	0/17 (0)	0/20 (0)
November	0/0 (0)	0/3 (0)	0/8 (0)	0/7 (0)
Total, rainy season	7/17 (41)	1/16 (6)	2/53 (4)	0/55 (0)
Total	11/31 (35)	6/30 (20)	3/85 (4)	4/86 (5)

We used Cox regression to calculate Hazard Ratios (HR) for mortality with 95% Confidence Intervals (CI). Robust standard errors were used to account for interdependency of outcome between twins. Age was used as the underlying time and was thus inherently controlled for in the mortality analyses. Test for proportionality of hazard rates were computed using Schoenfeldt residuals and by visual inspection of the cumulative risk curves. Cumulative mortality curves were drawn using the Kaplan-Meier method. We tested whether there were differences in the age at death in a linear regression model on the log-transformed age.

We tested interactions between baseline characteristics, season of enrolment (rainy season June to November, dry season December to May), and admission to neonatal nursery before enrolment by Wald test statistics. We analysed effect modification by investigating the homogeneity of the effect of the intervention in the different categories of the suspected modifier, also by Wald test statistics. Effect modifiers considered were age at and place of enrolment, place of residence, birth weight, head circumference, MUAC, and maternal MUAC, age, parity, schooling, and socioeconomic status.

Table 4 Causes of death by intervention and age at death

| | Deaths within first 2 months | | Deaths after 2 months of age | |
	VAS	OPV	VAS	OPV
Resp. diseases	5	1	2	1
Diarrhoea	2	0	0	0
Sepsis	1	0	0	1
Kernicterus	0	1	0	0
Chickenpox	0	0	0	1
Unknown*	3	2	1	3
Total	11	4	3	6

*Three families moved before autopsy, and a diagnosis could not be established in six children.

Table 5 The effect of VAS/OPV on anthropometric parameters at baseline, 4 weeks, and 6 months after enrolment

	Baseline				4 weeks				6 months			
	VAS	OPV	Difference#/GMR¤	RR	VAS	OPV	Difference#/GMR¤	RR	VAS	OPV	Difference	RR
	N = 77	N = 82	(95% CI)	(95% CI)	N = 63	N = 66	(95% CI)	(95% CI)	N = 67	N = 73	(95% CI)	(95% CI)
Age, days	2	2			32	34			183	183		
Length, cm*	44.9	45.2	0.99¤ (0.98-1.01)		48.3	49.5	0.45¤ (0.17-1.16)		63.0	63.6	−0.32 (−1.31;0.67)	
LAZ*	−3.01	−2.84	−0.17# (−0.54;0.20)		−3.38	−2.89	−0.28# (−0.77;0.22)		−2.16	−1.93	−0.13 (−0.59;0.34)	
Stunted*	85%	72%		**1.19** **(1.00-1.40)**	86%	74%		1.12 (0.94-1.33)	55%	37%		1.49 (0.98-2.23)
Weight, kg	2.05	2.13	0.96¤ (0.92-1.01)		2.84	3.10	**−0.26#** **(−0.46;-0.07)**		6.51	6.57	−0.06 (−0.43;0.31)	
WAZ	−2.95	−2.73	−0.20# (−0.47;0.08)		−3.31	−3.00	**−0.46#** **(−0.88;-0.04)**		−3.20	−3.06	−0.11 (−0.61;0.39)	
Under-weight	97%	99%		0.99 (0.94-1.03)	87%	73%		**1.20** **(1.01-1.43)**	48%	29%		**1.68** **(1.04-2.73)**
HC, cm	31.0	31.3	−0.27# (−0.85;0.31)		35.3	35.6	−0.22# (−0.76;0.32)		42.6	42.8	−0.16 (−0.72;0.40)	
HCAZ	−3.11	−2.89	−0.22# (−0.71;0.26)		−1.86	−1.47	−0.09# (−0.55;0.37)		−0.55	−0.43	−0.13 (−0.58;0.33)	
MUAC, cm	7.7	7.9	0.80¤ (0.63-1.02)		9.4	10.1	**−0.50#** **(−0.93;-0.07)**		13.9	14.1	−0.21 (−0.65;0.23)	
ACAZ	-	-			-	-	-		−0.35	−0.15	−0.19 (−0.62;0.23)	

*Length measures are adjusted for being stunted at baseline.
¤Geometric mean ratio (GMR) is provided for non-normally distributed data, #Difference for normally distributed data.
Abbreviations: RR relative risk; LAZ length-for-age z-score; WAZ weight-for-age z-score; HC head circumference; HCAZ head circumference-for-age z-score; MUAC middle upper arm circumference; ACAZ Arm circumference-for-age z-score.
Significant values in **bold**.

We compared the individual anthropometry measurements to the 2006 WHO growth reference [17]. Z-scores for length-for-age, weight-for-age, head circumference for age, and mid-upper-arm-circumference (MUAC)-for-age (only available for children aged 12 weeks or more) were derived. Children were classified as stunted (length-for-age z-score ≤−2) and underweight (weight-for-age z-score ≤−2) at all time points. We compared differences in z-scores by linear regression. For variables that were not normally distributed, geometric mean ratios (GMRs) were calculated from the log-transformed variable. Differences in growth between baseline and 4 weeks visits were compared using linear regression. We calculated relative risks (RR) of being stunted or underweight in Poisson regression models with robust standard errors [18]. Possible interaction with season of inclusion was explored.

Ethics statement
There have been no cases of poliomyelitis in Guinea-Bissau for at least a decade. As a "natural experiment" had worryingly shown that boys who had not received OPV at birth had significantly lower mortality than boys who had received OPV at birth [14], and as OPV is also provided at 6, 10 and 14 weeks of age and during national immunisation days, we found it ethically justified to conduct a trial not giving boys OPV at birth if they had been randomised to vitamin A. The protocol was approved by the Guinean Ministry of Health's Research Coordination Committee, and the Danish Central Ethics Committee gave its consultative approval. The trial was registered at www.clinicaltrials.gov, identifier NCT00625482.

Results
From 20 February 2008 to the trial was halted on 18 November 2008 a total of 237 boys were invited to participate. Two mothers refused participation, one child received vaccines before randomisation, and one child turned out not to be eligible due to a malformation. One child in the VAS group had weighed 2300 g at birth but had gained weight and weighed 2500 g at inclusion and was excluded from analysis (Figure 1). Hence, we ended up with 232 boys; 116 in the OPV group and 116 in the VAS group. As shown in Figure 1, at the 12 months visits, three children in each group had moved; however, only two of the children, one in each group, could not be confirmed alive. All travelling children were confirmed alive by relatives or neighbours.

Baseline characteristics of the two intervention groups are shown in Table 1. The medical examination made before enrolment showed no difference in heart frequency, respiratory frequency, or temperature between the cluster children and the non-cluster children enrolled from the neonatal nursery or from the maternity ward. Breastfeeding was initiated in all children. At the 2 months visit, all visited children were breastfed. At the 6 months visit, 4 children in the OPV group and 2 in the VAS group were not breastfed any more. Of these, one child (OPV) died before 12 months of age. At the 12 months visit, another 4 children had been weaned (1 OPV, 3 VAS).

Mortality cluster
When several death forms were brought back by the anthropometric team and the team conducting the 2-months visits in October-November 2008, we compiled the mortality statistics shown in Table 2. Season was monitored because previous analyses had shown that though the overall effect of VAS appeared to be beneficial for boys, there might not be a beneficial effect in the rainy season. This was strongly supported by the incoming reports; there was 10-fold increased mortality among boys receiving VAS in the rainy season and

a clear inversion of the pattern between dry and rainy season (Table 2). Based on these data we decided to temporarily halt the enrolment of LBW boys on 18 November 2008. As shown in Figure 2a, mortality in the group receiving VAS was 7 fold higher in the first month of life (HR = 7.20 (95% Confidence Interval (CI): 0.89 – 58.5)) and 3 fold higher at 2 months of age (HR = 2.85 (0.91 – 8.93)).

Subsequent examinations showed that the children who died had not received the same bottle of VAS and common contamination was therefore unlikely. However, the examination revealed that most of the children who died had been in the neonatal nursery (Table 3). Of the 14 boys admitted to the neonatal nursery during September 2008, two died before being discharged; of the 12 boys being discharged and enrolled in the present trial, six received VAS of whom five died whereas six received OPV of whom one died within two months of age (p = 0.05). One VAS boy enrolled in September who also died within the first 2 months of life had not himself been admitted to the neonatal nursery, but his twin had. These seven boys were between 9 and 43 days old when they died; the median age was 18 days. Among the additional children enrolled at all enrolment sites in October and November before we halted the study, there were no deaths (Table 3).

Main outcome: infant mortality
Followed to 12 months of age the mortality rate was 11.4 deaths per 100 person-years, somewhat lower than the anticipated 15/100 (Figure 2a-c). Fourteen VAS boys and 10 OPV boys died resulting in a HR of 1.46 (0.65 – 3.29) (Table 2). The estimates did not change if children who moved or were travelling were censored at the day they left. At 2 and 6 months of age the HR for VAS vs. OPV were 2.85 (0.91 – 8.93) and 1.69 (0.70 – 4.09), respectively. All deaths among children included in the rainy season occurred before two months of age and VAS boys were therefore overall younger than OPV boys when they died (median age at death of 28 days in VAS boys and 82 days in OPV boys, p = 0.04).

The number of very low birth weight babies (VLBW, birth weight < 1500 g) was 7 (6%) in each group. Two of the VLBW babies in the OPV group died during follow up, one of them was enrolled at the neonatal nursery during September 2008 (the cluster period). Another VLBW baby in the OPV group was also enrolled from the neonatal nursery during this period but survived. Three VLBW babies in the VAS group died during follow up, one of them was enrolled from the neonatal nursery in the cluster period. None of the other VLBW babies in the VAS group were enrolled during the cluster period.

Causes of death
Of the seven dead children enrolled in the cluster period, four (all VAS) died from respiratory diseases (Table 4). One child (OPV) died from kernicterus, and the cause of death could not be established in two children (VAS).

Secondary outcomes: growth
Eighty-six children from the OPV group and 87 from the VAS group were enrolled in the anthropometry sub study; 82 and 77 children, respectively, had at least one visit. An average of 74% of the children was found at home at each visit. Of the 173 children enrolled in the anthropometry study, nine VAS and two OPV boys died before the last anthropometry visit at 6 months after

enrolment, corresponding to a relative risk (RR) of loss to follow up due to death for VAS vs. OPV of 4.44 (0.99 – 20.08).

In the subgroup followed for growth, more children in the VAS group were stunted at baseline. We therefore adjusted length measures at the following visits for being stunted at baseline in analyses where adjustment changed the estimate by more than 10%. Two weeks after enrolment VAS children were significantly lighter and had a lower weight-for-age z-score and MUAC than OPV children. These differences were also found at the 4, 6, 10, and 12 week visits (data only shown for the 4 weeks visit, Table 5). There were no differences in length and head circumference between the two groups at any visit when length analyses were controlled for being stunted at baseline. At 6 months VAS children were more often underweight than OPV children (Table 5). Because of the imbalance of stunted children between the two groups, we studied growth between baseline and the 4 weeks visit. It turned out that even though stunted children, regardless of randomisation group, experienced significantly better linear growth than non-stunted children between baseline and 4 weeks, probably reflecting a catch up growth, VAS children had a significantly poorer linear growth (Difference adjusted for being stunted at baseline = −1.02 (−1.66; −0.38)) between baseline and 4 weeks). There was no interaction between growth and season (data not shown).

Discussion
Principal findings
A cluster of deaths occurred during the rainy season among the boys enrolled in the trial of VAS versus OPV and affected primarily those who had received VAS. The effect of VAS versus OPV differed significantly between the dry and the rainy season with a 10-fold higher mortality in the rainy season. VAS recipients had a significantly poorer growth measured by weight and MUAC up to 3 months after enrolment.

Strengths and weaknesses
The close follow up of LBW children has been conducted since 2002 by the same staff. The trial had to be stopped prematurely due to the cluster of deaths and the study therefore did not reach the anticipated sample size.

Mortality
A sudden increase in deaths among boys who had received VAS in the rainy season provoked our attention and the decision to halt inclusion. We subsequently detected that these boys had all been at the neonatal nursery within the same week. The deaths were mainly due to respiratory problems. Overall the study sample size was clearly too small to make firm conclusions on the effect of receiving VAS versus placebo, but it is noteworthy that there were a quite strong interaction between VAS and season, with a tendency for a beneficial effect in the dry season, but a significant negative effect in the rainy season.

Growth
We found worse growth for the VAS recipients than the OPV recipients in the first months of life irrespective of season. We have studied the effect of neonatal VAS given with BCG at birth and found a beneficial effect on growth for boys [19]. Also, a trial from Indonesia showed a beneficial overall effect of neonatal VAS on growth up to 3 years of age [20]. Another trial from Java, Indonesia, found complex interactions between VAS and season in children aged 6–48 months at supplementation with the least beneficial effect of VAS in seasons with a high burden

of respiratory diseases [21]. However, VAS was not harmful. The effect of OPV0 on growth has not been studied before.

Chance or cluster
The sudden increase in the number of deaths among boys who had received VAS and who had been in contact with the neonatal nursery made us speculate that they had been infected with a pathogen that either interacted negatively with VAS or was dealt better with by OPV vaccinated boys. A pathogen could easily have spread among the children through the suboptimal hygienic conditions. We could not identify any likely pathogen or immunological differences between the two groups which could explain the cluster, but this is perhaps not surprising as the mortality was no longer elevated at the time when we collected throat swaps and immunological samples. The pathological pictures of the dead children were quite different and the deaths did not occur immediately. Hence, it is unlikely that the children died of the same infection. However, it may be speculated that the pathogen weakened the children who died later, possibly by encounter with a new pathogen.

When we halted the trial we did not know whether there might be more deaths among children with whom we had not yet had contact. However, that was not the case; there were no additional early deaths among the children recruited in October and November. The problem apparently had passed. However, we did not restart the trial. Though this may have been due to a pathogen which was no longer present there was no reason to risk that the same might happen again. Furthermore, the boys who had received OPV0 clearly grew better in the first months of life than the boys who had received neonatal VAS. Hence, there was no indication that it was relevant to continue the trial.

With the study design it cannot be determined whether vitamin A was harmful or whether OPV stimulated a non-specific immune response which provided some protection against infections as also seen for other live vaccines [22].

When we initiated the trial, all available data suggested that neonatal VAS be beneficial for boys. However, subsequently data from Zimbabwe have been published, showing a 19% increase in mortality for boys [23]. Though the results are not directly comparable with the other trials because the trial was 2-by-2 factorial with provision of maternal VAS as well, and because the prevalence of HIV was very high and most deaths occurred in children of HIV positive mothers, the results nonetheless show that neonatal VAS can be harmful to boys under certain circumstances. We have previously found strong seasonal differences in the response to neonatal VAS [1]. In boys VAS had a strong beneficial effect in the dry season (0.45 (0.24 – 0.84)) but tended to have a negative effect in the rainy season 1.53 (0.84 – 2.79). This could be seen as support of a negative effect of VAS also in the present study, though it should be noted that no negative effect was seen in our other studies [2,24]. Hence we cannot rule out that neonatal VAS had a negative effect for boys in the present trial.

However, we are more inclined to believe that OPV0 was particularly beneficial. Though we have previously found increased male mortality after OPV0, it was based on an observational study and it is contradicted by other studies on OPV [25,26]. Observations from Chile and Brazil showed significant reduction in infantile diarrhoea mortality following the first massive vaccination campaigns with OPV [27,28]. A

recent study from Finland found that children who had received OPV had fewer episodes of otitis media at age 6–18 months than control children who received inactivated polio vaccine (IPV) [29].

The growth data support a beneficial effect of OPV0 rather than a negative effect of VAS since the differences in growth between the two groups gradually disappeared as more children in both groups got OPV1 scheduled to be given at 6 weeks of age.

Hence, rather than neonatal VAS being bad, we are more in favour of the hypothesis that the immunostimulation provided by OPV may have protected the children in the OPV group against pathogens circulating possibly by priming a Th1 type immune response, as hypothesised in several studies [30-32].

Conclusion
These observations may be important. The introduction of neonatal VAS is debated [33-39] and WHO has launched three mega trials of neonatal VAS with more than 100,000 children to inform global policy. The present study does not support a policy of providing VAS, but clearly it cannot be seen as strong evidence against this policy on its own rights.

Though OPV0 is official policy, many African children do not receive it [40]; for example, there are often special rules not to give OPV0 after two weeks of age. Furthermore, there are long-term plans to replace OPV with inactivated polio vaccine (IPV) since OPV is associated with a small risk of developing polio paralysis [41]. If OPV has beneficial non-specific effects as suggested by this and other studies [25,26,29,42], replacing OPV with IPV may not have a beneficial effect on overall survival. For example, we found that among children randomised to IPV as a control vaccine, girls had significantly higher mortality than the boys [43].

In conclusion, receiving VAS at birth instead of OPV was not beneficial for the LBW boys in this trial. Growth in the first few months of life was affected negatively and there was a tendency for higher mortality during the first weeks of life which was statistically significant in the rainy season. With the premature closure of the trial, however, the trial was clearly underpowered to establish a causal relation between the intervention and the outcomes, and the results cannot be generalised. We think it is most likely that OPV at birth provided a non-specific immune stimulation that proved beneficial in dealing with a circulating respiratory pathogen in the rainy season. However, the results of this study call for extra caution when testing the effect of NVAS in the future.

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Essential Childbirth And Postnatal Interventions For Improved Maternal And Neonatal Health

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Abstract

Childbirth and the postnatal period, spanning from right after birth to the following several weeks, presents a time in which the number of deaths reported still remain alarmingly high. Worldwide, about 800 women die from pregnancy- or childbirth-related complications daily while almost 75% of neonatal deaths occur within the first seven days of delivery and a vast majority of these occur in the first 24 hours. Unfortunately, this alarming trend of mortality persists, as 287,000 women lost their lives to pregnancy and childbirth related causes in 2010. Almost all of these deaths were preventable and occurred in low-resource settings, pointing towards dearth of adequate facilities in these parts of the world. The main objective of this paper is to review the evidence based childbirth and postnatal interventions which have a beneficial impact on maternal and newborn outcomes. It is a compilation of existing, new and updated interventions designed to help physicians and policy makers and enable them to reduce the burden of maternal and neonatal morbidities and mortalities. Interventions during the postnatal period that were found to be associated with a decrease in maternal and neonatal morbidity and mortality included: advice and support of family planning, support and promotion of early initiation and continued breastfeeding; thermal care or kangaroo mother care for preterm and/or low birth weight babies; hygienic care of umbilical cord and skin following delivery, training health personnel in basic neonatal resuscitation; and postnatal visits. Adequate delivery of these interventions is likely to bring an unprecedented decrease in the number of deaths reported during childbirth.

Introduction

The number of deaths reported during childbirth and postnatal period still remain alarmingly high. Worldwide, about 800 women die from pregnancy- or childbirth-related complications daily and approximately 287,000 women lost their lives to pregnancy and childbirth related causes in 2010 [1]. Every year an estimated 2.9 million babies die in the first 4 weeks of life [2,3]. Almost all (99%) neonatal deaths occurs in low- and middle-income countries (LMICs), yet most epidemiological and other research focuses on mere 1% of deaths occurring in high income countries (HICs) [4]. The fact that almost all of these deaths were preventable and occurred in low-resource settings, points to a dearth of adequate facilities in these parts of the world. Preterm birth, birth asphyxia (lack of breathing at birth), and infections

cause most neonatal deaths. The critical postpartum period starts from about an hour after the delivery of placenta and extends over the following six weeks. Postpartum care should respond to the special needs of the mother and baby during this critical period and should include prevention and early detection; treatment of complications and disease; attention to hygienic care; advice and support of exclusive breastfeeding; birth spacing; immunization; and maternal nutrition [5].

Since the postnatal period is a critical time to deliver interventions, failure to do so leads to detrimental effects on the survival and future health of both mother and neonate. Many women die as a result of complications during and following childbirth. The major complications that account for 80% of all maternal deaths are severe bleeding (mostly bleeding after childbirth), infections (usually after childbirth), high blood pressure during pregnancy (preeclampsia and eclampsia), and unsafe abortion. The remainder are caused by or associated with infectious diseases during pregnancy such as malaria and AIDS. A practical and viable strategy for reducing maternal and neonatal morbidity and mortality rates from preventable causes and meeting maternal health related Millennium Development Goal (MDG) targets, is by integrating improved childbirth facilities and postnatal care for newborns and mothers [6]. The 4th MDG focuses on reducing child mortality and is closely associated with maternal health MDG. In developing countries alone, if mothers start practicing early initiation of breastfeeding, it is estimated that it can save as many as 1.45 million lives annually by reducing deaths mainly due to lower respiratory tract infections and diarrhoeal diseases [7]. To reduce the high burden of neonatal mortality and morbidity, postnatal care should be integrated into existing health programs. Community based education and health promotive workshops on exclusive breastfeeding and preventing vertical transmission of HIV will help increase the coverage of the postnatal interventions and improve maternal and newborn health.

This paper reviews and highlights the effectiveness of essential childbirth and immediate postnatal interventions for mothers and newborns during the parturition and postnatal period. This paper will help decision makers to deploy necessary interventions for improved maternal and newborn outcomes.

Methodology

The methodology has been described in detail elsewhere [8]. In short, the review included all childbirth and postnatal interventions based on current World Health Organization

(WHO) guidelines and recent Lancet series which have an alleged impact on reducing maternal, neonatal and child mortality; suitable for delivery in LMICs; and those that can be delivered through the health sector (community level up to the referral level of health care) (Table 1). All relevant childbirth and postnatal intervention reviews were identified from the electronic databases such as the Cochrane database of systematic reviews, the Cochrane database of abstract reviews of effectiveness (DARE), the Cochrane database of systematic reviews of randomized control trials (RCT's), and PubMed. The reference lists of the reviews and recommendations from experts in the field were also used as sources to obtain additional publications. The principal focus was on the existing systematic reviews and meta-analysis. Based on the efficiency of the interventions, these were then classified in categories from A to E (where A signified strongly beneficial effect while E indicated harmful effect) on different levels of health sector (community/outreach/referral).

Childbirth interventions
Social support during childbirth
Historically and cross-culturally, women have been attended and supported by other women during childbirth. However, since the middle of the 20th century, in many countries as the majority of women gave birth in hospital rather than at home, continuous support during labour has become an exception rather than the routine. Concerns about dehumanization of women's birth experiences (in high-, middle-, and low income countries) have led to calls for a return to continuous, one-to-one support by women for women during labour [9]. Common elements of this care include emotional support (continuous presence, reassurance and praise), information about labour progress and advice regarding coping techniques, comfort measures (such as comforting touch, massage, warm baths/showers, promoting adequate fluid intake and output) and advocacy (helping the woman articulate her wishes to others).

A systematic review by Hodnett et al reported that women allocated to continuous support were more likely to have a spontaneous vaginal birth (risk ratio (RR) 1.08, 95% confidence interval (CI) 1.04, 1.12) and less likely to have intrapartum analgesia (RR 0.90, 95% CI: 0.84, 0.97) or report dissatisfaction (RR 0.69, 95% CI: 0.59, 0.79). In addition their labour were shorter (mean difference (MD) -0.58 hours, 95% CI: -0.86, -0.30), they were less likely to have a caesarean (RR 0.79, 95% CI: 0.67, 0.92) or instrumental vaginal birth (RR 0.90, 95% CI: 0.84, 0.96), regional analgesia (RR 0.93, 95% CI: 0.88, 0.99), or a baby with a low 5-minute Apgar score (RR 0.70, 95% CI: 0.50, 0.96) [10]. Continuous social support has shown significant clinical benefits for women and infants. All women should receive continuous social support throughout labour and childbirth.

Prophylactic antibiotic for caesarean sections
The single most important risk factor for post-partum maternal infection is caesarean delivery [11]. Women undergoing caesarean section have a 5 to 20-fold greater risk for infection compared with a vaginal delivery. Infectious complications that occur after caesarean delivery are an important and substantial cause of maternal morbidity and are associated with a significant increase in hospital stay [12]. Infectious complications following caesarean delivery include fever, wound infection, endometritis, bacteraemia, other serious infection (including pelvic abscess, septic shock, necrotizing fasciitis and septic pelvic vein thrombophlebitis) and urinary tract infection [11,13,14]. Fever

can occur after any operative procedure and a low grade fever following a caesarean delivery may not necessarily be a marker of infection [15].

Prophylactic antibiotics in women undergoing caesarean section substantially reduce the incidence of febrile morbidity (RR 0.45; 95% CI: 0.39, 0.51), wound infection (RR 0.39; 95% CI: 0.32, 0.48), endometritis (RR 0.38; 95% CI: 0.34, 0.42) and serious maternal infectious complications (RR 0.31; 95% CI: 0.19, 0.48) [16]. Based on these findings, we would recommend prophylactic antibiotics for women undergoing elective or non-elective caesarean sections however further studies are needed to explore potential adverse effects.

Prevention of postpartum haemorrhage
Excessive bleeding or postpartum haemorrhage (PPH) during or after childbirth is a life-threatening complication and a major contributor to maternal mortality worldwide [17]. Primary PPH is defined as heavy bleeding directly following childbirth or within 24 hours of thereafter [18]. One of the methods by which PPH is prevented is by active management of third stage of labour [19], while others include measures like uterine massage. Active management of third stage of labour (AMTSL) has three components which include the use of uterotonic agents, early cord clamping and controlled cord contraction. In 2012, the results of a large WHO-directed, multi-centre clinical trial [20] showed that administration of the uterotonic was the most important AMTSL component. This trial also demonstrated that the addition of Controlled Cord Traction had minimum effect on the reducing haemorrhage. Carbetocin (oxytocin) is a long acting synthetic analogue of oxytocin with pharmacological, clinical and agonist properties similar to oxytocin. It acts by combining to oxytocin receptors present in the uterus and causes increased tone and rhythmic contractions of the uterus and also increases the frequency of existing contractions.

i) Oxytocin for PPH

Prophylactic oxytocin showed benefits in reducing blood loss >500ml (RR 0.50; 95% CI: 0.43, 0.59) and need for therapeutic oxytocics (RR 0.50; 95% CI: 0.39, 0.64) compared to no uterotonic [21]. While another review showed no influence of oxytocin before and after the expulsion of placenta on incidence of PPH (blood loss >500ml) (RR 0.81; 95% CI: 0.62, 1.04); retained placenta (RR 1.54, 95% CI: 0.76, 3.11); length of third stage of labour (minutes) (Mean difference (MD) -0.30, 95% CI -0.95, 0.36); postpartum blood loss (ml) (MD 22.32, 95% CI: -58.21, 102.86); changes in haemoglobin (g/dL) (MD 0.06, 95% CI: -0.60, 0.72); blood transfusion (RR 0.79, 95% CI 0.23, 2.73); use of additional uterotonic (RR 1.10, 95% CI: 0.80, 1.52); incidence of maternal hypotension (RR 2.48, 95% CI: 0.23, 26.70) and incidence of severe PPH (blood loss ≥1000ml) (RR 0.98, 95% CI: 0.48, 1.98) [22].

ii) Active management of third stage of labour

In this section we included reviews that compared AMTSL with expectant management (when the placenta is allowed to deliver spontaneously or aided by gravity and nipple stimulation). According to the latest guideline of WHO, AMTSL as a prophylactic intervention is composed of three steps: 1) administration of a uterotonic, preferably oxytocin, immediately after birth of the baby; 2) controlled cord traction (CCT) to deliver the placenta; and 3) massage of the uterine fundus after the placenta is delivered. In 2012, the results of a large WHO-directed, multi-centre clinical trial [20] showed that the most important AMTSL component was the administration of the uterotonic. In view of the data from this trial and the existing

evidence concerning the role of routine uterine massage in the prevention of PPH, the WHO issued new recommendations which state that although administration of a uterotonic remains central to the implementation of AMTSL, the performance of CCT and immediate fundal massage are optional components [23].

Active management of third stage of labor showed reduction in the risk of haemorrhage at time of birth (>1000ml) (RR 0.34, 95% CI: 0.14, 0.87) and of maternal haemoglobin (Hb) <9g/dL following birth (RR 0.50, 95% CI: 0.30, 0.83) [24]. Compared with oxytocin, ergometrine-oxytocin was associated with a small reduction in the risk of PPH (OR 0.82, 95% CI: 0.71, 0.95) [25]. On the other hand, no significant differences were found between early versus late cord clamping on severe PPH (RR 1.04, 95% CI 0.65, 1.65) or for PPH (>500ml) (RR 1.17 95% CI: 0.94, 1.44) [26]. Another review by Pena-Marti et al did not find studies that compared fundal pressure versus controlled cord traction as part of AMSTL [27]. These findings suggest active management is superior to expectant management in terms of reduction in the risk of maternal haemorrhage at time of birth. However, statistically significant results in the improved outcomes of blood loss and PPH could not be found when active management was employed. On the other hand, prophylactic oxytocin showed benefits in reducing blood loss >500ml and need for therapeutic oxytocics.

Induction of prolonged pregnancy
Five to ten percent of pregnancies continue beyond 294 days (42 completed weeks) and are described as being 'post-term' or 'postdate' [28]. Both the mother and the infant are at increased risk of adverse events when the pregnancy continues beyond term [29]. Hilder et al 1998 reported that after 41 weeks, neonatal and post neonatal death risk increased significantly. The obstetric problems associated with post-term pregnancy include induction of labour with an unfavourable cervix, caesarean section, prolonged labour, PPH and traumatic birth. It is likely that some of these unwanted outcomes result from intervening when the uterus and cervix are not ready for labour [29].

Compared with a policy of expectant management, a policy of labour induction was associated with fewer (all-cause) perinatal deaths (RR 0.31, 95% CI: 0.12, 0.88). The number needed to treat to benefit (NNTB) with induction of labour in order to prevent one perinatal death was 410 (95% CI: 322, 1492) [30]. Another meta-analysis of trials also suggested that a policy of elective induction of labour for pregnancies at or beyond 41 weeks is associated with significantly fewer perinatal deaths (RR 0.31; 95% CI: 0.11, 0.88) compared to expectant management, but no significant difference in the incidence of stillbirth (RR 0.29; 95% CI: 0.06, 1.38) was noted. There was significant decrease in incidence of neonatal morbidity from meconium aspiration (RR 0.43, 95% CI: 0.23, 0.79) and macrosomia (RR 0.72; 95% CI: 0.54, 0.98) [31]. In case of absence of a specific disorder, induction of labour can be proposed in patients between 41(+0) and 42(+6) weeks (grade B). It is important to convey to the decision makers and patients that the choice of prolonging beyond 42(+0) weeks appears to involve an increase risk and decision should be weighed and balanced against the potential disadvantages of induction (Professional consensus). Stripping the membranes can reduce the duration of pregnancy by increasing the number of patients going into labour spontaneously during the week afterward (grade B) [32]. This policy is associated with fewer deaths. There does not

seem to be any increased risk of assisted vaginal or abdominal delivery. If the woman chooses to wait for spontaneous labour onset it would be prudent to have regular fetal monitoring as longitudinal epidemiological studies suggest increased risk of perinatal death by increasing gestational age.

Management of postpartum haemorrhage
Primary PPH requires a multidisciplinary approach. First line treatment is with uterotonic (such as ergometrine, oxytocin, prostaglandins) accompanied with bimanual compression of the uterus. The second line therapy is surgical, usually hysterectomy to prevent death from uterine haemorrhage.

i) Uterine massage
The review by Hofmeyr et al included two randomised controlled trials [33]. The first trial randomised women to receive uterine massage or no massage following delivery of the placenta, after active management of the third stage of labour including use of oxytocin. The numbers of women with blood loss >500ml was small, with no difference (RR 0.52, 95% CI: 0.16, 1.67) while the mean blood loss was significantly less in the uterine massage group at 30 minutes (MD -41.60ml, 95% CI: -75.16, -8.04) and 60 minutes (MD -77.40ml, 95% CI: -118.71, -36.09). There were no cases of retained placenta in either group. The need for additional uterotonic was also significantly reduced in the uterine massage group (RR 0.20, 95% CI: 0.08, 0.50). For use of uterine massage before and after delivery of the placenta, another trial assigned women to receive oxytocin, uterine massage or both after delivery of the baby but before delivery of the placenta. There was no added benefit for uterine massage plus oxytocin over oxytocin alone with respect to blood loss ≥500ml (RR 1.56, 95% CI: 0.44, 5.49) or need for additional use of uterotonic (RR 1.02, 95% CI: 0.56, 1.85) [33].

ii) Use of uterotonic
Oral or sublingual misoprostol when compared with placebo was found to be effective in reducing severe PPH (sublingual: RR 0.66; 95% CI: 0.45, 0.98) and blood transfusion (oral: RR 0.31; 95% CI: 0.10, 0.94). Compared with conventional injectable uterotonic, oral misoprostol was associated with higher risk of severe PPH (RR 1.33; 95% CI: 1.16, 1.52) and use of additional uterotonic, but with a trend towards fewer blood transfusions (RR 0.84; 95% CI: 0.66, 1.06) [34]. The comparison of misoprostol (dose 600-1000 mcg) with placebo did not show any impact on reducing maternal mortality (RR 7.24, 95% CI: 0.38, 138.6), hysterectomy (RR 1.24, 95% CI: 0.04, 40.78), additional use of uterotonic (RR 0.98, 95% CI: 0.78, 1.24), blood transfusion (RR 1.33, 95% CI: 0.81, 2.18), or evacuation of retained products (RR 5.17, 95% CI: 0.25, 107). Misoprostol use was associated with a significant increase in maternal pyrexia (RR 6.40, 95% CI: 1.71, 23.96) and shivering (RR 2.31, 95% CI: 1.68, 3.18) [35]. These findings suggest that misoprostol is effective in reducing severe PPH and blood transfusion. In comparison with conventional injectable uterotonic, oral misoprostol was associated with higher risk of severe PPH and use of additional uterotonic, but with a trend to fewer blood transfusions.

Postnatal (mother)
Advice and provision of family planning
The provision of contraceptive education is now considered a standard component of postpartum care. Family planning advice and education about contraception are commonly provided to women who have just given birth and is frequently provided as part of discharge planning [36]. Decisions about contraception made right after counseling may differ considerably from contraceptive use postpartum [37]. As common as postpartum

Table 1 Characteristics of the included reviews on childbirth and postnatal interventions

Reviews	Objective	Type of Studies included (number)	Cochrane/ non-Cochrane	Pooled Data (Y/N)	Outcomes reported
Hotnett 2013 [10]	To assess the effects of continuous, one-to-one intrapartum support compared with usual care.	RCTs: 21	Cochrane	Yes	spontaneous vaginal birth, intrapartum analgesia, dissatisfaction, caesarean, instrumental vaginal birth, regional analgesia
Smail 2010 [16]	To assess the effects of prophylactic antibiotics compared with no prophylactic antibiotics on infectious complications in women undergoing cesarean section.	RCTs and qRCTs: 86	Cochrane	Yes	febrile morbidity, wound infection, endometritis and serious maternal infectious complications
Cotter 2001 [21]	To examine the effect of oxytocin given prophylactically in the third stage of labour on maternal and neonatal outcomes.	RCTs: 14	Cochrane	Yes	Blood loss, removal of placenta, blood pressure
Soltani 2010 [22]	To assess the effect of the timing of administration of prophylactic uterotonics (before compared to after placental delivery) on the outcomes related to the third stage of labour.	RCTs: 3	Cochrane	Yes	postpartum haemorrhage, retained placenta, length of third stage of labour, postpartum blood loss, changes in haemoglobin, blood transfusion; the use of additional uterotonics the incidence of maternal hypotension and the incidence of severe postpartum haemorrhage
McDonald 2004 [25]	To compare the effects of ergometrine-oxytocin with oxytocin in reducing the risk of PPH (blood loss of at least 500 ml) and other maternal and neonatal outcomes.	RCTs: 6	Cochrane	Yes	blood loss of at least 500 m
Begley 2011 [24]	To compare the effectiveness of active versus expectant management of the third stage of labour.	RCTs and qRCTs: 5	Cochrane	Yes	maternal primary haemorrhage, maternal haemoglobin
McDonald 2013 [26]	To determine the effects of early cord clamping compared with late cord clamping after birth on maternal and neonatal outcomes	RCTs:15	Cochrane	Yes	postpartum haemorrhage
Pena-Marti 2007 [27]	To determine the efficacy of fundal pressure versus controlled cord traction as part of the active management of the third stage of labour.	RCTs: 0	Cochrane	No	None
Gulmezoglu 2012 [30]	To evaluate the benefits and harms of a policy of labour induction at term or post-term compared to awaiting spontaneous labour or later induction of labour.	RCTs: 19	Cochrane	Yes	perinatal deaths, cesarean sections
Hussain 2011 [31]	The purpose of this review was to study the possible impact of induction of labour (IOL) for post-term pregnancies compared to expectant management on stillbirths.	Studies: 25 RCTs: 14	Non-Cochrane	Yes	Stillbirths
Hofmeyr 2013 [33]	To determine the effectiveness of uterine massage after birth and before or after delivery of the placenta, or both, to reduce postpartum blood loss and associated morbidity and mortality.	RCTs: 2	Cochrane	No	Blood loss
Tuncalp 2012 [34]	To assess the effects of prophylactic prostaglandin use in the third stage of labour.	RCTs: 72	Cochrane	Yes	severe PPH, blood transfusion
Mousa 2007 [35]	To assess the effectiveness and safety of pharmacological, surgical and radiological interventions used for the treatment of primary PPH	RCTs: 3	Cochrane	Yes	maternal mortality, hysterectomy, use of uterotonics, blood transfusion, or evacuation of retained products, maternal pyrexia
Lopez 2010 [39]	Assess the effects of educational interventions for postpartum mothers about contraceptive use	RCTs: 8	Cochrane	Yes	effect on contraceptive use
Dodd 2004 [45]	To assess the clinical effects of treatments for postpartum anaemia, including oral, intravenous or subcutaneous iron/folate supplementation and erythropoietin administration, and blood transfusion.	RCTs: 6	Cochrane	Yes	lactation at discharge from hospital
French 2004 [46]	The effect of different antibiotic regimens for the treatment of postpartum endometritis on failure of therapy and complications was systematically reviewed.	RCTs: 47	Cochrane	Yes	treatment failures
Kesho Bora 2009 [47]	Triple-antiretroviral (ARV) prophylaxis during pregnancy and breastfeeding compared to short-ARV prophylaxis to prevent mother-to-child transmission of HIV-1 (PMTCT): the Kesho Bora randomized controlled clinical trial in five sites in Burkina Faso, Kenya	1 study in five different location	Non Cochrane	No	Extended triple ARV regimen consisting of the anti-HIV drugs zidovudine, lamivudine andlopinavir/ritonavir, from the last trimester of pregnancy and continued during breastfeeding up to the age of six months.
McCall 2010 [49]	To assess efficacy and safety of interventions designed for prevention of hypothermia in preterm and/or low birthweight infants applied within ten minutes after birth in the delivery suite compared with routine thermal care.	RCTs: 6	Cochrane	Yes	heat losses in infants < 28 weeks' gestation, risk of death within hospital stay
Dyson 2005 [52]	To evaluate the effectiveness of interventions which aim to encourage women to breastfeed in terms of changes in the number of women who start to breastfeed.	RCTs: 7	Cochrane	Yes	increasing breastfeeding initiation rates
Lewin 2010 [53]	To assess the effects of LHW interventions in primary and community health care on maternal and child health and the management of infectious diseases.	RCTs: 82	Cochrane	Yes	increasing breastfeeding initiation rates
Lassi 2010 [54]	To assess the effectiveness of community-based intervention packages in reducing maternal and neonatal morbidity and mortality; and improving neonatal outcomes.	RCTs and qRCTs: 18	Cochrane	Yes	Maternal mortality, neonatal mortality, perinatal morality, stillbirths, newborn care practices
Imdad 2011 [55]	To assess the effectiveness of breastfeeding promotion interventions on breastfeeding rates in early infancy.	RCTs and qRCTs: 53	Non-Cochrane	Yes	EBF at 4-6 weeks postpartum
Debes 2013 [56]	To review the evidence for early breastfeeding initiation practices and to estimate the associationbetween timing and neonatal outcomes.	prospective studies, includingRCTs, and cohort studies = 18	Non-Cochrane	Yes	All-cause neonatal mortality, infection-related neonatal mortality
Lumbiganon 2011 [57]	To evaluate the effectiveness of antenatal BF education for increasing BF initiation and duration.	RCTs: 17	Cochrane	No	BF educational interventions were not significantly better than a single intervention
Imdad 2013 [62]	To evaluate the effects of application of chlorhexidineto the umbilical cord to children born in low income countries on cord infection (omphalitis) and neonatal mortality.	3 RCTs	Non-Cochrane	Yes	All cause neonatal mortality, omphalitis
Zupan 2004 [60]	To assess the effects of topical cord care in preventing cord infection, illness and death.	RCTs and qRCTs: 21	Cochrane	Yes	colonization with antibiotics
Ziino 2002 [67]	To determine if the administration of epinephrine to apparently stillborn and extremely bradycardic newborns reduces mortality and morbidity	RCTs: 0	Cochrane	No	-

Table 1 Characteristics of the included reviews on childbirth and postnatal interventions *(Continued)*

Lee 2011 [68]	To estimate the mortality effect of immediate newborn assessment and stimulation, and basic resuscitation on neonatal deaths due to term intrapartum-related events or preterm birth, for facility and home births.	RTs: 2 qRCT: 2 Observational studies: 20	Non-Cochrane	Yes	preterm birth
Ungerer 2004 [69]	To assess the effect of prophylactic versus selective antibiotic treatment for asymptomatic term neonates born to mothers with risk factors for neonatal infection.	RCTs: 2	Cochrane	No	-
Mtitimila 2004 [72]	To compare effectiveness and adverse effects of antibiotic regimens for treatment of presumed early neonatal sepsis.	RCTs: 2	Cochrane	Yes	Mortality, treatment failure or bacteriological resistance.
Gordon 2005 [73]	To compare the effectiveness and adverse effects of different antibiotic regimens for treatment of suspected late onset sepsis in newborn infants.	RCTs:13	Cochrane	No	Mortality, treatment failure
Sazawal 2003 [74]	This meta-analysis provides estimates of mortality impact of the case-management approach proposed by WHO.	RCTs: 7	Non-Cochrane	Yes	All-cause mortality, pneumonia specific mortality
Zaidi 2011 [75]	We conducted systematic searches of multiple databases to identify relevant studies with mortality data.	RCTs: 7	Non-Cochrane	Yes	All-cause mortality, pneumonia specific mortality
Bhutta 2009 [76]	We reviewed available evidence for community-based antibiotic management strategies for serious neonatal infections.	RCTs:9	Non-Cochrane	Yes	All-cause mortality, pneumonia specific mortality
Lawn 2010 [79]	to review the evidence, and estimate the effect of KMC on neonatal mortality due to complications of preterm birth.	RCTs:9 Observational studies: 5	Non-Cochrane	Yes	neonatal mortality
Conde-Agudelo 2011 [80]	To determine whether there is evidence to support the use of KMC in LBW infants as an alternative to conventional care after the initial period of stabilization with conventional care.	RCTs:3	Cochrane	Yes	nosocomial infection, severe illness, lower respiratory tract, not exclusively breastfeeding at discharge, and maternal dissatisfaction
Edmond 2006 [84]	This review summarizes the evidence on feeding LBW infants and serves as the basis for the development of guidelines on feeding LBW infants in developing countries.	Systematic reviews, RCTs, observational studies and descriptive studies	Non-Cochrane	No	What to feed and optimal duration of breastfeeding
Soll 2009 [86]	To determine the effect of multiple doses of exogenous surfactant compared to single doses of exogenous surfactant on mortality and complications of prematurity in premature infants at risk for or having respiratory distress syndrome.	RCTs:3	Cochrane	Yes	pneumothorax and risk of mortality
Soll 1998 [92]	o assess the effect of intratracheal administration of synthetic surfactant in premature newborns with established respiratory distress syndrome (RDS).	RCTs:6	Cochrane	Yes	Pneumothorax, pulmonary interstitial emphysema, patent ductusarteriosus, risk of intraventricular hemorrhage, risk of bronchopulmonary dysplasia, risk of neonatal mortality
Soll 2012 [93]	To compare the effects of early vs. delayed selective surfactant therapy for newborns intubated for respiratory distress within the first two hours of life. Planned subgroup analyses include separate comparisons for studies utilizing natural surfactant extract and synthetic surfactant.	RCTs:4	Cochrane	Yes	pneumothorax and pulmonary interstitial emphysema
Greenough 2008 [98]	To compare the efficacy of: (i) synchronized mechanical ventilation, delivered as high frequency positive pressure ventilation (HFPPV) or patient triggered ventilation - assist control ventilation (ACV) or synchronous intermittent mandatory ventilation (SIMV)) with conventional ventilation (CMV) (ii) different types of triggered ventilation (ACV, SIMV, pressure regulated volume control ventilation (PRVCV) and SIMV plus pressure support (PS)	RCTs:14	Cochrane	Yes	Air leak, duration of ventilation, duration of weaning
Lemyre 2002 [99]	In preterm infants with recurrent apnea, does treatment with NIPPV lead to a greater reduction in apnea and need for intubation and mechanical ventilation, as compared with treatment with NCPAP? Does NIPPV increase the incidence of gastrointestinal complications, i.e. gastric distension leading to cessation of feeds, or perforation?	RCTs:2	Cochrane	Yes	rates of apnea
Ho 2002 [100]	In spontaneously breathing preterm infants with RDS, to determine if continuous distending pressure (CDP) reduces the need for IPPV and associated morbidity without adverse effects	RCTs:6	Cochrane	No	blood used for exchange transfusion
Thayyil 2006 [102]	To compare the effectiveness of single volume exchange transfusion (SVET) with that of double volume exchange transfusion (DVET) in producing survival without disability and reducing bilirubin levels in newborn infants with severe jaundice.	RCTs:1	Cochrane	Yes	blood used for exchange transfusion
Mills 2001 [101]	To evaluate the efficacy of fibreoptic phototherapy.	RCTs:31	Cochrane	Yes	serum bilirubin

contraceptive education has become, research to evaluate such interventions is still sparse [38].

Oral contraceptive education program (one time) versus routine counselling led to a decrease in the incidence of known pregnancy by one year (odds ratio (OR) 0.81; 95% CI: 0.11, 6.04), increase in the rate of continuation of oral contraceptives at one year (OR 0.67; 95% CI: 0.11, 3.99) and a greater chance of switched contraceptives by one year (OR 2.0; 95% CI: 0.37, 10.92) [39]. Contraceptive counseling (one time) versus no counseling led to an increase in the use of any contraceptive at 8 to12 weeks postpartum (OR 19.56; 95% CI: 11.65, 32.83) and an increase in the choice of modern contraceptive (using or plan to use) at 8 to 12 weeks postpartum (OR 1038.09; 95% CI: 64.15,16799.73) [39]. Health education including contraception

with an immediate session versus no immediate session increased the use of contraception at 3 months (OR 1.50; 95% CI: 0.88, 2.54) and at 6 months (OR 1.62; 95% CI: 1.06, 2.50) [39]. After a later session versus no session, use of contraception at 6 months did not increase significantly (OR 0.95; 95% CI: 0.50, 1.80). Special postpartum care (including contraception) versus routine services (multiple well-baby contacts) led to decreased incidence of a repeat pregnancy (self-report) by 18 months (OR 0.35; 95% CI: 0.17, 0.70) [39]. These findings suggest that postpartum education about contraception leads to more contraception use and fewer unplanned pregnancies. Such education may be effective in increasing the short-term use of contraception. However, there are only limited data examining a more important longer-term effect on the prevention of unplanned pregnancies.

Detection and treatment of maternal anaemia
Anaemia after the birth of a baby (postpartum anaemia) is a common problem throughout the world and for most women is self-limiting, resolving within a week [40]. For some women however, particularly in resource-poor countries, it is a major cause of maternal morbidity (poor health) and mortality [41-43]. In this setting, anaemia may result from inadequate dietary intake, parasitic infection or malaria, and may be exacerbated by the physiological effects of pregnancy and blood loss at the time of birth [44]. Traditional treatments include iron supplementation and blood transfusion for severe anaemia. A hormone, erythropoietin, may help improve iron levels in the blood and the woman's ability to lactate.

When compared with iron therapy only, erythropoietin increases the likelihood of lactation at discharge (RR 1.90; 95% CI: 1.21, 2.98) and decrease the need for blood transfusion (RR 0.20; 95% CI: 0.01, 3.92) [45].However, the review did not identify any trial that assessed treatment with blood transfusion. Currently, limited evidence exists for the treatment of anaemia with erythropoiten and high quality trails are needed to assess the treatment of postpartum anaemia with iron supplementation and blood transfusion.

Detection and management of postpartum sepsis
Inflammation of the lining of the womb (postpartum endometritis), also known as puerperal fever, is caused by infection entering the womb (uterus) during childbirth. It occurs in about 1 to 3% of births, and is up to ten times more common after caesarean section. Prolonged rupture of membranes and multiple vaginal examinations also increase the risk. Endometritis causes fever, uterine tenderness and unpleasant-smelling lochia, and it can have serious complications such as abscess formation, sepsis and blood clots. It is also an important cause of maternal mortality worldwide, although this is very rare in HICs with the use of antibiotics.

Fifteen studies comparing clindamycin and aminoglycoside with another regimen found more treatment failures with the other regimen (RR 1.44; 95% CI: 1.15, 1.80). Failures of those regimens with poor activity against penicillin resistant anaerobic bacteria were more likely (RR 1.94; 95% CI: 1.38, 2.72) [46]. The combination of gentamicin and clindamycin appears suitable for the treatment of endometritis while regimens with activity against penicillin resistant anaerobic bacteria are better than those without them.

Screening and initiation or continuation of antiretroviral therapy for HIV
Antiretroviral (ARV) drugs reduce viral replication and can reduce mother-to-child transmission of HIV either by lowering plasma viral load in pregnant women or through post-exposure prophylaxis in their newborns. In HICs, highly active antiretroviral therapy (HAART) which usually comprises three drugs has reduced the mother-to-child transmission rates to around 1-2%. Recent evidence published in Lancet Infectious Diseases based on the Kesho Bora Studies shows that giving a combination of three ARV drugs to pregnant mothers with HIV infection from the last trimester, through delivery and six months of breastfeeding reduces the risk of transmitting HIV to the baby and improves survival. Infants of mothers whose virus is fully suppressed (undetectable) by triple-ARVs at the time of delivery have a very low risk of HIV infection (only 2.7% by the age of one year). It is therefore important to start ARVs early in pregnancy, ideally before pregnancy, for all women who require ART (CD4 count at or below 350 cells/mm3).

The Kesho Bora study shows that a significant reduction in infant infection can be achieved when pregnant women with a CD4 immune cell count of 200-500 cells/mm3 are given a combination of three ARVs to prevent transmission. This treatment should start in their last trimester of pregnancy, continuing through birth and six months of breastfeeding. This was shown to reduce the risk of transmitting HIV to the baby and improved survival compared with babies of mothers with HIV who are given the current WHO-recommended short-course ARV regimen in late pregnancy and around the time of delivery [47]. These findings suggest that a regimen combining triple ARV is most effective for preventing transmission of HIV from mothers to babies. The risk of adverse events to both mother and baby appears low in the short-term but the optimal antiretroviral combination and the optimal time to initiate this to maximize prevention efficacy without compromising the health of either mother or baby remains unclear.

Immediate essential newborn care
Thermal care for preterm babies and/or low birth weight infants
An optimal thermal environment is desirable for preterm infants. When an infant is challenged by cold, the baby attempts to conserve body heat by vasoconstriction and to maintain body temperature via thermogenesis by the metabolism of brown adipose tissue and an increase in oxygen consumption. The increase in energy expenditure may reduce weight gain [48]. A number of measures have been suggested to assist in the maintenance of body temperature for infants except the traditionally used incubators.

The intervention includes (1) barriers to heat loss applied to any part of the body of the preterm and/or low birth weight (LBW) infant within 10 minutes after birth in the delivery suite. These would consist of coverings such as transparent plastic wraps and bags made of low-density polyethylene (LDPE) or semi-permeable membranes such as opsite or Tegaderm and other additional swaddling materials or wraps (excluding delivery room blankets) such as the 'silver swaddler'; 2) External heat sources (non-routine) initiated within 10 minutes after birth in the delivery suite such as skin-to-skin care and heated/gel/chemical mattresses. Plastic wraps or bags were found to be effective in reducing heat losses in infants <28 weeks' gestation (Weighted Mean Difference (WMD) 0.68°C; 95% CI: 0.45, 0.91), but not in infants between 28 to 31 week's gestation. Plastic caps were effective in reducing heat losses in infants <29 weeks' gestation (MD 0.80°C; 95% CI: 0.41, 1.19). There was insufficient evidence to suggest that either plastic wraps or plastic caps reduce the risk of death within hospital stay. On the other hand, skin-to-skin care was shown to be effective in reducing the risk of hypothermia when compared to conventional incubator care for infants (RR 0.09; 95% CI: 0.01, 0.64). The transwarmer mattress reduced the incidence of hypothermia on admission to NICU in very LBW infants (RR 0.30; 95% CI: 0.11, 0.83) [49]. These findings suggest that any intervention other than primary care designed for prevention of hypothermia, and applied within 10 minutes after birth in the delivery suite, may be beneficial in practice including plastic wraps and bags, skin-to-skin contact, and transwarmer mattresses. These interventions keep infants warmer and decreased the incidence of hypothermia. To prevent the morbidity and mortality in preterm infants due

to hypothermia, consideration should be given to using these interventions in the delivery suite.

Advise on support of early initiation of breastfeeding
The benefits of breastfeeding on mother and newborn have been well documented, and the WHO recommends that all mothers initiate breastfeeding within the first hour after giving birth [50,51]. Timing of start of breastfeeding is very important, with studies suggesting much greater benefits of early versus late feeding. Early initiation of breastfeeding is defined as feeding within the first day after delivery while late (delayed) initiation of breast feeding is when it starts after the first day of delivery.

A review of interventions to promote breastfeeding showed increased rates of initiation of breastfeeding (RR 1.53; 95% CI: 1.25, 1.87) [52]; another review also showed similar results (RR 1.45; 95% CI: 1.14, 1.84) [53]. Community-based intervention packages for reducing maternal and neonatal morbidity and mortality also showed an increase in rates of breastfeeding (RR 1.94; 95% CI: 1.56, 2.42) [54]. Early versus late initiation of breastfeeding was found to be associated with decreased neonatal mortality (RR 0.52; 95% CI: 0.27, 0.98) while the effect of breastfeeding when compared to no breastfeeding also decreased neonatal mortality (RR 0.30; 95% CI: 0.17, 0.53) [55]. Another review showed that early breastfeeding initiation was associated with lower risks of all-cause neonatal mortality among all live births (RR 0.56; 95% CI: 0.40, 0.79) and among LBW babies (RR 0.58; 95% CI: 0.43, 0.78), as well as infection-related neonatal mortality (RR 0.55; 95% CI: 0.36, 0.84) [56]. When evaluating antenatal breastfeeding education, a formal breastfeeding education workshop vs. routine care increased the initiation rate of breastfeeding (RR 1.19; 95% CI: 0.97, 1.45); peer counseling versus routine care showed higher increments in the initiation rates of breastfeeding (RR 1.82; 95% CI: 1.13, 2.93). Less significant increases were observed at 3 months and 6 months after the education workshop [57]. Another review by Imdad et al 2011 compared breastfed versus non breastfed infants and showed a significant 70% reduction in the risk of neonatal mortality. It also showed that early initiation of breastfeeding versus late reduced neonatal mortality significantly by 48%.

Promotion and provision of hygienic cord and skin care
An umbilical cord infection may be clinically obvious while sometime tracking of bacteria along the umbilical vessels might not be apparent but can lead to septicemia, or other focal infections such as septic arthritis as a result of blood-borne spread [58,59]. In such cases, affected babies may also present with fever, lethargy or poor feeding. Soon after a normal delivery, the skin of the newborn baby including the umbilical stump is colonized mainly by nonpathogenic bacteria such as coagulase negative Staphylococci and Diphtheria bacilli. Pathogenic bacteria such as Coliforms and Streptococci may also be present on the skin and can track up the umbilical stump causing infection. It is therefore essential to keep the cord clean.

Antiseptic versus dry cord care/placebo decreased cord infection rates (RR 0.53; 95% CI: 0.25, 1.13); alcohol showed lower cord infection rates as well (RR 0.63; 95% CI: 0.19, 2.06); triple dye also lowered infection (RR 0.68; 95% CI: 0.13, 3.49); salicylic sugar powder showed significant reductions in infection rates (RR 0.21; 95% CI: 0.01, 4.38). Antiseptics that were aqueous based and alcohol based were effective for cord separation: (WMD -4.76; 95% CI: -5.34, -4.19) and (WMD -10.05; 95% CI: -10.72, -9.38) respectively, when compared with powder based antiseptics

[60]. A single study [61] evaluating the effect of chlorhexidine cleansing of the newborn skin showed reduced rate of bacterial colonization by Staphylococcus aureus (RR 0.65; 95% CI: 0.55, 0.77), Streptococci (RR 0.53; 95% CI: 0.27, 1.04); and E. Coli infections [61]. Chlorhexidine versus no treatment in cleaning skin of LBW newborn decreased neonatal mortality (RR 0.72; 95% CI: 0.55, 0.95) [61]. Another review also indicated that the use of chlorhexidine led to a 23% reduction in all-cause neonatal mortality in the intervention group compared to control (RR 0.77; 95 % CI: 0.63, 0.94) [62]. A study conducted in Nepal found that there was a 28% reduction in mortality among LBW infants when chlorhexidine was used to clean the skin [63].

Neonatal resuscitation with bag and mask for babies who do not breathe at birth
At birth, the lungs of newborn babies are filled with fluid. This fluid must be cleared and replaced with air after birth. While most babies manage by themselves, one in every 20 to 30 newborns receives resuscitation at birth, mostly for absent or ineffective breathing. Effective ventilation is the key to successful neonatal resuscitation. Positive pressure ventilation is initiated with manual ventilation devices which may or not deliver positive end-expiratory pressure (PEEP).

A review by OO'Donnell et al found insufficient evidence to determine the efficacy and safety of PEEP during positive pressure ventilation at neonatal resuscitation [64]. Ventilation is frequently initiated with a manual resuscitation bag and face-mask (BMV) followed by endotracheal intubation (ETT) if depression continues. These techniques may be difficult to perform successfully resulting in prolonged resuscitation or severe neonatal depression. The laryngeal mask airway (LMA) may achieve initial ventilation and successful resuscitation faster than a bag-mask device or endotracheal intubation. The review by Grein et al found no difference between the LMA and ETT with the exception of a clinically insignificant difference in time to complete insertion of the device favoring the ETT [65]. Recent American Academy of Pediatrics guidelines reported that LMA that fit over the laryngeal inlet have been shown to be effective for ventilating newborns weighing more than 2000 g. A laryngeal mask should be considered during resuscitation if facemask ventilation is unsuccessful and tracheal intubation is unsuccessful or not feasible. While, endotracheal intubation may be indicated for initial endotracheal suctioning of non-vigorous meconium-stained newborns, if bag-mask ventilation is ineffective or prolonged, when chest compressions are performed or for special resuscitation circumstances, such as congenital diaphragmatic hernia or extremely low birth weight [66]. Despite formal guidelines for the use of epinephrine in neonatal resuscitation, the evidence for these recommendations has not yet been rigorously scrutinized. A review evaluating the effectiveness of epinephrine in the context of apparent stillbirth or extreme bradycardia found no studies meeting the criteria for inclusion [67]. A meta-analysis of three facility-based studies found decreased rates of intrapartum related neonatal deaths with resuscitation training (RR 0.70, 95% CI: 0.59, 0.84). The evidence for basic resuscitation in community settings showed significant reductions in all-cause neonatal or perinatal mortality, ranging from 25-61%, and asphyxia specific mortality, ranging from 61-70% [68]. There is no existing evidence from randomized, controlled trials to support or refute the administration of epinephrine to reduce mortality and morbidity in apparently stillborn or extremely bradycardic newborn infant. Similarly, no randomized, controlled trial exists to address the issues of

optimum dosage and route of administration of epinephrine. On the other hand, facility based resuscitation training have reported reductions in intrapartum related neonatal mortality and community based resuscitation training found reduction in all cause and asphyxia related neonatal mortality.

Neonatal infection management
Presumptive antibiotic therapy for the newborn at risk of bacterial infection
Early onset of bacterial infection is an important cause of morbidity and mortality in newborn infants. Various factors that increase the risk of neonatal infection have been identified. It is unclear whether asymptomatic newborn infants born to mothers with one or more of these risk factors should receive antibiotics prophylactically rather than selectively if only clinical or microbiological evidence of sepsis emerges.

A review [69] identified two small trials undertaken in the 1970s. Both trials had methodological weaknesses and there was no evidence of an effect on any on these outcomes. Therefore, a large randomized controlled trial is needed in asymptomatic term infants born to mothers with risk factors for infection in their babies, which compares the effect of prophylactic versus selective antibiotics on morbidity, mortality and costs.

Case management of neonatal sepsis, meningitis and pneumonia
Neonatal sepsis is defined as a clinical syndrome of bacteremia with systemic signs and symptoms of infection in the first 4 weeks of life. Infection remains a major cause of illness and death in the neonatal period [70,71]. Treatment is initially with ampicillin plus either gentamicin or cefotaxime, narrowed to organism-specific drugs as soon as possible. Neonatal pneumonia is lung infection in a neonate and its signs may be limited to respiratory distress or progress to shock and death. Diagnosis is by clinical and laboratory evaluation for sepsis. Both pneumonia and neonatal sepsis can be treated in hospital or community setting.

For early onset neonatal sepsis (<48 hours), monotherapy versus combination therapy showed a decrease in mortality in the first 28 days of life (RR 0.75; 95 % CI: 0.19, 2.90) [72]. For late onset neonatal sepsis, Beta-lactam antibiotics versus a combination of beta-lactam plus aminoglycoside decreased mortality prior to discharge (RR 0.17; 95% CI: 0.01, 3.23); and also a reduction in treatment failure (RR 0.17; 95 % CI: 0.01, 3.23) [73]. The case-management for pneumonia showed reduction in total mortality by 27% (95% CI: 18, 35%) and pneumonia specific mortality by 42% (22-57%) [74]. Similar findings were reported in the relatively recent review which reported 25% reduction in all-cause neonatal mortality (RR 0.75 95% CI: 0.64, 0.89) and 42% reductions in pneumonia-specific mortality (RR 0.58 95% CI: 0.41, 0.82) [75]. However, two studies evaluating community-based neonatal care packages including injectable antibiotics found 44% and 34% reductions in neonatal mortality (RR 0.56, 95% CI: 0.41,0.77; RR 0.66, 95% CI: 0.47, 0.93 respectively), but the interpretation of these results is complicated by co-interventions [75]. Similar findings were reported by Bhutta et al in a review on community-based management of neonatal sepsis; the review reported 27% reduction in all-cause neonatal mortality (95% CI: 18, 35%), and 42% reduction in pneumonia specific mortality (95% CI: 22,57%) [76]. On the basis of available evidence it can be concluded that antibiotics have a clear role in reducing neonatal mortality in LMICs and can be effectively administered at homes via trained

health workers as well as for hospital-based management of neonatal sepsis.

Interventions for small and ill babies
Kangaroo mother care for preterm babies
Preterm birth (before 37 completed weeks of gestation) is the most important direct cause of neonatal mortality and it accounts for an estimated 27% of the four million neonatal deaths every year [4,77]. In the early 1970s, motivated by problems arising from shortage of incubators and also the impact of mother and newborn separation, Colombian paediatrician Edgar Ray developed a technologically simple method later named Kangaroo Mother Care (KMC). Acceptance of the KMC method is increasingly widespread and it is considered equivalent to conventional neonatal care for stable preterm infants and more parent and baby friendly [78].

KMC led to a decrease in neonatal mortality (RR 0.49; 95% CI: 0.31, 0.77) [79] (RR 0.68; 95% CI: 0.48, 0.96) [80], as well as severe morbidity (RR 0.34; 95% CI: 0.18, 0.65) [79], (RR 0.57; 95% CI: 0.40, 0.80) [80]. This evidence is sufficient to recommend the routine use of KMC in facilities for babies <2000 g at birth. The potential effect of KMC is greatest in LMICs, where other options for care of preterm babies remain limited with few neonatal care facilities, mainly in distant referral hospitals and those that are often understaffed and ill-equipped.

Extra support for feeding the small and preterm baby
The composition of weight gained by the fetus varies with gestational age. About 80% of all weight gained between 24 and 28 weeks of gestation is water, but this proportion decreases to about 60% between 36 and 40 [81] weeks. It is usual clinical practice therefore to provide infants weighing <1500 g with about 80ml/kg for the first day of life and increase fluids by about 10-15ml/kg/day to a maximum of 160ml/kg/day by the end of the first week of life. Similarly, LBW infants >1500 g are usually given about 60ml/kg for the first day of life and the fluid intake is increased by about 15-20ml/kg/day to a maximum of 160ml/kg/day by the end of the first week of life [81-83].

A meta-analysis of studies comparing restricted with liberal fluid regimens demonstrated that restricted fluid regimens were found to be associated with a lower risk of patent ductus arteriosus (RR 0.40; 95% CI: 0.26, 0.63), necrotizing enterocolitis (RR 0.30; 95% CI: 0.13, 0.71), and death (RR 0.52; 95% CI: 0.28, 0.96) [84]. LBW babies, who are often due to preterm births, account for significant complications and poor health during infancy. According to studies included in this review, breastfeeding is the best option for LBW infants, unless unavailable, whereby donor human milk is the next best choice. Supplementation of breast milk with calcium and phosphorus is also recommended for babies with birth weight less than 1500g. Nutritional supplements, which are given separately from breast milk, available as single vitamin preparations (vitamin A, vitamin D, vitamin K) or single mineral preparations (iron, zinc, calcium and phosphorus) are also beneficial (Paper 4, vitamin A supplementation in children).

Prophylactic use of synthetic surfactant
Pulmonary surfactant is a substance produced by the lung alveoli and prevents the lungs from collapsing during expiration by decreasing surface tension. It is noted that babies who are born before 30 weeks, approximately 60% of them will develop respiratory distress syndrome (RDS) because lung maturity is

directly proportional to the level of surfactant that is present in the newborn [85].

A review evaluated outcomes in infants given synthetic surfactant (pre-ventilatory or post-ventilatory) compared with control treatment which consisted of intratracheal administration of normal saline or air placebo. The different types of synthetic surfactant used in these trials were DPPC plus high density lipoprotein, powdered DPPC and phosphatidylglycerol and DPPC plus phosphatidylglycerol in saline. Studies also compared surfactant [86] given as either multiple or single doses to infants who were either premature (<30 weeks gestation or <1250g), at risk of respiratory distress syndrome or premature infants with established respiratory distress syndrome requiring assisted ventilation. Prophylactic synthetic surfactant versus normal saline or placebo decreased rates of pneumothorax (RR 0.67; 95% CI: 0.50, 0.90); neonatal mortality (RR 0.70; 95% CI: 0.58, 0.85); pulmonary interstitial emphysema (RR 0.68; 95% CI: 0.50, 0.93); and mortality at 1 year (RR 0.83; 95% CI: 0.70, 0.98) [86]. Multiple versus single dose of surfactant decreased rates of pneumothorax (RR 0.70; 95% CI: 0.52, 0.94); pulmonary interstitial emphysema (RR 0.62; 95% CI: 0.54, 0.71), mortality (RR 0.59; 95% CI: 0.44, 0.78), and necrotizing enterocolitis (RR 0.18; 95% CI: 0.07, 0.44). No significant changes were seen in rates of patent ductus arteriosus or intraventricular haemorrhage [86]. Infants who underwent prophylactic administration of synthetic surfactant had a decreased risk of pneumothorax, pulmonary interstitial emphysema and neonatal mortality. Also infants who were given synthetic surfactant showed an increased risk of developing patent ductus arteriosus and pulmonary haemorrhage. Results also show that multiple doses of surfactant as prevention or treatment resulted in a statistical significance reduction in the incidence of pneumothorax, mortality and necrotizing enterocolitis.

Therapeutic surfactant use for respiratory distress syndrome
Even though surfactant therapy has shown to improve outcomes for premature infants with RDS it is important to note that this therapy should not be used as an alternative to prolonging premature deliveries in order to increase lung maturity, or giving mothers antenatal corticosteroids with the aim to prevent RDS from developing [87-91].

A meta-analysis supports decrease in the risk of pneumothorax (RR 0.64, 95% CI: 0.55,0.76), pulmonary interstitial emphysema (RR 0.62, 95% CI: 0.54, 0.71), patent ductus arteriosus (RR 0.90, 95% CI: 0.84, 0.97), intraventricular haemorrhage (RR risk 0.88, 95% CI: 0.77, 0.99), broncho-pulmonary dysplasia (RR 0.75, 95% CI: 0.61, 0.92), neonatal mortality (RR 0.73, 95% CI: 0.61, 0.88), broncho-pulmonary dysplasia or death at 28 days (RR 0.73, 95% CI: 0.65, 0.83), mortality prior to hospital discharge (RR 0.79,95% CI: 0.68, 0.92) and mortality during the first year of life (RR 0.80, 95% CI: 0.69, 0.94). Treatment with synthetic surfactant increases the risk of apnea of prematurity (RR 1.20, 95% CI: 1.09, 1.31) [92]. Early versus delayed selective surfactant treatment decreased chronic lung disease rates (typical RR 0.69; 95% CI: 0.55, 0.86; typical Risk Difference (RD) -0.04; 95% CI: -0.06 , -0.01); acute lung injury including a decreased risk of pneumothorax (typical RR 0.69; 95% CI: 0.59, 0.82); pulmonary interstitial emphysema (typical RR 0.60; 95% CI: 0.41, 0.89) and broncho-pulmonary dysplasia (BPD) or death at 28 days was also evident (typical RR 0.94; 95% CI: 0.88, 1.00) [93]. Existing evidence shows that giving synthetic surfactant

to infants with established RDS improves clinical outcome. Infants who are treated with synthetic surfactant were found to have a decreased risk of pneumothorax, pulmonary interstitial emphysema, intraventricular haemorrhage, and Broncho pulmonary dysplasia. There was also a reduction in the incidence of neonatal mortality, mortality prior to hospital discharge and at 1 year of age. Infants who received synthetic surfactant treatment for established RDS also had an increased risk of apnea of prematurity. All results that are mentioned in this section reached statistical significance upon analysis. The results in the review of Soll 2009 et al were for both prevention and treatment of respiratory distress syndrome. They showed that multiple doses of surfactant resulted in a decreased risk pneumothorax, mortality and necrotizing enterocolitis.

Continuous positive airway pressure (CPAP) to manage preterm babies with respiratory distress syndrome
Apnea of prematurity, which is commonly seen in infants who are born before 34 weeks of gestation, is defined as a pause in breathing for greater than twenty seconds or an apneic event that is less than twenty seconds but is associated with bradycardia and/or cyanosis [94,95]. Continuous positive airway pressure (CPAP), has shown to be effective without long term effects; however, this has not been fully observed. Another treatment option is with ventilation (NIPPV, nasal intermittent positive pressure ventilation) which is delivered through the nasal route, and this also has seen to be effective in preterm infants whose apnea is frequent and severe [96]. As with the other treatment options there are some drawbacks with the use of NIPPV also, it has been noted that providing ventilation via nasal prongs is associated with an increased risk of gastrointestinal perforation [97].

A meta-analysis demonstrates that high frequency positive pressure ventilation (HFPPV) compared to conventional ventilation (CMV) was associated with a reduction in the risk of air leak (RR 0.69, 95% CI: 0.51, 0.93). Assist control ventilation (ACV) or synchronized intermittent mandatory ventilation (SIMV) compared to CMV was associated with a shorter duration of ventilation (WMD -34.8 hours, 95% CI: -62.1, -7.4). ACV compared to SIMV was associated with a trend to a shorter duration of weaning (WMD -42.4 hours, 95% CI: -94.4, 9.6). Neither HFPPV nor triggered ventilation was associated with a significant reduction in the incidence of BPD [98]. NIPPV vs. NCPAP decreased rates of failure of therapy (intubation) (RR 0.30; 95% CI: 0.01, 6.84), rate of apnea (events/hr) (MD -0.10 events/hr; 95% CI: -0.53, 0.33) and change in rate of apnea (events/hr) (MD -1.19 events/hr; 95% CI: -2.31, -0.07). NIPPV when compared to NCPAP may be a useful method in preterm infants with apnea [99]. Continuous distending pressure (CDP), on the other hand, is found to be associated with a lower rate of failed treatment (death or use of assisted ventilation) (RR 0.65 95% CI: 0.52, 0.81), overall mortality (RR 0.52 95% CI 0.32, 0.87), and mortality in infants with birth weights above 1500 g (RR 0.24 95% CI: 0.07, 0.84). The use of CDP is associated with an increased rate of pneumothorax (RR 2.64 95% CI: 1.39, 5.04) [100]. A review by Greenough et al [98] shows that there are more benefits in treating neonates with HFPPV or triggered ventilation compared to conventional ventilation. There was a reduction in both air leaks and duration of ventilation. Even though benefits were documented in this review, we encourage that more trials are done in order to determine the effectiveness of ventilation, along with other benefits or long term risk associated with these methods.

Management of newborns with jaundice

Extremely high levels of bilirubin (severe jaundice) can lead to brain damage. Severe jaundice in newborns can occur as a result of a variety of causes including rhesus hemolytic disease, ABO incompatibility, atypical antibodies etc. Removal of blood from the affected infant and replacing with fresh blood from the blood bank (exchange transfusion) is used as a treatment for severe jaundice in newborn infants.

Phototherapy is used to treat newborn infants with hyperbilirubinaemia. Fibreoptic phototherapy is a new mode of phototherapy which is reported to lower serum bilirubin (SBR) while minimizing disruption of normal infant care. Fibreoptic phototherapy was found to be more effective at lowering SBR (serum bilirubin) than no treatment but less effective than conventional phototherapy. Fibreoptic phototherapy was equally as effective as conventional phototherapy in preterm infants and when two fibreoptic devices were used simultaneously (change in SBR after 24 hours of treatment: (WMD 1.7%; 95% CI: -2.65, 6.05) and change in SBR per day over whole treatment period: (WMD 2.82%; 95% CI: -1.84, 7.48 respectively). A combination of fibreoptic and conventional phototherapy was more effective than conventional phototherapy alone (duration of phototherapy): (WMD -12.51 hr; 95% CI: -16.00, -9.02, meta-analysis affected by heterogeneity) [101].

Fibreoptic phototherapy has a place in the management of neonatal hyperbilirubinaemia. It is probably a safe alternative to conventional phototherapy in term infants with physiological jaundice.

Double volume exchange transfusion is commonly used in newborns with severe jaundice in order to prevent kernicterus and other toxicity related to hyperbilirubinemia. A single trial fulfilling the criteria for inclusion identified 20 full term babies requiring exchange transfusion for hemolytic jaundice due to ABO incompatibility. These infants were randomly allocated to receive single or double volume exchange transfusion. Total bilirubin levels immediately after exchange transfusion were not significantly different in either group. There was insufficient evidence to support or refute the use of single volume exchange transfusion as opposed to double volume exchange transfusion in jaundiced newborns [102].

Discussion

This paper summarized all the essential childbirth and postnatal interventions for improved maternal and newborn health. The interventions were preventive and therapeutic aimed at preventing illnesses and improve survival of mothers and babies. The importance of these interventions has been addressed in previous publications [103-106]. However this review further underscored their standing by collating the existing evidence to assist health professionals and policy makers to reduce the existing burden of maternal and neonatal morbidity and mortality.

Among the childbirth interventions, the review highlighted the role of injecting oxytocin immediately after childbirth for the prevention and management of postpartum hemorrhage, which is lethal and is responsible for large number of maternal deaths if unattended. Similarly, practicing good hygiene and recognition of early signs of infection after childbirth can be instrumental in saving lives. Detection and management of pre-eclampsia and use of magnesium sulphate can lower a woman's risk of developing eclampsia and other life-threatening complications. For postnatal interventions, care of the neonate and mother in the hours following the delivery is vital and must be adequate to prevent the high risk of mortality and morbidity associated with it. The benefits of breastfeeding have been well documented; however the timing of start of breastfeeding is very important, with studies suggesting much greater benefits of early vs. late feeding [56]. Hygienic care of cord and skin of the baby after delivery for lowering the risk of infections have the potential to reduce neonatal deaths. Neonatal resuscitation is vital for preventing neonatal deaths due to birth asphyxia. Babies with respiratory problems should be assessed and administered surfactant or other ventilatory assistance such as CPAP immediately. Babies with LBW are advised to receive thermal care, as well as KMC along with appropriate extra support for feeding. Childbirth and postnatal care should not be limited to a definite period whereby only the current health status of both mother and child are addressed but should also link the mother to family-planning services and the baby to child health care which will cater to the future needs of both child and mother [107]. The focus of delivering effective postnatal care must be on the timely delivery of intervention packages, i.e. on the first day after birth.

Childbirth and postnatal care faces many challenges in LMICs whereby establishing contact between the pregnant mother, postpartum mother, or neonate is difficult since home births and seclusion may be a community practice or tradition. However, the importance of community based delivery strategies to increase access to needed care is paramount to bringing about a positive change in the developing countries. Although not all the interventions discussed in this paper can be delivered in community, training community midwives and detailing proper linkages with local health facilities is very vital. Referrals from community to health facilities for interventions such as, management of postpartum hemorrhage and cesarean sections is very critical. Therefore, training midwives and follow-ups through home visits may assist in increasing the coverage and improving the quality of home-based postnatal care services for mothers and newborns. This goal can be achieved through increased utilization of basic postnatal services by mothers and newborns, increased identification and referral of post-partum women and newborns with health problems to health care facilities, and provision of quality home based postnatal care for mothers and newborns [108].

This paper is a comprehensive and through summary of essential childbirth and postnatal interventions for health care practitioners and decision makers who can integrate these interventions into health system for improved maternal and child health. If implemented properly to target a wider audience, keeping in mind the barriers to implementation, then major progress may be made in meeting the MDG's and higher maternal and neonatal maternal mortality would be ceased. The strength of this paper is that it included and summarized evidence from all the recent Cochrane and non-Cochrane reviews on childbirth and postnatal interventions for mothers and newborns. However, at times the quality of all included studies within the review could not be ensured which limited the quality of the data obtained.

Conclusion

Maternal and newborn health exists in a synergistic relation. Most maternal deaths are avoidable provided timely and

adequate delivery of health-care solutions to prevent or manage complications. An access to antenatal care in pregnancy, skilled care during childbirth, and care and support in the weeks after childbirth should be provided to all women. The review discussed all childbirth and postnatal interventions which have an impact on reducing maternal, neonatal mortality and which are suitable for delivery in LMICs. The implementations of discussed interventions promise a much needed improvement is maternal and neonatal outcomes around the world. However, some of these interventions must be prioritized over others depending on the clinical indications and keeping in view the limited resources in developing countries. Timely provision of these interventions holds unparalleled significance, particularly those that are delivered during and immediately after childbirth, in places where majority of the births occur, at home.

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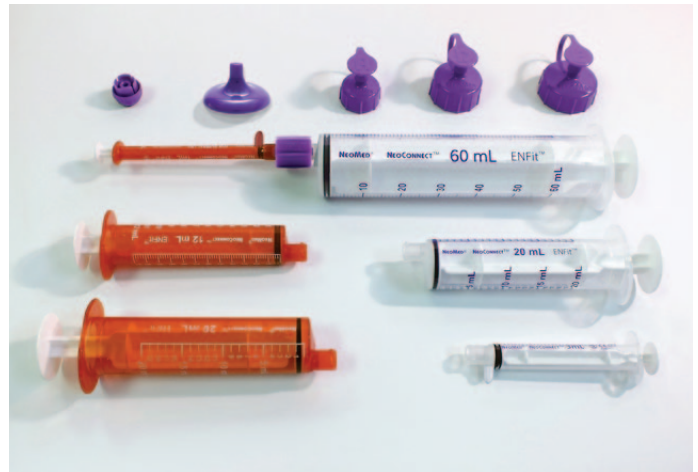
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