Vol. 27 No. 3
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A Propofol Story: Is the Drug That Killed Michael Jackson Safe for Mothers and Their Babies?

I. Kozlov MD, B. M. Petrikovsky MD PhD, B. Dynkin, M. Petrikovsky

Introduction

Propofol is a hypnotic/amnestic used in the initiation and maintenance of general anesthesia, and is most commonly associated in the public consciousness with the death of Michael Jackson. On June 25, 2009, he was found dead in his home by his personal physician Dr Conrad Murray. Jackson had reportedly been administered a combination of Propofol and anti-anxiety benzodiazepines in his home, prior to his death. The forensic anesthesiologist's report indicated that acute Propofol intoxication was the primary cause of death with the benzodiazepines only having a contributory effect. According to Murray, Jackson had been using Propofol to ease his persistent, severe insomnia when other powerful sedatives could not resolve his condition. Bottles of Propofol, both empty and full, were found at Jackson's bedside. The court held that Murray was criminally responsible for his death for a number of reasons. Propofol is not meant to be used at home and should be used only in a hospital with proper monitoring at all times. Murray also lacked the proper equipment needed for the correct usage and monitoring of a patient who has been administered Propofol. Furthermore, Propofol is not properly prescribed as an anti-insomniac, but only properly used for the induction and maintenance of anesthesia and procedural sedation. The drug was also mixed with a contraindicated benzodiazepine and administered daily for approximately two months. Thus, Jackson's death was caused by a flagrant and deliberate misuse of the drug and could never have occurred had the drug been properly administered for an appropriate usage.

The negative publicity associated with Propofol's role in Michael Jackson's death poses a serious risk of adversely impacting its usage in properly indicated clinical roles and research as to additional safe and beneficial usages. Propofol is the premier agent for inducing general anesthesia because it effects anesthesia faster than alternate hypnotics and the patient is able to recover consciousness from Propofol-induced anesthesia both more rapidly and in better humors than from anesthesia maintained through alternate hypnotics. When administered under proper controls and monitoring, Propofol is at least as safe as alternate drugs indicated for the same uses. As such, responsible research into the proper and beneficial uses of a particularly effective drug should not be hindered by a tragedy that resulted from its deplorable and unfortunate abuse.

The authors are with the Department of Obstetrics and Gynecology and Anesthesiology, Wyckoff Heights Medical Center, Brooklyn, New York.

Propofol is an intravenous sedative-hypnotic agent for use in the induction and maintenance of anesthesia or sedation. Intravenous injection of a therapeutic dose of Propofol induces hypnosis, with minimal excitation, usually within 40 seconds from the start of injection (the time for one arm-brain circulation). As with other rapidly acting intravenous anesthetic agents, the half-time of the blood-brain equilibration is approximately 1 to 3 minutes, accounting for the rate of induction of anesthesia. The mechanism of action, like all general anesthetics, is poorly understood. However, Propofol is thought to produce its sedative-anesthetic effects by the positive modulation of the inhibitory function of the neurotransmitter GABA through the ligand-gated $GABA_A$ receptors.

The pharmacokinetics of Propofol are well described by a three-compartment linear model with compartments representing the plasma, rapidly equilibrating tissue, and slowly equilibrating tissue.

Following an IV bolus dose, there is rapid equilibration between the plasma and the brain, accounting for the rapid onset of anesthesia. Plasma levels initially decline rapidly as a result of both distribution and metabolic clearance. Distribution accounts for about half of this decline following a bolus of Propofol. However, distribution is not constant over time, but decelerates as body tissues equilibrate with plasma and become saturated. The rate at which equilibration occurs is a function of both the rate and the duration of the infusion. When equilibration concludes, there is no longer a net transfer of Propofol between tissues and plasma.

Propofol clearance ranges from 28 to 50 mL/kg/min (1.6 to 3.4 L/min in 70 kg adults). It is chiefly eliminated by hepatic conjugation to inactive metabolites, which are excreted by the kidney. A glucuronide conjugate accounts for about 50% of the administered dose. Propofol has a steady-state of distribution (10-day infusion) approaching 60 L/kg in healthy adults. No difference in pharmacokinetics due to gender has been observed. The terminal half-life of Propofol after a 10-day infusion ranges from 1 to 3 days.

Reproduction studies have been performed in rats and rabbits at intravenous doses of 15 mg/kg/day (approximately equivalent to the recommend human induction dose on a mg/m2 basis) and have revealed no evidence of impaired fertility or harm to the fetus due to Propofol. Propofol, however, has been shown to cause maternal deaths in rats and rabbits and decreased

pup survival during the lactating period in dams treated with 15 mg/kg/day (approximately equivalent to the recommended human induction dose on a mg/m2 basis). The pharmacological activity (anesthetic effect) of the drug on the mother is probably responsible for the adverse effects seen in the offspring. There are, however, no adequate and well-controlled studies in pregnant women.

The FDA has labeled Propofol as a Category B drug. The rationale behind the use of Propofol in obstetrics is to induce short-term amnesia to assuage the fear of needle usage that might impede the implementation of epidural/spinal anesthesia and to prevent or significantly decrease nausea and vomiting, thus increasing the patient comfort and well-being. The goal of this report is to share our preliminary experience with the use of Propofol in obstetrical practice based on retrospective chart review.

Methods and Materials

Propofol was used in term obstetrical patients. Propofol was administered intravenously in small incremental doses of 5-10 mg up to 60 mg per minute until the desirable level of sedation is reached. We asked the patient if she was comfortable and relaxed. Local 5ml 2% lidocaine was injected subcutaneously in lumbar area at the L4-L5 level. A 17 gauge Tuohy needle was placed in the epidural space using a loss of resistance technique. A 27 gauge Whitacre needle was then placed through the epidural needle. After witnessing flow of CSF through the spinal needle, 1.2ml of 0.75% Bupivacaine was injected intrathecally. A 19 gauge wired epidural catheter was then place through the epidural needle and was taped, leaving 6cm of catheter in the epidural space. The level of spinal block was usually around T4.

Results

Short-term amnesia, eliminating fear of needles was achieved in all cases when Propofol was used. In the study group none of the patients reported a sensation of pressure associated with uterine manipulation during cesarean section compared to 80% in historical controls. Nausea and vomiting was largely eliminated in the study group (5% versus 40% in historical controls). All patients were fully awake at the time of actual delivery. None of the fetuses in the study group were sedated or depressed at birth. Apgar score (1 min) varied between 7 and 10 in all newborns of the study group.

Discussion

Propofol is an injectable anesthetic that is currently used both in veterinary and human medicine for the induction and maintenance of anesthesia and for procedural sedation. Although little is known about the pharmacokinetics of Propofol in fetuses, it is used in obstetric procedures, particularly in cesarean section. It also has been successfully used for sedation for gastrointestinal endoscopy during pregnancy (2). A clear advantage of using Propofol during obstetrical surgery is the elimination of a patient's fear of needles through the facilitation of short-term amnesia. Another clear advantage is the prevention of nausea, vomiting, and visceral abdominal pain, all caused by the overstimulation of the vagal nerve. Benefits for the anesthesiologist include working with well-sedated patients rather than anxious and erratically moving patients, and the absence of recollection of epidural placement of the patient. Traditional epidural/spinal anesthesia eliminates sensation of pain by acting on the central nervous system. However, part of the sensation originating from the uterus still reaches the brain via the parasympathetic nervous system (vagus) and is not affected by epidural anesthesia. Our preliminary study demonstrated that the use of Propofol can be beneficial for the mother and is not associated with neonatal depression or any adverse effects on the newborn. A prospective study is currently being planned to further assess the possible effect of Propofol on fetal and maternal well-being.

When Propofol is really needed:

1 When the patient is in excruciating pain in active labor and is unable to sit still for needle placement.
2 Difficult needle placement for epidurals (obesity, scoliosis, etc.) which may require multiple attempts.
3 When the patient is very anxious and/or has a fear of needles.
4 To prevent parasthesia.

In these situations Propofol is useful because:

1 Propofol is a very short-acting drug, capable of inducing amnesia.
2 The patient is able to sit still, allowing the anesthesiologist ample time to place the needle.

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Sibling Visitation in NICU

Rahmi Örs,MD

There are many strict rules for visitation of children in hospitals. Most hospital administrations do not allow anyone to visit under at least 12 years of age. Children, other than brothers and sisters of a baby, cannot come to see the babies in NICU. Sibling visitation in NICU is exceptional situation. Siblings are part of the family and they have concerns about their new sibling. The prolonged hospitalization of the new member of the family may complicate the emotional situation of the siblings. It must keep in mind that it is important for parents and siblings to be together during long NICU days. Days and nights are long and time goes on in NICU. NICU environment is more stressful for mothers. Family support is very important for all NICU mothers. Sibling visitation is an important part of the family-centered perinatal care approach. In a recent study, it was shown that siblings seem to improve children's emotional adjustment to the new member of the family and to enhance children's participation in the family adaptation process.

The sibling visitation in NICU is a very different situation compared to other visitors. It must be flexible with special rules (hours, needs, etc). Sibling visitation policies vary greatly among NICUs all around the world, ranging from no visiting to open visiting. Of course, safety of siblings, as well as NICU babies, is of critical importance. The family must follow the special rules for each hospital.

What is the lower age limit to visit in NICU? Some hospitals do not allow under 2 years of age while some hospitals do not allow under 3 years of age. The practice changes from hospital to hospital. There is no generally accepted criteria which is absolute contraindication.

The other issue is visitation of babies having major congenital anomalies or severe disease in NICU. I think that there are some limitations to visiting such babies. Most of the time, a young child does not understand what is going on. This visitation may adversely affect the psychology of siblings. We can discuss this situation with parents. We can reach a common decision with them.

Reactions during an NICU visit can vary depending upon a sibling's age and personality. Some children are negatively affected by the NICU environment. In two studies of sibling visits to NICUs, there were no adverse effects noted. Sibling visits are usually limited to a maximum of 30 minutes.

Most of time, everybody in the NICU is very busy. During each visit, a child must be supervised by an adult family member to prevent disturbing others at all times. Guidence for under 12 years of age is obligatory. During flu season (November through spring), this age limit is raised to 16 years of age.

The most common fear for NICU babies after visitation is the transmission of microbes from siblings. Infection control precautions should be followed. It is expected that all visitors are healthy. A Sibling Visitation Health Screen questionnaire for each sibling must filled by healthcare personnel or a nurse prior to the first visit. Visitation must restricted for any child who has had a rash, fever, cold, diarrhea, flu or other illness within the last four weeks. We have to be sure that siblings who come to visit are all up-to-date on their vaccines. Siblings developing a rash may not visit until the rash is gone after the chicken pox vaccine.

Sibling visitation may be suspended completely on the advice of the Infection Control Department or during times of unit emergency.

Rahmi Örs, MD is the Professor of Pediatrics and Neonatologist at University of N.E. Meram Medical Faculty in Turkey.

New Horizons In Neonatal Hemodynamic Monitoring: Clinical Applications and Predictive Monitoring

Timur Azhibekov, MD and Istvan Seri, MD, PhD, HonD

Hemodynamic instability in the neonatal period, particularly in premature neonates, remains an important and challenging clinical problem that neonatologists have to address on a daily basis. More than 30% of preterm neonates born at <30 weeks gestation and the vast majority of extremely low birthweight neonates present with signs of hemodynamic compromise during the first 24 hours of life.[1,2]

Multiple attempts have been made to define hypotension in the neonate, to develop criteria for initiating interventions, and/or to identify the most appropriate, pathophysiology-targeted medication to correct it.[3,4] There are a number of clinically relevant questions about neonatal hypotension including but not restricted to its gestational- and postnatal-age dependent and population-based definition and the triggers and the type of interventions. To date these and other related questions remain unanswered. More so, none of the suggested approaches has been shown to improve clinically relevant, long-term outcomes while there is sufficient evidence that severe cardiovascular compromise in the neonatal period is associated with increased morbidity, mortality and poor prognosis.[5-8] Challenges to define hypotension include variation in blood pressure values based on gestational age, existing comorbidities (lung disease, infection, etc.), and the fact that in patients of the same gestational age and degree of maturity the same blood pressure values can be associated with either adequate or compromised systemic and organ perfusion. To make matters even more complicated, even in the same patient but under different conditions, the same blood pressure values can represent either adequate or compromised systemic and/or organ perfusion. In addition, focusing on blood pressure alone, even if the lower limits of blood pressure were known in the given individual, is misleading when treating a patient who is in the compensated phase of shock. In this phase, blood pressure remains in the "normal range" and thus doesn't represent the status of oxygen delivery in the non-vital organs with low-priority vascular beds.

Irrespective of the phase of neonatal shock, several pathophysiologic mechanisms result in hypotension. Being a derivative of systemic flow (effective cardiac output) and systemic vascular resistance, blood pressure can be affected by either one of these factors alone, or by a combination of changes in both factors. When cardiovascular compromise progresses to its uncompensated phase, identification of the leading mechanism(s) can be difficult. Recognition of the primary pathophysiologic mechanism may be less challenging at earlier stages, when compensatory mechanisms are in effect if, in addition to blood pressure, systemic and organ blood flow and oxygen delivery could be continuously monitored.

As for the management approaches, ongoing controversy about the initial choice of the most appropriate vasoactive agent has remained a topic for discussion for decades and attempts to find the most appropriate vasoactive medication for the treatment of neonatal hypotension in general have failed to do so. None of the medications used (dopamine, dobutamine, epinephrine, vasopressin, or milrinone) has been shown to be superior or even, in some studies, effective in treating hypotension. In addition and most importantly, no trial has shown improvement in clinically relevant, long-term outcomes. The present state of utter confusion is not surprising though, since patients studied have mostly represented populations with heterogeneous etiology and underlying pathophysiology of neonatal shock. The only bright spots are the findings of studies on patients with the same underlying condition leading to hypotension such as neonates with septic shock, or neonates and infants after cardiac surgery. The vasoactive medications used interchangeably in most trials in neonates also have significant differences in their mechanisms of action and pharmacodynamics profile. Therefore, the different classes of vasoactive medications such as the vasopressor-inotropes (dopamine, epinephrine), inotropes (dobutamine), lusitropes (milrinone), and vasopressors (vasopressin) should not be used interchangeably; rather the choice of the particular medication needs to be tailored to the predominant pathophysiology of hypotension. However, even this approach has not been and, likely, cannot be appropriately tested in well-designed prospective trials.

Thus, without the ability of obtaining additional data that accurately represent both blood pressure and systemic and organ blood flow and oxygen delivery in neonates at risk, timely diagnosis of impeding cardiovascular compromise and appropriate, pathophysiology-based decision to intervene with the most appropriate medication in a given individual are challenging if not impossible. Establishing operational thresholds[9] would also be of importance, especially at the population level. There is hope, however, that significant advances in our understanding of and ability to diagnose and rigorously study neonatal cardiovascular compromise will take

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place in the very near future. Advances in biomedical technology and computer science have recently led to the development of a comprehensive, neonatal hemodynamic monitoring system capable of continuously and simultaneously acquire multiple hemodynamic parameters.[9-11] Using different monitoring and data-capturing devices, the monitoring and data-acquisition system acquires and downloads waveforms of continuous hemodynamic variables such as perfusion (blood) pressure and systemic and organ blood flow. At present, blood pressure needs to be measured invasively, while systemic circulation is assessed by monitoring cardiac output and effective systemic blood flow and calculating systemic vascular resistance using electrical impedance continuously and non-invasively as well as by intermittent use of functional echocardiography. Changes in regional blood flow are assessed by monitoring cerebral, renal, mesenteric, and muscle regional tissue oxygen saturation and microcirculation using NIRS and Laser Doppler technology, respectively. Finally, conventionally monitored parameters (heart rate, respiratory rate, arterial oxygen saturation and transcutaneous CO_2) are also simultaneously captured.[10,11] In the near future, the addition of monitoring devices to follow changes in organ function, such as amplitude integrated EEG, will further enhance our ability to decipher the complex interactions among the different hemodynamic parameters ultimately determining tissue oxygen delivery. In addition to timely recognition of the leading pathogenetic mechanism, the use of comprehensive hemodynamic monitoring systems will assist in evaluating the response to treatment and guide further management.

Finally, we foresee that in the not-so-distant future, using the information obtained by these comprehensive hemodynamic monitoring systems, early recognition of clinically relevant patterns of hemodynamic changes preceding pathological alterations in systemic and organ blood flow will become possible. By identifying the patterns of changes, i.e. trends, we will develop algorithms that could predict impeding cardiovascular compromise and allow the physician to intervene before shock advances to its later phases. We already have examples lending support to this notion, even if the data analysis used for trending is less comprehensive than the systems to be used in the future. Continuous monitoring, capture and analysis of heart rate characteristics is the first step in this emerging field of predictive monitoring and data analysis[12] and it has been shown to decrease mortality from late onset neonatal sepsis.[13,14] The use of these systems that include continuous data monitoring and acquisition, sophisticated data handling and analysis of large physiologic data sets and validation of the findings followed by the developed algorithms requires a multidisciplinary approach with close collaboration among clinicians and researchers of different specialties, biomedical engineers, statisticians and computer scientists. The hope is that the novel data obtained by utilizing the advances in biomedical knowledge and technology and a multidisciplinary approach will lead to clinically relevant improvements in neonatal care including a decrease in morbidity and mortality associated with cardiovascular instability in the neonatal period, and improvement in relevant long-term outcomes.

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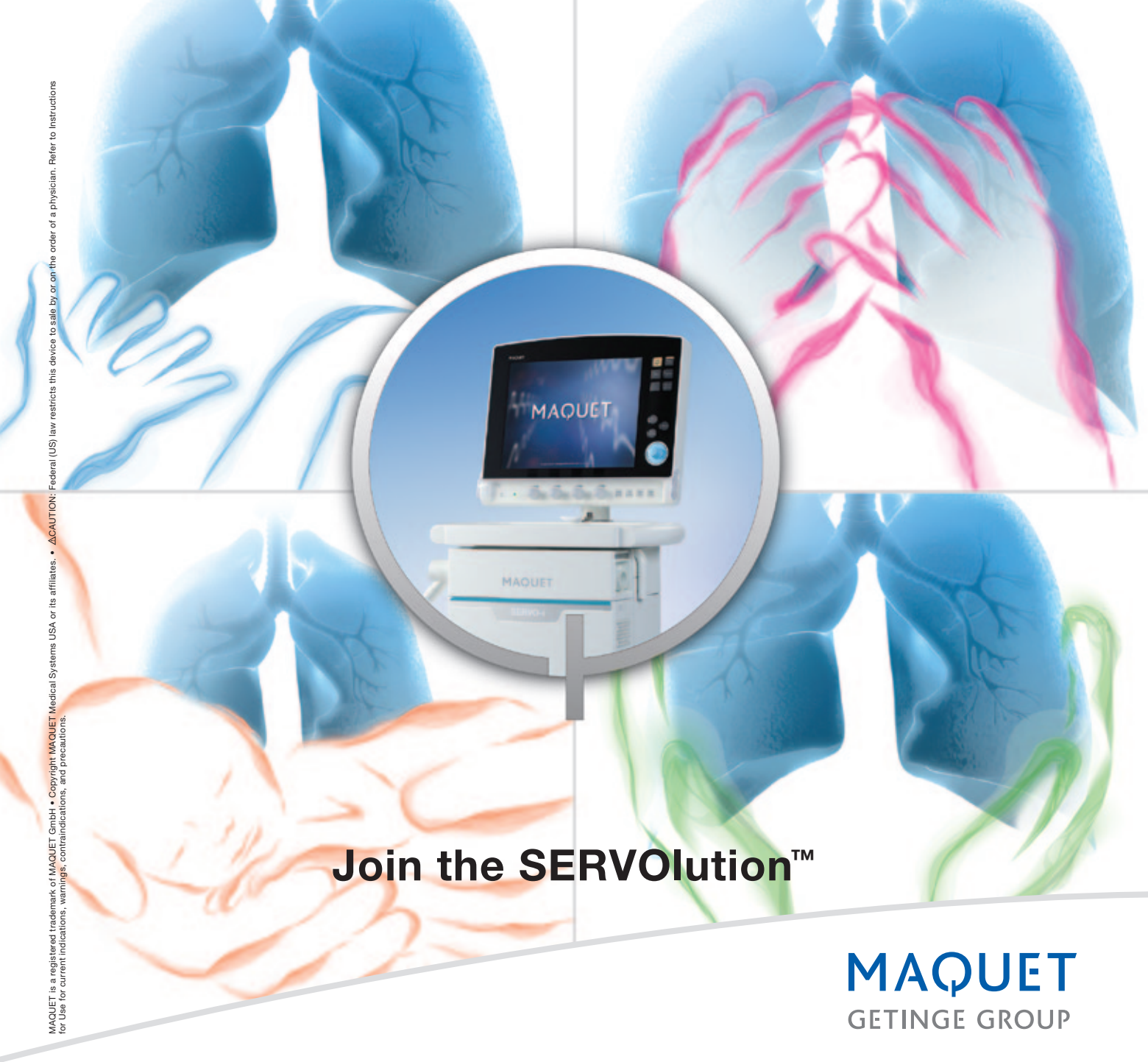

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News

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Studies Weigh Impact of C-sections

A person's weight later in life could be traced to a mother's decision to have a cesarean section. Study of a large collection of data suggests that C-sections are associated with being overweight and obese in adult life. Researchers pooled data from 15 studies with a combined population of 142,702 for their analysis. The studies classified overweight as a body mass index of 25 or higher and obesity as 30 or higher, and covered various types of vaginal and cesarean deliveries. Compared with babies delivered vaginally, those delivered by C-section were 26% more likely to be overweight and 22 percent more likely to be obese. The type of vaginal or cesarean delivery—natural, forceps or vacuum extraction vaginal births, or pre-labor or in-labor cesarean deliveries—made no difference. The analysis included a large sample from 10 countries. At the same time, all studies were observational, and the authors write that further study would be required to establish a causal connection between birth method and adult B.M.I. Information in this article first appeared in the New York Times Well blog. Copyright New York Times

Crowded NIC Unit to Expand

Mount Sinai Hospital's neonatal intensive care unit is getting a $5-million injection to deal with overcrowding issues. The Newton Glassman Charitable Foundation donation will allow the unit to expand, giving more babies, and their parents, increased room and privacy for their care. Bassinets will no longer be housed in the large and noisy common area but will be allotted private rooms complete with cots and comfortable furniture for parents. Space per infant will grow from six square metres to 13 square metres. Each room will able to support the two highest levels of care so patients will not be moved as their conditions change. The changes are also expected to make the unit quieter. The expanded family facilities, to open in the fall, will include a shared kitchenette, dining and lounge areas, kids' play spaces and even overnight guest rooms.

The Price is Wrong for Some Births

New research out of California suggests that the cost of giving birth at a hospital in the state can vary by tens of thousands of dollars, with price ranges dubbed as "largely random" and unexplainable by market factors. Charges for a non-complicated vaginal delivery in the most populated US state ranged from $3,296 to $37,277, and $8,312 to $70,908 for a non-complicated cesarean section, according to researchers at the University of California at San Francisco. Institutional and market factors could only explain 35 to 36% of the variation in charges, according to the study. Health advocates nationwide are calling for more transparency in an industry where pricing variables are largely opaque. Data released by the US Centers for Medicare and Medicaid Services showed hospital charges for the same medical procedures vary by thousands of dollars across the country, even within the same city. The study concluded that the market doesn't work and the system doesn't regulate it, so hospitals can charge what they want—and patients have no access to comparative prices. Researchers studied about 100,000 births as well as three sets of variables that could affect costs: patient characteristics, such as the mother's age and length of stay, hospital characteristics, such as profit or nonprofit status, and market factors including the wage index, which measures the cost of living. They determined these factors combined only explained about 35% of the variability in charge. The California Hospital Association said it does not dispute that charges vary widely, but said the study is flawed because the authors looked at costs before they are discounted by insurers. The relevant numbers are the discount prices negotiated between insurers and hospitals, which aren't public information, the association said.

neonatal INTENSIVE CARE

ISSN 1062-2454
Published seven times each year by

Goldstein and Associates, Inc.

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Brave New Babies

Babies across the US are having portions of their DNA deciphered as part of a five-year project to understand and navigate infant genetic testing. Children's Mercy Hospital geneticist Stephen Kingsmore and a handful of other scientists are taking gene sequencing to the next level, using the technology to design treatment for infants with rare and unusual illnesses, and in some cases, finding therapies for genetic abnormalities never seen before. About 5% of all babies born in the US, some 200,000 a year, probably suffer from a rare disorder, said Michael Watson, executive director of the American College of Medical Genetics and Genomics in Bethesda, Maryland. Infant genetic testing may succeed in shedding light on conditions such as progeria, the disease of premature aging. Testing some babies might lead to more knowledge about the disease and perhaps enable early experimental treatment, Watson said. Sequencing gives a readout of the genome, the instructions each of the body's cells carries for making and maintaining tissues. Genomes change from one generation to the next and certain alterations can result in diseases, some of them both rare and serious. That's why sequencing the genes of infants holds so much promise. Not everyone is keen on the program. About a quarter of the parents with sick children who are eligible for free genome sequencing through his program decline it, Kingsmore said.

Lulling Your Baby to Hearing Loss

It's all the rage to have a soothing sounds playing to get your infant to fall to sleep. But research shows those devices can be loud enough to damage hearing. Infant sleep machines emit white noise or nature sounds to drown out everyday disturbances to a baby's sleep. Some sleep experts advise parents to use these noisemakers all night, every night, to ensure the best rest for a newborn. Many parents say their babies become so used to the sounds of rainfall or birds that they will not nap without them. But researchers at the University of Toronto listened to 14 sleep machines at maximum volume and found they produced between 68.8 to 92.9 decibels at 30 centimeters, about the distance one might be placed from an infant's head. Three exceeded 85 decibels, which is the safety limit for adults in the workplace on an eight-hour shift for accumulated exposure as determined by National Institute for Occupational Safety and Health. One machine was so loud that two hours of use would exceed workplace noise limits. Safe use is possible, the study's authors suggest, saying that farther away is less dangerous, a lower volume is better and shorter durations of time, all things that deliver less sound pressure to the baby. Brian J. Fligor, an audiologist and a spokesman for the American Academy of Audiology, said that the new study may have overestimated the sound exposure to infants by roughly seven decibels. Dr Fligor questioned the authors' way of accounting for the differences between the ear canals of adults and newborns. Information in this article first appeared in the New York Times. Copyright New York Times.

Trial Moves Forward for Newborns

Edimer Pharmaceuticals, a biotechnology company focused on developing a therapy for the rare genetic disorder X-linked Hypohidrotic Ectodermal Dysplasia (XLHED), has announced the enrollment and completed dosing of the first XLHED-affected neonate in a Phase 2 trial of EDI200—the company's novel, proprietary, recombinant protein. XLHED is an ultra-rare orphan disease of ectoderm development associated with a lack of

sweat glands, poor temperature control, respiratory problems, and hair and tooth malformations. Affected individuals are at risk for serious and potentially life-threatening hyperthermia and respiratory infections. EDI200 replaces EDA-A1, the protein missing in XLHED and a key regulator of skin and tooth development. If fully developed and approved, EDI200 will be the first protein therapeutic to provide a sustained correction of the symptoms of this disorder. The Phase 2 clinical trial is designed to evaluate the safety, pharmacokinetics, pharmacodynamics and efficacy of EDI200 in XLHED-affected male newborns in the first two weeks of life. EDI200 dosing will be initiated between the second and 14th days of life, with each study subject receiving two doses per week for a total of five doses.

FDA Looks at Genetic Modifications

An advisory committee of the US Food and Drug Administration has staged meetings on medical procedures that, if successful, would produce genetically modified human beings—changing every cell in the bodies of children born as a result of their use. The FDA calls them mitochondrial manipulation technologies. The procedures involve removing the nuclear material either from the egg or embryo of a woman with inheritable mitochondrial disease and inserting it into a healthy egg or embryo of a donor whose own nuclear material has been discarded. Any offspring would carry genetic material from three people—the nuclear DNA of the mother and father, and the mitochondrial DNA of the donor. Roughly 1,000 to 4,000 children born in the US each year will develop a mitochondrial disease, most by age 10, with symptoms that can range from mild to devastating. These diseases typically prevent mitochondria from converting food into energy and are the result of genetic abnormalities, although some cases can be caused by exposures to toxins. Disorders caused by mutations in the mitochondrial DNA are passed down from the mother. The FDA advisory panel says that its meeting will consider only scientific aspects of mitochondrial manipulation and that any "ethical and social policy issues" are outside its scope.

Guidelines Save Money

New research has found that when the most recent Centers for Disease Control and Prevention (CDC) guidelines for the evaluation of neonatal early-onset sepsis (EOS) were implemented, a quarter of all EOS evaluations in one hospital were eliminated and thousands of dollars were saved—without any apparent increase in sepsis cases. A study from the Division of Newborn Medicine, Boston Children's Hospital, and Harvard Medical School, Boston, Massachusetts, and published in the February issue of Pediatrics, found that the change is encompassed in the CDC's 2010 guidelines covering the use of intrapartum antibiotic prophylaxis (IAP) to prevent perinatal group B Streptococcus (GBS). The 2010 guidelines replaced 2002 guidelines, which drove up the number of EOS evaluations so that approximately 12% to 15% of healthy-appearing term and late preterm infants were evaluated for GBS. About half of those infants were treated with antibiotics. Researchers conducted a retrospective cohort study of infants born at 36 weeks' gestation or more from 2009 to 2012 in Brigham and Women's Hospital in Boston. The researchers compared a 12-month period in which the hospital followed the 2010 CDC guidelines with 12 months in which the 2002 algorithm was in use. The authors also conducted a cost-minimization analysis to compare costs and resource use between the periods. The 2002 guidelines

advised that infants be evaluated for GBS if their mothers failed to receive adequate indicated IAP for GBS. The 2010 guidelines changed the standard for evaluation of infants born to mothers with inadequate IAP, advising EOS evaluation only if additional risk factors were present, including a gestational age of less than 37 weeks, rupture of membrane of 18 hours or longer, maternal fever, or chorioamnionitis. The study showed that EOS evaluation frequency fell from 126 per 1000 live births (LB) at 36 weeks' or longer gestation during the 2002 guideline period to 68 per 1000 live births at 36 weeks' or longer gestation in the 2010 guideline period. The elimination of EOS evaluations performed for inadequate GBS IAP alone was responsible for that fall. Those evaluations fell from 32 per 1000 LB at 36 weeks' or longer gestation to 1 in 1000 LB during the 2010 guideline timeframe. When the researchers removed evaluations for inadequate IAP alone from the calculation of EOS evaluation frequency, there was no significant difference between the 2 periods.

Human Bank Has Got Milk

Christchurch's Neonatal Intensive Care Unit (NICU) has officially opened the first hospital-based pasteurized human milk bank in New Zealand. Dr Maggie Meeks, NICU pediatrician, says this is a significant achievement after years of planning and working closely with stakeholders towards the goal of pasteurizing mothers' excess milk for the benefit of other babies in the NICU. The NICU admits more than 800 babies a year, with around 3% from the West Coast and many would fit the criteria to benefit from the pasteurized donated milk. Dr Meeks says preterm babies are unable to breastfeed immediately after birth because of their lack of a mature coordinated suck and swallowing abilities. As a result their mothers need to express their breast milk, which is then fed to the babies through a gastric tube. The normal physiology of breast milk production following delivery is that it increases slowly over the first few days. With expressing only small amounts of colostrum are produced initially (0.1 -20mls in the first 24 hours). The set up costs of the human milk bank has been around $150,000. The operational costs are currently being met by the NICU and are part of the reason why this milk will only be available to the high-risk infants in NICU.

Dim Bulbs Not a Problem

No baby should die or be disabled because a light bulb can't be replaced. A nonprofit organization called D-Rev is designing first-rate medical equipment better suited to developing countries, then licensing it to for-profit distributors in those areas. One example is an inexpensive light therapy system called Brillance, which is being used to treat infant jaundice in some countries as India, where equipment is often found languishing in dusty corners because of burned-out bulbs and other seemingly simple problems. D-Rev's engineers developed equipment that was rugged enough to roll smoothly across dusty, rural hospital floors, and able to cope with erratic power supplies. D-Rev is one of dozens of small Silicon Valley start-ups aiming to use market dynamics to solve social problems. But seven years after its founding—and a decade into the rise of "social entrepreneurism"—D-Rev and its peers have found that the marriage of nonprofit motives to for-profit markets can be rocky. D-Rev has had to become far more involved than it expected in financial models, licensing deals, consulting services and manufacturing arrangements. In essence, it is redesigning not only high-tech products but also supply chains and procurement systems. D-Rev's operating budget grew to about

$1.4 million in 2013 from $880,000 in 2012. Donors include the Mulago Foundation, the Greenbaum Foundation and Focusing Philanthropy. Individual donors contributed 38% of D-Rev's budget in 2012.

Addicted Babies an 'Epidemic'

With the country's attention focused on overdoses and deaths because of heroin, Gov. Paul R. LePage of Maine has turned the spotlight on babies born in his state to drug-addicted mothers. LePage said that 927 "drug-addicted babies" were born in Maine in 2013, more than 7% of all births. Speaking to the Legislature, the governor called the births a "troubling epidemic" that was "tearing at the social fabric of our communities." The average cost for drug-addicted births in 2009, the latest year for which figures were available, was $53,000. LePage's stern warning on drugs followed a much-noted State of the State message by his fellow New England governor, Peter Shumlin of Vermont, who described the problem in Vermont as "a full-blown heroin crisis." It drew considerable media attention to the problem in the state, attention that was magnified by the death of the actor Philip Seymour Hoffman, 46, who the police say appeared to have overdosed on heroin. Shumlin, a Democrat, devoted his entire address to the subject of opiate addiction, and called on Vermont to view it as a disease to be treated, not just as a law enforcement problem to be solved by putting people in jail. LePage, a Republican with Tea Party backing, devoted most of his speech to what he described as the scourge of welfare, but he allotted several minutes at the end to drug addiction. Mr. LePage cast the drug problem in terms of law enforcement and economics.

Fresh Ideas for Human Milk

Breastfeeding basics for all RNs, human milk donations for all infants under 33 weeks, and becoming a collection site for donated milk—these are three best practices that emerged from Medela's new effort highlighting successes in increasing human milk consumption in the NICU. Medela is supporting the first-place winner, Memorial Hospital of Gulfport, Miss., and the runner-up, Rainbow Babies and Children's Hospital, University Hospitals Case Medical Center, Cleveland, Ohio, with $10,000 and $5,000 in Medela products respectively, after a nationwide call for submissions. Human milk acts much like medicine to premature babies who are vulnerable to potentially fatal diseases such as necrotizing enterocolitis (NEC), an intestinal disease associated with a high mortality rate among preemies. One in nine babies in the US is born prematurely. Memorial Hospital increased exclusive breastfeeding rates from 1% in December 2009 to a high of 67% in January 2013 by educating staff, providing donated human milk to preemies, collecting human milk for donation, and providing breastpumps bedside for mothers separated from infants, among other measures. Rainbow Babies and Children's Hospital, University Hospitals Case Medical Center, Cleveland, Ohio improved key metrics such as breastmilk feeding within 72 hours of life with measures such as providing Medela Symphony for each patient room and the Symphony initiation kit for every mother with an infant admitted to the NICU; participating in research to enhance knowledge of breastfeeding and improve support services; and using grant to pay for pump rentals when insurance won't cover it.

Telemedicine Honored

Children's Medical Center Dallas was recognized as a semifinalist in the 2013 Healthcare Informatics Innovator Awards program. As part of its telemedicine initiative, the 595-bed Texas-based Children's Medical Center Dallas deployed the teleNICU (neonatal intensive care unit) in 2013 in order to meet the demand for access to pediatric subspecialists, which is a problem in the state. The Children's Medical Center NICU unit is designated as a Level IV NICU—the highest possible rating, which means that Children's is equipped and staffed to care for the most fragile patients with complex medical conditions. Additionally, the technology and equipment used within the program allows Children's to connect and consult with other hospital NICUs located anywhere within Texas and beyond. The teleNICU equipment and technology is highly specialized and designed so that the instrumentation used for exams is able to transmit telemetry information back to Children's. All data transmitted is secured and encrypted at rest and in transit). A Children's neonatologist can see and hear the vital signs from the exam equipment as if he or she was conducting the exam in person. As a result, all nurseries through Level III NICU will be able to collaborate interactively with Children's. Caregivers at an outlying hospital can conduct a full exam within their own familiar environment while a Children's neonatologist participates interactively in the exam from Children's teleNICU studio.

Knocked Up…With Help

A growing share of American women are seeking medical help to become pregnant. Data from the Centers for Disease Control & Prevention show that roughly 12.5% of women between the ages of 25 and 44 had sought such help—everything from counseling

to artificial insemination—during the 2006-2010 survey period, up from 11.2% in 1995. Among women 35 to 39 years old who have experienced one or more births, 15.8% got medical help, up from 13.1% in 1995. For women in this age group who have never had children, the share rose slightly to 19.6% from 19.1%. The findings are part of the CDC's National Survey of Family Growth, which was conducted between June 2006 and June 2010. More than 12,000 women were interviewed, not all of whom had fertility problems or were seeking to get pregnant. While the CDC survey is nationally representative, individual demographic percentages—for example, women in their late 30s who have had no children—may have a larger margin of error because they rely on smaller sample sizes. Also, the CDC's definition of "medical help to get pregnant" is broad—ranging from getting advice and infertility testing to artificial insemination, which is fairly rare. Women who are white, better-educated and wealthier are more likely to make use of infertility services, the CDC said. Still, the agency's latest figures highlight the effects of one of America's biggest demographic trends: Young and middle-aged Americans are delaying childbearing, often until their 30s or mid-30s, or even beyond. The average age of a U.S. mother at first birth rose to 25.8 years old in 2012, up from 25.6 years in 2011 and around 21 in 1970, CDC data show. Research has shown that improved access to contraception, growing numbers of women in the workforce and the higher costs of raising families are factors in women putting off having children.

Multidrug Resistance is Not Futile

A sizable share of gram-negative bacilli bacteremia cases in the neonatal intensive care unit (NICU) are now multidrug resistant (MDR), new data show. However, the risk factors identified may help take the guesswork out of empirical antibiotic therapy in NICU patients. A team out of Taiwan conducted a cohort study of bacteremia that occurred in a NICU during a recent 8-year period, focusing on 376 cases caused by gram-negative bacilli. The study results, published online January 13 in Pediatrics, showed that nearly a fifth of the cases were caused by an MDR strain. The researchers analyzed prospectively collected data from 1106 cases of bacteremia diagnosed between 2004 and 2011 in the neonatal intensive care unit of a university-affiliated teaching hospital in Taiwan. Overall, 35.5% of the cases of bacteremia were caused by gram-negative bacilli, and 18.6% of the cases in this subset were caused by an MDR strain. The most common mechanism of resistance was production of extended-spectrum beta-lactamase, seen in two thirds of cases. In multivariate analyses among neonates with gram-negative bacilli bacteremia, the odds of having an MDR strain were sharply increased for those who had received a third-generation cephalosporin (odds ratio, 5.97; 95% confidence interval [CI], 2.37 - 15.08; P < .001) or carbapenem (odds ratio, 3.60; 95% CI, 1.26 - 10.29; P = .017) in the past month or who had underlying renal disease (odds ratio, 7.08; 95% CI, 1.74 - 28.83; P = .006). Neonates with an MDR strain had poorer outcomes: They were more likely to develop septic shock (40.0% vs 22.2%), receive inadequate initial antibiotic therapy (72.9% vs 7.8%), experience infectious complications (21.4% vs 10.5%), and die within 30 days of the onset of bacteremia (28.6% vs 10.5%).

Size Matters for Nursing Pay

New data from Nursing100.com shows the lowest 10% of neonatal nurses earn an average of $44,190 per year, while the highest 10% earn about $95,130. Nurses working in a neonatal

intensive care unit will make more than a generalized registered nurse, the data shows. However, things like geographic location, level of experience, level of education and any type of certifications will also affect the neonatal intensive care nurse's salary. The facility one works for also plays a role, as larger hospitals usually pay a higher salary than smaller hospital systems.

Promising Results

The investigational antiviral drug pocapavir had promising effects on an infant with enterovirus infection, according to data presented at the St. Jude/PIDS Pediatric Infectious Diseases Research Conference. Dr Sanet Torres-Torres of the department of infectious diseases at Children's Mercy Hospital, and colleagues evaluated a female neonate who presented with coagulopathy that required respiratory support. The patient tested positive for enterovirus and had severe enteroviral sepsis. Torres-Torres and colleagues initiated treatment with the investigational drug candidate pocapavir (V-073, ViroDefense, Inc.), which is being developed for poliovirus but has also shown activity against non-polio enteroviruses. The enterovirus was identified by the CDC as Coxsackievirus B3 and parental consent was obtained to use pocapavir, 20 mg/kg/day for treatment. Ten days of therapy were completed and viral cultures were negative. However, serum PCR remained positive. Coagulopathy resolved when the patient was aged 29 days and she was subsequently discharged at aged 56 days.

Agreement Reached

ONY, a pioneer in neonatal pharmaceutical development, has reached an agreement with Recordati Rare Diseases to co-promote NeoProfen (ibuprofen lysine) Injection. NeoProfen is indicated to close a clinically significant Patent Ductus Arteriosis (PDA) in premature infants weighing between 500 and 1500 grams, who are no more than 32 weeks gestational age when usual medical management (e.g., fluid restriction, diuretics, respiratory support, etc.) is ineffective. ONY, is the manufacturer and marketer of Infasurf (calfactant), a lung surfactant for the prevention and treatment of Respiratory Distress Syndrome (RDS) in premature infants.

Preventing Cardiac Neonatal Lupus

Medical interest is growing at the prospect of preventing fetal heart block from neonatal lupus by using hydroxychloroquine to treat women with systemic lupus erythematosus and other anti-Ro antibody-positive rheumatologic diseases throughout pregnancy. That's according to Dr Megan E.B. Clowse, who spoke about new date on the issue at the Winter Rheumatology Symposium sponsored by the American College of Rheumatology. Maternal anti-Ro antibodies readily transfer across the placenta starting at about week 16 of gestation. Roughly 2% of fetuses whose mothers are positive for these antibodies develop congenital complete heart block caused by inflammation at the atrioventricular node. It's an irreversible condition with significant morbidity and even mortality. If the mother has previously given birth to a baby with any manifestation of neonatal lupus—even if limited to neonatal rash—the risk of congenital complete heart block in subsequent pregnancies climbs to about 15%, according to Dr Clowse, a rheumatologist at Duke University. She and her co-investigators at Duke conducted one of the two studies that have led to her change in practice. It was a retrospective observational study of the recent Duke experience with pregnancies complicated by the presence of maternal anti-Ro antibodies. Twenty of the 33 subjects had systemic lupus erythematosus (SLE); most of the rest had unspecified rheumatologic disease or Sjögren's syndrome. Only 1 of 14 women treated with 200-400 mg/day of hydroxychloroquine throughout pregnancy had a baby with congenital heart block, while 7 of 19 pregnancies where hydroxychloroquine wasn't prescribed resulted in this fetal cardiac disorder. This translated into an 86% relative risk reduction of fetal congenital complete heart block in hydroxychloroquine recipients.

The High Cost of Baby Visits

Parents of the 78,000 babies a year who spend months in neonatal care after being born are spending a large amount of money each week to visit them, according to a British survey. Travelling to see their newborns, with eating and drinking and parking charges mean parents of children born prematurely or very sick at full term face an average £282 weekly bill. The average eight-week stay for such babies costs £2,256, the survey of 1,300 parents and 178 British hospitals by the neonatal care charity Bliss found. Food and drink cost £53 a week, while travel expenses including petrol and parking were more than £100 a week, participants said. While some newborns only need care for days, those who are more seriously ill can end up staying for up to a year. It costs the NHS £1,118 a day to look after a baby in intensive care where one in four of the 78,000 neonatal-care babies a year end up, £791 for those in a high-dependency unit and £505 for those requiring special care. Bliss wants extended maternity leave and pay for mothers of babies in neonatal care and for parents to receive free parking and accommodation as well as for hospitals to provide free meals and childcare for their other young children.

Talk to Preemies

Premature infants face a number of challenges, including a known risk of language delay. But a new study suggests that exposing "preemies" to more adult language in the neonatal intensive care unit can increase their language abilities at 18 months. "Parents have the power to make a difference in their child's development and academic success. Just by enjoying your child—singing, playing, telling stories—while riding in the car or having dinner, sharing your day with them," said the study's senior author, Dr Betty Vohr, a professor of pediatrics at the Alpert Medical School at Brown University in Providence, Rhode Island. That type of quality time should be a part of a baby's time in the neonatal intensive care unit (NICU), according to Vohr. But oftentimes in the NICU, people are quieter. Nurses and physicians may not interact much with the infants, and parents' visiting hours may be limited. Vohr said some working parents choose to work during the time their babies are in the NICU to save their family leave for when the baby comes home, which could limit the time they're available to talk to their baby. One of every eight babies born in the US is preterm—meaning born before 37 weeks of pregnancy, according to the US Centres for Disease Control and Prevention. The study, published online in Pediatrics, included 36 preterm infants. Their average age of gestation was 27 weeks and their average weight was 1.2kg, the authors said. At what would have been the 32nd and 36th weeks of gestation—an average of approximately 5 and 9 weeks after birth—the researchers recorded 16 hours of sounds the babies heard using a digital language processor. The processors kept track of adult words, conversational turns and child vocalizations. A conversational turn was when a vocal sound from the infant was followed by an adult's response within 5 seconds, or the opposite—when an adult spoke, followed by a

noise from the child within 5 seconds. Crying didn't count as a vocalization. The average total word count heard by an infant was 1 289 words at 32 weeks. There were an average of 15 conversational turns and 77 child vocalizations, according to the study. By 36 weeks, adult words reached 8 255. Conversational turns occurred on 36 occasions, and child vocalizations were heard 153 times. The investigators found that for every increase of 100 adult words per hour a baby heard at 32 weeks, there was a 2-point improvement in language scores, according to the study. At 36 weeks, every 100 adult words per hour heard led to a 1.2-point increase in language scores at 7 months.

Tummies Not as Upset

A daily dose of a probiotic may ease digestive upset in babies, according to new research out of Italy. A clinical trial randomly assigned 468 infants less than a week old to receive either a daily oral dose of Lactobacillus reuteri or an identical tasting placebo. Parents recorded the daily frequency of bowel movements and spitting up as well as the amount of time babies cried inconsolably. Investigators—who published the study in JAMA Pediatrics—followed the families with weekly phone calls or personal meetings. After one month, the babies who got the probiotic showed a significant decrease in crying time and an increase in frequency of bowel movements compared with those who got the placebo. By three months, their frequency of spitting up was reduced as well. The babies taking the probiotic had fewer emergency department visits and needed less medication for stomach problems. Their parents lost fewer days of work, and there were no adverse side effects. The results were adjusted to account for the effects of breast or bottle-feeding, vaginal or cesarean delivery, and other factors.

CPAP Success on the Bubble

The first clinical study of a low-cost neonatal breathing system created by Rice University bioengineering students demonstrated that the device increased the survival rate of newborns with severe respiratory illness from 44 to 71%. The results from a 10-month study of 87 patients at Queen Elizabeth Central Hospital (QECH) in Blantyre, Malawi. Based on data from the study, it is estimated that treatment with low-cost "bubble CPAP" could save the lives of 178,000 low-birth-weight babies in Africa each year. The researchers found that premature infants with complications like sepsis, very low birth weight and respiratory distress syndrome (RDS) benefited most from the new technology. Survival rates more than doubled for babies with RDS and more than tripled for babies in the other two categories after treatment with bubble CPAP. The technology is a low-cost version of the continuous positive airway pressure (CPAP) systems that are a standard feature of most neonatal units in the developed world. CPAP helps babies breathe more easily by keeping their lungs inflated, but with a price around $6,000, conventional neonatal CPAP machines are too expensive for hospitals in the developing world. In 2010, a team of Rice bioengineering students invented a low-cost bubble CPAP device. The technology, which costs about 15 times less than conventional CPAP machines, was created as part the Rice 360°: Institute for Global Health Technologies' award-winning, hands-on engineering education program, Beyond Traditional Borders (BTB).

State Struggle to Sign Up Latinos

For President Obama's Affordable Care Act to be considered a success, the country's citizens need to sign up. Easier said than done—especially with the nation's Latino population. And nowhere is the issue more significant than in California. The state has an estimated 15% of the country's uninsured population—half of those are Latinos. Enrollment of Latinos has fallen below the hopes of the law's proponents, accounting for 20% or fewer of those who had signed up on the state-run health insurance exchange by the end of December. State officials are rushing to expand marketing efforts and hire additional Spanish-speaking staff, hoping to sharply increase that number. California has begun taking steps to increase enrollment among Latinos, including adding enrollment counselors to its Spanish-language hotline center. Health plans have also begun advertising on food trucks that cater to Latino neighborhoods, and marketing campaigns are being reformulated to convey a message that officials believe will resonate there. Enrollment problems are playing out in other states with large Hispanic populations as well, including Arizona and Texas. But California stands out as the most troubling case because it has the most Latinos of any state. For months leading up to the rollout of the Affordable Care Act, state officials conducted focus groups and drew up elaborate marketing plans, with groups spending more than $100 million to publicize the new law, including extensive Spanish-language campaigns. And while many Republicans and conservative state leaders have criticized the new health care system, polls show that Latinos embrace the change. Many critics blame language for the slow start among Latinos—the Spanish-language website was littered with translation errors for weeks after its start. Others say there are not enough counselors to provide the kind of personal attention needed by many people who have never had health insurance. But fears of deportation may be a major factor, too. Health care clinics and community groups who have worked with Latinos for years say they routinely face skepticism among families who worry that signing up for insurance will attract immigration authorities, who could move to deport family members living here illegally.

Euthanasia Policy Under Fire

The American College of Pediatricians is criticizing policies that make children eligible for euthanasia. The ACP said it is "appalled" by Netherlands' recent legalization of Neonatal Euthanasia and Belgium's legalization of euthanasia for terminally ill children of any age, and alerts healthcare professionals to the possibility of similar legislation in the United States. "The concept of euthanasia is based on a utilitarian worldview that defines the value of the individual in terms of that individual's contribution to society. This ideology relegates neonates, especially those infants with congenital defects, to an expendable status. Physicians are healers not killers. An individual's future quality of life cannot be predicted by caregivers. The role of the physician is to promote health, cure when possible, and relieve pain and suffering as part of the care they provide. The intentional neglect for, or taking of, a human life is never acceptable, regardless of health system mandates. The killing of infants and children can never be endorsed by the American College of Pediatricians and should never be endorsed by any other ethical medical or social entity."

Home Births Riskier: Study

New research suggests that patients delivered at home by midwives had a roughly four times higher risk of neonatal deaths than babies delivered in the hospital by midwives. The increased neonatal mortality risk is associated with the location of a planned birth, rather than the credentials of the person delivering the baby. The number of homebirths in the US has grown over

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In this feature, Neonatal Intensive Care interviews clinicians and healthcare providers about the actual application of specific products and therapies. This interview is with Neil Kirby, Ph.D, President & CEO of Edimer.

Neonatal Intensive Care: Please explain the signs that XLHED carriers may exhibit.
Neil Kirby: X-linked hypohidrotic ectodermal dysplasia (XLHED) is a disorder of ectoderm development in which sweat and secretory gland hypoplasia predisposes affected infants to serious and potentially life-threatening hyperthermia and pneumonia. Those XLHED patients who survive infancy face a host of ectoderm-related clinical conditions including failure to thrive, oligodontia and misshapen teeth, mid-face hypoplasia, eczema, chronic dry eyes, asthma, respiratory infections, sinusitis and chronic nosebleeds.

NIC: Tell us about the treatment and how it works.
NK: EDI200 is a fully humanized EDA-A1 replacement molecule under development as a novel therapeutic for XLHED. In normal human development, EDA-A1 acts as an ectoderm signaling molecule that binds specifically to the EDA-A1 receptor (EDAR) triggering initiation and maturation of ectoderm appendages into sweat and secretory glands, tooth buds and hair follicles. In the case of XLHED, EDA-A1 deficiency results in the absence or functional hypoplasia of the ectoderm appendages. EDI200 comprises the human IgG1 Fc domain linked to the human EDA-A1 receptor-binding domain. In the course of normal ectodermal signaling, EDA-A1 monomers associate as trimers and higher order multimers that are required for activation of the EDA-A1 receptor (EDAR). The N-terminal Fc receptor portion of the EDI200 molecule serves to stabilize the intermolecular EDA-A1 associations required for EDAR binding, and to provide a potential mechanism for transplacental delivery.

NIC: Why is this treatment important?
NK: There are no therapies currently available for XLHED that prevent or correct the underlying ectodermal abnormalities. This study will provide essential data on the safety, pharmacokinetics, immunogenicity and potential data on the pharmacodynamics/efficacy of EDI200 required in order to gain FDA and other country-specific approvals.

NIC: Can you tell us anything about the patient who is already being treated?
NK: The first subject has been enrolled in study ECP-002 and has completed dosing.

NIC: How is the trial set-up? How are you identifying patients and providing treatment in this short timeframe?
NK: The trial is designed to evaluate the safety, pharmacokinetics, immunogenicity, pharmacodynamics and efficacy of EDI200 in XLHED-affected male newborns in the first two weeks of life. EDI200 dosing is initiated between the 2nd and 14th days of life, with each study subject receiving two doses per week for a total of five doses. A key inclusion criterion for the treatment protocol is verification of the XLHED diagnosis through EDA mutation testing. As part of the screening process, genetic testing results may be provided by the family to the study site via a secure and confidential method, including the option for electronic transmission. If genotyping confirmation is not available at the time of screening, the families of prospective subjects will be referred to resources available to facilitate rapid genotype testing at an accredited laboratory. Potential subjects are identified through a wide variety of venues, including health care providers, patient advocacy groups, social media, etc. Information on the trial is also publicly available by visiting clinicaltrials.gov, identifier NCT01775462.

NIC: When do you expect to publish the results of these findings?
NK: We will publish the data once we have completed the study, including follow-up analyses.

NIC: When do you expect the treatment to be available?
NK: We will continue to work closely with regulatory agencies around the world to make the product available as soon as possible.

Input on questions was provided by Tara KiMila. If you would like to participate in this feature, as a company or healthcare provider, please contact Christopher Hiscox or Steve Goldstien at s.gold4@verizon.net.

Delayed Cord Clamping: A Review

Omid Fathi, MD; Fayez Bany-Mohammed, MD; Muhammad Aslam, MD

Abstract

The concept of the umbilical cord as it relates to immediate fetal well-being has been a source of considerable debate dating back to antiquity. Delayed cord clamping is a simple technique to allow the newborn infant to reclaim a considerable amount of its uteroplacental circulation. The benefits to both preterm and term infants include greater hemodynamic stability, decreased necrotizing enterocolitis and sepsis, less intraventricular hemorrhage, increased iron and ferritin stores and subsequently less anemia and need for blood transfusions. Yet despite tremendous evidence to support these numerous health benefits to the neonate, this maneuver is not quite mainstream. A potential downside to this technique is the risk of polycythemia, hyperviscosity symptoms and subsequent hyperbilirubinemia; although the actual risk is unclear. The purpose of this review is to examine the evidence regarding the risks versus benefits of delayed cord clamping in both preterm and term infants with some emphasis on transition physiology. In addition, this review aims to see if any long-term benefits with respect to neurodevelopmental outcomes and immune protection can be gained from delayed cord clamping. Lastly, cord milking will be discussed, as a potential "substitute" when delayed cord clamping may not be feasible.

Introduction

The timing of umbilical cord clamping has continued to garner considerable interest and study in recent years, and while there is no lack of information on the subject, it continues to generate controversy and inconsistency in its practice. Historically, the role of the umbilical cord has been a source of wonderment for physicians and scholars alike.[1] Hippocrates and Galen were among the first to speculate about the umbilical cord as a conduit for fetal nutrition. The first known documentation of immediate umbilical cord clamping after delivery appears to be from the 1600s, and even then there was debate among physicians about whether such a practice was truly beneficial for the infant. The following two centuries continued to bring new delivery room devices (umbilical cord ties, clamps) that seemed to only further perpetuate immediate or early cord clamping. It is also interesting to note that in her original papers in 1953 and 1958, Virginia Apgar readily suggested that delayed cord clamping (DCC) was suboptimal and "part of a slow delivery." The first substantial study to demonstrate the actual physiological effects of DCC was demonstrated by Yao et al in 1968.[2] The amount of residual placental blood volume, and the rapid rate that it can be transfused to the neonate immediately after birth were staggering to behold. More recently, both the obstetrical and neonatal communities have revisited the benefits of DCC in both preterm and term infants. These benefits include greater restoration of effective circulatory volume, improved hemodynamic stability, less Intraventricular hemorrhage (IVH), and less iron deficiency anemia.[3] Few other suggested and explored benefits are immunological enhancement as well as neurodevelopmental protection. The purpose of this review is to explore the recent evidence for DCC with respect to transition physiology, briefly review cord "milking" as compared to DCC and discuss neonatal outcomes in both term and preterm infants.

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Term Infants and Delayed Cord Clamping

There exist a number of studies investigating both the benefits and conceptual risks of DCC in full term infants. They all echo the same key findings: increase in hemoglobin and hematocrit concentrations (both immediate and for up to six months of age), higher iron stores and increased circulating ferritin.[4] All of this amounts to decreased rates of iron deficiency anemia in infants. While this has been touted as quite a significant benefit in developing countries, the ease and simplicity of such a maneuver should not be overlooked for any newborn. The increase in blood volume that accompanies DCC has been postulated to increase a newborn's risk of jaundice and subsequent need for phototherapy. The recent Cochrane review of DCC in 2013 did indeed report a statistically significantly higher rate of jaundice requiring phototherapy in infants that had received DCC. On the other hand, a recent RCT by Andersson et al seems to actually suggest the opposite; that there may not exist a significantly increased risk for hyperbilirubinemia.[5] Another recent systematic review by Garafalo and Abenhaim only further supports this sentiment.[3] While the risk of hyperbilirubinemia, polycythemia and symptoms related to hyperviscosity may potentially be real (especially in those populations already predisposed), these reviewers could find no report of any major invasive intervention required.

Preterm Infants and Delayed Cord Clamping

The benefits of DCC in preterm infants appear to be much more widespread and instrumental in not only immediate stability

for preterm babies, but also in possibly avoiding long-term morbidity. The most recent Cochrane review in 2012 assessed fifteen studies totaling 738 infants ranging from 24 – 36 weeks gestation.[6] DCC was done anywhere from 30 to 180 seconds. There was a statistically significant association with less need for blood transfusions, decreased IVH, decreased necrotizing enterocolitis (NEC) and late-onset sepsis. No clear difference was seen in mortality, albeit several of the included studies suffered from incomplete reporting and wide confidence intervals. Most initial studies focused on the same potential benefits and risks as seen in term babies (increased iron stores, hemoglobin, risk of jaundice).[7] However, more recent studies have shown DCC to allow for greater immediate hemodynamic stability of preterm infants, not only in the delivery room, but also after admission to the NICU.[6,8] It is no surprise, therefore, that this period of relative stability during such a crucial period of postnatal life (first 48 hours) has downstream benefits as seen with less IVH and NEC. The potential for a nearly 50% reduction in IVH with DCC was cited as the single most important clinical benefit for preterm infants in a recent Committee Opinion from American College of Obstetricians and Gynecologists.[9]

Cord Clamping and Perinatal Transition

The inception of breathing in relation to clamping of the cord is one important variable that facilitate a smooth transition from fetal to postnatal life. Cord clamping blocks both umbilical vein and arteries simultaneously leading to a reduction in right ventricular preload (by ~ 40%) with a concurrent increase in the left ventricular afterload.[10] Since most healthy infants cry soon after birth and establish lung volume and pulmonary blood flow, they tolerate these hemodynamic changes and transition smoothly, despite early cord clamping. Several observational studies showed that heart rate consistently drop when the cord was clamped before the onset of respiration, while no such change was seen in vigorous infants who began breathing before cord occlusion.[11] A recent study by Bhatt et al in preterm lambs confirmed this observation and demonstrated that clamping the umbilical cord before onset of respirations resulted in progressive fall in the right ventricular output during the first 90 seconds and remained low until ventilation began at 2 minutes.[12] In the group where ventilation was established first and cord clamping delayed, pulmonary blood flow increased to a stable baseline (due to physical recruitment of the lung), heart rate remained stable before and after clamping and pulmonary blood flow rose progressively through establishment of ventilation and further with the immediate functional closure of the ductus arteriosus that occurred with cord clamping. At 2 min after cord clamping, pulmonary blood flow in the Ventilation 1st group was twice that in the Clamp 1st group. The study demonstrated that establishment of lung expansion prior to umbilical cord clamping results in stable heart rate, progressive rise in pulmonary blood flow leading to a smoother transition to newborn life with stable cerebral hemodynamics (as measured by carotid artery pressure).
The situation may even be dire for compromised infants due to cord compression (e.g. from oligohydramnios or nuchal cord). In this situation, selective intermittent occlusion of the thin-walled umbilical vein, while not occluding the thicker-walled umbilical arteries, reduce the inflow of oxygenated blood from the placenta while maintaining 'bleeding' via the umbilical arteries into the low resistance placental circulation. Immediate cord clamping will likely deny the already hypovolemic infant the benefit of ~ 16 ml/kg of placental blood. Therefore, it's argued that, in compromised infants, a delay in cord clamping to transfuse the infant with its own blood, would be most beneficial.[10]

Delayed Cord Clamping vs. Cord Milking

There has also been recent attention paid to the practice of "cord milking" whereby the blood present in the attached or clamped umbilical cord (20 – 30 cm) is manually expressed into the baby (3-5 times). Some institutions may augment DCC by milking the remainder of the cord prior to clamping, but generally this maneuver has gained interest as a substitute for when DCC is not feasible, whatever the reason. Two recent studies were able to compare cord milking (with cord attached[13] and after cord was clamped[14]) with immediate cord clamping in term and near-term infants and the results/benefits were very similar to those conveyed by DCC, that being effective uteroplacental transfusion with increased levels of hematocrit at 36-48 hours of life and improved iron status at 6 weeks of life.[14] Three randomized controlled trials comparing cord milking to immediate cord clamping in premature infants were published recently.[15-17] March et al randomized women admitted to a tertiary care center in Boston and expected to deliver between 24 to 28 completed weeks of gestation to cord milking before clamping to immediate cord clamping. Of 113 women who were enrolled and randomized, 75 completed the study and delivered extremely premature infants. Neonates in the cord milking group had higher hematocrits at birth, were less likely to require transfusion and were less likely to develop an IVH. Takami et al, in Japan, evaluated cerebral tissue oxygenation index and cerebral fractional tissue oxygen extraction in 50 "stable" very low birth weight (VLBW) infants (gestational age <29 weeks, birth weight <1250 g), 26 allocated to cord milking group and 24 to immediate cord clamping, using near-infrared spectroscopy and doppler echocardiography. They found that hematocrit, left ventricular (LV) end-diastolic dimension, LV cardiac output, and superior vena cava flow were higher in the milked group than in the control group in the first 24 hours of life. Tissue oxygenation index increased and cerebral fractional tissue oxygen extraction decreased in the milked group within 24 hours as well. They concluded that umbilical cord milking stabilized cerebral oxygenation and perfusion in VLBW infants by improving LV diastolic function via increasing LV preload.[16] Finally, Hosono et al conducted a randomized controlled trial that compared cord milking to immediate cord clamping in preterm infants ≤29 weeks of gestation. The study was able to demonstrate immediate improvement in hemoglobin, urine output, blood pressure and cardiac performance indices in the first 48 hours in premature infants when compared to controls.[17] Since DCC is well studied compared to cord milking, the question always arises whether cord milking provide equivalent benefits to DCC. To that effect, Rabe et el, in a randomized trial, compared the two techniques in 58 infants that were all less than 33 weeks gestation.[18] The infants in this study were either randomized to 30 seconds of DCC or cord milking done four times during resuscitation. The study did not find any statistically significant differences in mean hemoglobin values in the first hour of life, need for transfusions or indices of hemodynamic stability. While this is only one randomized controlled trial, their initial findings do seem to suggest that cord milking may be an effective alternative where DCC may not be possible. It also assuring that a recent study found that cord milking at preterm delivery is associated with a low risk of clinical hyperviscosity.[19]

Immunological Benefit

The initial Mercer study in 2006 was able to demonstrate a

statistically significant reduction in sepsis in those infants that had received DCC.[20] Placental transfusion has long been known to also increase the number of circulating stem cells that the newly born infant will receive. Conceptually, it would make sense that this should relay some immunological benefit to the infant. One study by Kugelman et al was not able to find any significant differences between infants that had received DCC and those that had not.[21] Their two study groups demonstrated equal levels of compliment and immunoglobulins, same numbers of sepsis evaluations, and equal numbers of actual documented infections. A similar study of 382 full-term infants by Andersson et al found a very transient increase in circulating IgG levels in their DCC group compared to controls, but that this increase or conceptual benefit was equalized at four months of age.[22] The same study also found no difference in infectious symptoms as reported by parents during the first four months of life between the DCC group and immediate clamping group. While the latter findings may be somewhat subjective in nature, both aforementioned studies have not been able to replicate any protective immunological benefit as seen in the 2006 Mercer study. At the very least, more investigation into this particular facet of DCC is warranted.

Neurodevelopmental Benefit

The reproducible physiological effects of DCC are clear: greater effective circulatory volume, increased cerebral oxygenation, decreased IVH, and decreased NEC. The next logical domain to explore is whether or not these beneficial effects translate into better neurodevelopmental outcome. Mercer et al were able to re-evaluate 72 of their infants in which they had enrolled in their original 2006 study.[23] This was done at a 7 month developmental follow-up visit. They found no difference in the Bayley Scales of Infant Development (BSID) scores between the DCC and immediate cord clamping groups. However when controlled for different morbidities, they did find that male infantsin the DCC group had statistically higher scores than their male counterparts that did not receive DCC. No difference was noted in the female infants regardless of whether or not they had received DCC. Andersson et al evaluated 382 full-term infants at four months of age using the Age & Stages Questionnaire II; there was a very slight advantage in problem solving and personal-social scores in the DCC group compared to the ICC group. All other scores across the more broadly tested domains were not statistically different.[22]

Summary

Delayed cord clamping is an effective way to restore a newborn infant's uteroplacental blood volume. It has clear benefits in the preterm population including increased hemodynamic stability, improved cardiac function, as well as decreased rates of NEC and IVH. Infants born at term can also benefit from this technique as it can improve their iron/ferritin stores and help prevent iron deficiency anemia. The only real risk appears to be possible polycythemia and subsequent hyperbilirubinemia. It is unclear at this time if this risk is quantifiable as it has not been completely reproducible in different studies. It does, at the very least, bring to light that delayed cord clamping should be more cautiously considered in those infants already with risk factors for polycythemia like infants of diabetic mothers or infants who have intrauterine growth restriction.[24] More studies need to be done with respect to long-term neurodevelopmental effects as well as any immune protection this technique may provide.

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the last decade. In the largest study of its kind, using Centers for Disease Control data on nearly 14 million linked infant birth and neonatal death data, term singleton US births, researchers at New York-Presbyterian/Weill Cornell Medical Center found the absolute risk of neonatal mortality was 3.2/10,000 births in midwife hospital births, and 12.6/10,000 births in midwife home births, and it further increased in first-time mothers to 21.9/10,000 births in midwife home deliveries. Neonatal mortality was defined as neonatal deaths up to 28 days after delivery. The excess total neonatal mortality for deliveries performed by home midwives was 9.3/10,000 births or about 18-19 excess neonatal deaths a year from midwife homebirths. Based on the most recent 2012 births data, the authors concluded that if home births by midwives continue to grow at the present 10% yearly rate, then the excess total neonatal mortality of home births by midwives would nearly double from about 16-17 in 2009 to about 32 in 2016. The main authors of the study, said that obstetric practitioners have an ethical obligation to disclose the increased absolute and relative risks associated with planned home birth to expectant parents who express an interest in this delivery setting, and to recommend strongly against it.

Wombs Find New Homes

Nine women in Sweden have successfully received transplanted wombs donated from relatives and will soon try to become pregnant, according to the University of Gothenburg. The women were born without a uterus or had it removed because of cervical cancer. Most are in their 30s and are part of the first major experiment to test whether it's possible to transplant wombs into women so they can give birth to their own children. Life-saving transplants of organs such as hearts, livers and kidneys have been done for decades and doctors are increasingly transplanting hands, faces and other body parts to improve patients' quality of life. There have been two previous attempts to transplant a womb—in Turkey and Saudi Arabia—but both failed to produce babies. Scientists in Britain, Hungary and elsewhere are also planning similar operations but the efforts in Sweden are the most advanced. The university said the nine womb recipients were doing well. Many already had their periods six weeks after the transplants, an early sign that the wombs are healthy and functioning. One woman had an infection in her newly received uterus and others had some minor rejection episodes, but none of the recipients or donors needed intensive care after the surgery. All left the hospital within days.

Genomic Sequencing Studied

The National Institutes of Health have awarded $5 million in four pilot grants under a research program in which genomic sequencing may reveal many problems that could be treated early in a child's life, avoiding the diagnostic odyssey that parents can endure when medical problems emerge later.

The Benefits of Breathing Heliox for Infants with Bronchopulmonary Dysplasia

Chris Campbell

There is no such thing as a one-sized-fits-all treatment for a medical condition. Some treatments put tremendous strains on a human body. When it comes to a fragile preterm infant struggling to breathe, extra care is needed so treatments don't do more harm than good.

The team of Wolfson et al.—from the Department of Physiology, Temple University School of Medicine, and Section of Newborn Pediatrics, Pennsylvania Hospital—studied this issue when it came to the area of breathing difficulties and finding treatments that reduce the strain on these tiny patients. Originally published in the May 1984 edition of the Journal of Pediatrics, researchers reported on a study of 12 infants with Bronchopulmonary Dysplasia (BPD). The study found that during Heliox breathing there was significant decrease in pulmonary resistance, resistive work of breathing and mechanical power of breathing, whereas ventilation remained unchanged.

The studied found therapeutic value in Heliox—a lower density gas mixture—by reducing muscle fatigue in these vulnerable preterm infants and also making more calories available for growth and recovery because the babies weren't working as hard to breathe.

The Condition

It's called Bronchopulmonary Dysplasia (BPD), which has associated functional changes including tachypnea, decreased lung compliance and elevated airway resistance.[1-5]

Basically, BPD vastly increases the workload when it comes to breathing, sapping the energy level of patients and draining their calories. For a preterm infant, that last part greatly slows down their ability to grow at a crucial time.

The researchers theorized that since previous studies had found that adults benefited from a Heliox—through decreased airway resistance—then infants with BPD should also benefit because of the excessive amounts of energy they were being forced to expend.[6-12]

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Methods

The 12 infants were selected from the Neonatal Intensive Care Unit of Pennsylvania Hospital and criteria included the presence of clinical signs of respiratory distress, including tachypnea and retractions. All infants were breathing spontaneously and had abnormal pulmonary functions at the time of the study, as well as having had mechanical ventilation and supplemental oxygen therapy. The existing clinical management of the infants included oxygen concentrations ranging from 0.21 to 0.33.

According to researchers, the infant was calmed and held in the cradled position for the 20-minute duration of the study. In the control condition, the infant spontaneously breathed a gas mixture of 0.21 to 0.33 balanced by nitrogen. Two pre-blended and analyzed Heliox gas mixtures (80:20, 70:30) were substituted during the experimental period.

The infants who were breathing room air received the 80:20 Heliox mixture. The five patients with inspired oxygen concentration of 0.28 to 0.33 during control gas breathing received the 70:30 Heliox mixture during the experimental phase, delivered in sequence for 5 to 10 minutes through a common valve to an anesthesia bag (1 L), which served as a reservoir. Delivered gas flow rates were constant at 5 L/min, and a blow-off valve prevented pressurization of the reservoir.

Mechanics of breathing were studied by simultaneously monitoring esophageal pressure, inspiratory and expiratory flow rates, and tidal volume.

Control gas breathing determinations were made after the infant adapted to the mask (<1 minute). The reservoir was effectively flushed, and measurements during Heliox breathing were made at least 5 minutes after the gas was introduced, to provide time for equilibration. Similarly, recovery determinations (control gas after Heliox) were made in infants at least 5 minutes after the switch back to the control gas mixture. This sequence provided a representative volume and frequency history in each infant. Mechanics and energetics of breathing were based on the average of at least 6 uniform breaths.

The Findings

After studying the infants, the researchers found that clinically they "appeared to breathe more regularly and with less effort during the Heliox phase. The amplitude of the esophageal pressure wave, or peak-to-peak pressure, decreased during Heliox breathing as compared with control."

The study also found "noteworthy" that the computed resistive work of breathing was reduced overall during Heliox breathing.

In the study's discussion area, the researchers wrote that "based on theoretical concepts and experimental conditions, these functional alterations in breathing appear to be related to the differences in the physical properties of the control and helium gas mixtures."

Researchers said that one major benefit of the Heliox is that by breathing more regularly and with less resistance, "this modality may reduce respiratory muscle fatigue." This would greatly reduce the stress on a preterm infant.

The second benefit was found in the area of calories. The energy expended as an infant struggles to breathe may reduce the available calories for growth and further complicate recovery, the study said.

"We estimated that Heliox breathing resulted in a caloric savings of approximately 2 kcal/kg/day. By reducing the caloric expense of breathing, Heliox breathing could potentially conserve calories for growth."

The study found that "alternative explanations for the changes in pulmonary mechanics and energetics of breathing can be excluded with reasonable certainty."

Researchers monitored the entire process to ensure minimal mask leakage, and uninterrupted transition from control gas to Heliox to prevent the possibility of dilution. All measurements were taken during steady-state conditions, represented by a typical volume and frequency recording.

"Our results suggest that breathing a lower density gas mixture such as Heliox effectively reduces the WOB in infants with BPD."

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Increased Maternal Body Mass Index and Overweight: Impacts on Breastfeeding Outcomes and Implications for NICU Staff

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The Neonatal Intensive Care Unit (NICU) proves a formidable opponent for infants. Many given needs of the infant, both term and preterm, are difficult to attain despite the best of intentions. Basic human needs of the infant including access to breast milk, breastfeeding, and skin-to-skin care prove challenging. Pumping breast milk becomes a necessity and mothers spend countless hours, given with dedication and love, to collect colostrum and breast milk for their precious babies. With current knowledge so strongly supporting the use of human milk, every drop is needed yet overweight and obese mothers face barriers that normal-weight mothers do not. These issues should be highlighted and discussed with NICU caregivers to ensure understanding, knowledge, and evidence-based strategies to promote breast milk production and reduce negative impacts associated with increased maternal weight.

Multiple associations have been reported pairing maternal obesity with suboptimal lactation outcomes. Intent to breastfeed or provide breast milk, initiation of breastfeeding, and duration of lactation show a negative correlation with overweight mothers. In 2011, a systematic review of the effect of maternal obesity showed the prevalence of obesity in pregnant women to be 28.9% and rising (Lepe, Bacardi Gascon, Castaneda-Gonzalez, Perez Morales, & Jimenez Cruz, 2011). Today, the Center for Disease Control (CDC) classifies overweight by a body mass index (BMI) of ≥25.0, obesity as a BMI ≥30 (CDC, 2011). This steady and rising rate of weight increase among women of child-bearing age is a public health concern warranting immediate vigilance and active attention.

Duration of breastfeeding is of primary concern and the constant chase to increase rates is an ongoing struggle. In the NICU, pump-dependent women work even harder to express milk and collect it for their babies. Multiple studies have demonstrated an inverse relationship between high BMI and shorter breastfeeding duration (Amir & Donath, 2007, Baker, Michaelsen, Sorensen, & Rasmussen, 2007, Oddy, Li, Landsborough, Kendell, Henderson, & Downie, 2006, Wojcicki, 2011). Women within the three classes of obesity I, II, and III can be further denoted as less likely to breastfeed for a longer duration with obese women in class III, BMI ≥40 less likely to breastfeed or provide breast milk at six months postpartum (Donath & Amir, 2008).

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Breast milk expression patterns and associations have also been studied comparing women with increased BMI to their thinner counterparts. Associations between increased BMI and breast milk expression and production were studied in 2011. Women who had not previously expressed milk and were obese or overweight had significantly shorter durations of milk production. These women were more likely to initiate breast pumping before two months postpartum, but less likely to be successful (Leonard, Labiner-Wolfe, Geraghty, & Rasmussen, 2011). This group of women experience more difficulties producing and expressing milk and are likely to become discouraged, leading to cessation of lactation.

Lactogenesis II, the onset of copious amounts of milk and transition from colostrum to milk, is often delayed in women with high BMI; one common cause of this delay is cesarean delivery (Nommsen-Rivers, Chantry, Peersen, Cohen, & Dewey, 2010). Overweight mothers are 50% more likely to need cesarean section delivery than normal weight mothers, and obese women are almost two times as likely to deliver in this manner (Weiss, Malone, & Emig, 2004). Poor milk yield is frequently noted in this population; contributing factors include: difficulties with properly fitting the pump breast shields as well as excess adipose tissue in the breast causing constriction around the milk ducts inhibiting the flow of milk (Leonard, et al, 2011). Mothers with high BMIs are more likely to provide human milk for shorter periods of time. This group of women may be more likely to initiate pumping due to a perceived lack of milk production due to the delay in lactogenesis II. Low milk yield while pumping may result in these mothers abandoning their previous intentions to provide milk. It is possible that with coaching and support, these mothers could have continued pumping, established milk supply, and overcome difficulties resulting in success with longer durations of lactation noted. Disparities between the weight classes could decrease (Leonard, et al, 2011).

Another biological rationale for lower milk yields and earlier cessation of breastfeeding is linked to reduced levels of prolactin in response to infant suckling. Sustained prolactin levels are needed to promote the onset of lactogenesis II. In one study, prolactin levels were collected after 30 minutes of time at the breast, at 48 hours, and seven days post-delivery. Diminished prolactin levels were reported in both overweight and obese mothers (Rasmussen & Kjolhede, 2004). These findings are important as lower levels of prolactin compromise milk production and can lead to early abandonment of the provision of breast milk.

Among the many known benefits of human milk are the unique, unparalleled immunological components including: secretory Immunoglobulin A (sIgA), lactoferrin, and human milk oligosaccharides (HMOs). Human milk components play a key role in immune protection, protecting the infant's gut during a critical period of development, cell signaling, pathogen phagocytosis, and the development of active immunity. BMI has a definite negative impact on HMOs, immunological components, and pathogen presence in the breast milk of overweight and obese women. Milk collected shortly after delivery, one month, and six months postpartum was compared in women of normal weight and those with higher BMIs. HMOs were reportedly lower in women with high BMIs with an increase in Staphylococcus and Lactobacillus noted (Collado, Laitinen, Salminen, & Isolauri, 2012). Anti-inflammatory components aiding in the reduction of disease processes such as Necrotizing Enterocolitis, Chronic Lung Disease, and Retinopathy of Prematurity are passed via human milk (Meier, Engstrom, Patel, Jeiger, & Bruns, 2010). All are known to be decreased in the breast milk of high BMI mothers (Smilowitz, Totten, Huang, Grapov, Durham, Lammi-Keefe, Lebrilla, & German, 2013).

Astute neonatal staff members are positioned to make a true difference in breastfeeding rates and the provision of human milk for the neediest of infants. By embracing evidence, anticipating mothers at risk, and educating and supporting both mothers and their families, NICU caregivers can coach mothers to success. Research shows high levels of delayed lactogenesis II, decreased milk yield, lower breastfeeding initiation rates, and decreased longevity of breastfeeding among overweight and obese mothers. Life-sustaining passive immunity, much needed in the neonatal population, is reduced. By providing skilled, neonatal lactation support for these mothers, the potential to improve breastfeeding rates and the provision of human milk in our NICU population increases. By identifying these mothers, the potential to improve breastfeeding success, improve maternal health, and increase human milk consumption is an attainable goal. Neonatal staff hold the key to the "responsible extrauterine gestation" of the neonate in their care. Carefully assessing lactation key points, prioritizing breastfeeding support, and intervening on a daily basis are crucial to the complete and total well-being of these babes.

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Treatment of Neonatal Jaundice with Filtered Sunlight in Nigerian Neonates: Study Protocol of A Non-Inferiority, Randomized Controlled Trial

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Abstract

Background: Severe neonatal jaundice and its progression to kernicterus is a leading cause of death and disability among newborns in poorly-resourced countries, particularly in sub-Saharan Africa. The standard treatment for jaundice using conventional phototherapy (CPT) with electric artificial blue light sources is often hampered by the lack of (functional) CPT devices due either to financial constraints or erratic electrical power. In an attempt to make phototherapy (PT) more readily available for the treatment of pathologic jaundice in underserved tropical regions, we set out to test the hypothesis that filtered sunlight phototherapy (FS-PT), in which potentially harmful ultraviolet and infrared rays are appropriately screened, will be as efficacious as CPT.

Methods/design: This prospective, non-blinded randomized controlled non-inferiority trial seeks to enroll infants with elevated total serum/plasma bilirubin (TSB, defined as 3 mg/dl below the level recommended by the American Academy of Pediatrics for high-risk infants requiring PT) who will be randomly and equally assigned to receive FS-PT or CPT for a total of 616 days at an inner-city maternity hospital in Lagos, Nigeria. Two FS-PT canopies with pre-tested films will be used. One canopy with a film that transmits roughly 33% blue light (wavelength range: 400 to 520 nm) will be used during sunny periods of a day. Another canopy with a film that transmits about 79% blue light will be used during overcast periods of the day. The infants will be moved from one canopy to the other as needed during the day with the goal of keeping the blue light irradiance level above 8 µW/cm^2/nm.

Primary outcome: FS-PT will be as efficacious as CPT in reducing the rate of rise in bilirubin levels. Secondary outcome: The number of infants requiring exchange transfusion under FS-PT will not be more than those under CPT.

Conclusion: This novel study offers the prospect of an effective treatment for infants at risk of severe neonatal jaundice and avoidable exchange transfusion in poorly-resourced settings without access to (reliable) CPT in the tropics.

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Background

Severe neonatal jaundice (NNJ) or hyperbilirubinemia and its progression to acute bilirubin encephalopathy (ABE) and kernicterus is a leading, yet preventable, cause of newborn re-hospitalizations, deaths, and disabilities globally [1-5]. Phototherapy (PT), which involves exposing a newborn's skin to electric lamp-generated blue light, is the standard treatment for removing excessive bilirubin, except in extreme cases when exchange transfusion becomes necessary [6].

Numerous studies from poorly-resourced countries suggest that severe NNJ represents perhaps the largest unrecognized cause of neonatal morbidity and mortality in the world [4,7]. In sub-Saharan Africa, especiallwy in Nigeria and Kenya, NNJ is a leading cause of death in newborn nurseries [8-13] and long-term neurological impairment in survivors [14-18]. Unfortunately, PT may not be available in these countries because of the lack of devices and/or of reliable electrical power [19,20]. In these areas, modern PT devices are not readily affordable, often break down because of electrical power surges, and are difficult to maintain due to the unavailability of replacement parts. Even where PT devices are available, most hospitals lack the resources necessary to replace fluorescent lamps, which is recommended after 2,000 to 3,000 hours of use, and, as a consequence, simply leave ineffective tubes in place until they burn out. Moreover, very few hospitals have appropriate irradiance meters for measuring the intensity of the blue light emitted by the lamps, resulting in few or no devices providing the optimal level of irradiance required for intensive (>30 µW/cm^2/nm) conventional phototherapy (CPT) [21,22]. However, it is not uncommon, especially in areas without access to CPT, for the parents/guardians of jaundiced infants to place their babies in direct sunlight unaware of the potential harm or safety risks.

The scientific potential of sunlight as a possible treatment for NNJ was first demonstrated by Cremer and colleagues in 1958 [23]. His team found that placing naked infants in sunlight decreased bilirubin levels. This observation led to the production of the first PT device using fluorescent blue light tubes. These early studies subsequently led to the development of commercially available, easily controlled, electricity-requiring artificial blue light sources for effective, on-demand PT of newborns in industrialized countries. The potential efficacy of direct

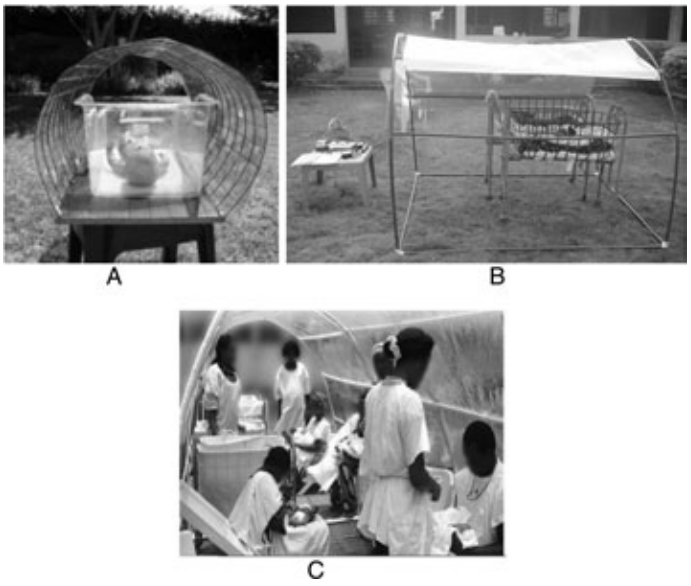

Figure 1. Filtered sunlight canopies. A: Experimental filtered sunlight canopy with a baby doll; B: Baby placed under a filtered sunlight canopy in an open lawn in a primary care setting; C: Mother-infant pairs with health workers under a group filtered sunlight canopy in a hospital setting.

sunlight PT compared with CPT has also been demonstrated in an in vitro study [24].

Using direct sunlight for PT has a number of clinical and practical drawbacks that could make its use undesirable. Sunlight contains altitude-, seasonal-, and time-of-day-dependent levels of harmful ultraviolet A, B, and C radiation, which can seriously and permanently damage human skin. It also contains significant levels of warming infrared radiation, which, in the absence of sufficient cooling, could raise core body temperatures to unsafe levels. However, several technological solutions exist for filtering unwanted radiation from any light source, including sunlight, while preserving the desirable attributes of a given energy spectrum [25]. When filtered to exclude the harmful spectral radiation, the use of sunlight can be valuable in environments that have no access to electric lamp PT.

The most practical filters of sunlight are the commercially available window-tinting films, widely used in vehicles and residential and commercial structures in sunny climates. Although window-tinting films are traditionally affixed to a glass surface, these films can also be stretched over a support frame, under which an infant basket (Figure 1A), bassinet, or crib (Figure 1B) can be placed. Our preliminary laboratory bench studies in California and field studies in Nigeria have shown that such films effectively remove potentially harmful radiation, while allowing the transmission of beneficial blue light required for effective PT. The levels of irradiance recorded exceeded that delivered by the most potent newborn PT devices. In one of the field tests in a rural hospital in Nigeria, seven jaundiced infants were placed under portable individual or group filtered sunlight PT (FS-PT) using film-covered canopies placed in direct sunlight in the hospital courtyard (Figure 1B,C). Body temperature and blue light irradiance were monitored every hour, and the infants were watched closely for the development of clinical dehydration and sunburn. FS-PT was tolerated well by both newborns and their mothers and allowed for maternal bonding during treatment. None of the infants developed significant hypothermia (defined as <35.5°C), and displayed no evidence of dehydration or sunburn. Six of the infants had at least one temperature episode >38.0°C during their course of FS-PT, but none exceeded 39°C, and all recovered after being returned indoors. The average time to being able to return to FS-PT was 19.7 minutes, with only two instances over 60 minutes. Moreover, placing infants on a moistened towel during high ambient temperatures (>40°C) quite readily maintained body temperatures of infants in cribs.

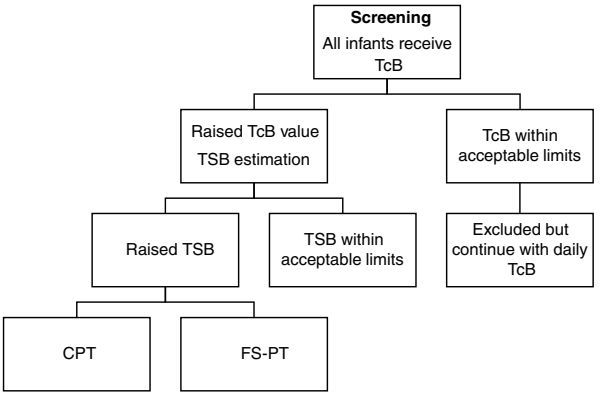

Figure 2. Enrolment flow chart. CPT, conventional phototherapy; FS-PT, filtered sunlight phototherapy; TcB, transcutaneous bilirubin; TSB, total serum/plasma bilirubin.

Observational study on the safety and potential efficacy of filtered sunlight phototherapy

A recent comprehensive systematic review of available evidence worldwide on PT found no randomized controlled trials (RCTs) dealing with either sunlight or environmental light [26]. Prior to our proposed RCT to establish the effectiveness of FS-PT compared with CPT in a larger sample of infants, we conducted an observational study to evaluate safety and potential efficacy of two previously tested films for use in an inner-city maternity hospital in Lagos, Nigeria. FS-PT safety was determined through close monitoring of infant temperature, hydration status, and skin for signs of possible sunburn. Therapy was deemed safe on a given day if the infant did not have to be removed from phototherapy due to needing physician treatment for sunburn or dehydration, due to persistent temperature instability defined as two or more episodes of temperatures <35.0 or >39.0°C, or due to failure to return to normothermia (defined as 35.5 to 38.0°C) within 1 hour of being removed from FS-PT. Efficacy was evaluated by measuring the rate of rise/decline in total serum/plasma bilirubin (TSB) levels. Treatment was deemed safe and efficacious if the infant was able to stay in the FS-PT canopy for ≥5 hours per day and the rate of rise of TSB was <0.2 mg/dl/hour for infants ≤72 hours of age or if TSB decreased for infants >72 hours of age. This study was concluded in August 2012, details of which are scheduled for publication shortly. In summary, 203 term and near-term newborns (≤14 days old) with clinically significant jaundice as assessed by TSB levels were enrolled. They received treatment under a FS-PT canopy over a period of 227 days. Hourly measurements of axillary body temperatures and monitoring of sunburn, dehydration, and irradiances of FS-PT were performed. The results showed that FS-PT was efficacious in 94% (164/175) of the infants studied. Average irradiance from FS-PT was 37 ±14 (range 8 to 65) $\mu W/cm^2/nm$ as measured by the Bili-Blanket Meter II (General Electric, Fairfield, CT, USA). No infant developed sunburn or dehydration, nor met exclusion criteria. Based on these favorable findings with our selected films (Gila Titanium and Air Blue 80 produced by

CP Films Inc. Subsidiary of Eastman Chemical Co. Fieldale, VA, USA), we set out under the second phase of this project to demonstrate primarily in a RCT that FS-PT is just as efficacious as CPT in the treatment of infants with or at risk of severe NNJ.

Methods/design

Aims and hypotheses

The primary goal of this study is to demonstrate that the efficacy of FS-PT is no worse than that of CPT, with a non-inferiority margin of 10%. In effect, our null hypothesis is that this margin is above 10% suggesting that FS-PT is inferior to CPT.

The secondary goal of the study is to demonstrate that the proportion of infants who require exchange transfusion under FS-PT is no worse than that under CPT, with a non-inferiority margin of 5% based on a clinical rationale that FS-PT is non-inferior to CPT and still better than no treatment. This was also informed by the results of a meta-analysis of RCTs comparing CPT with no treatment which estimated that 10 infants needed to be treated with CPT to prevent an exchange transfusion [26].

Study design

This is a prospective, non-blinded, single center, randomized two-stage controlled non-inferiority clinical trial. During the first stage of the study, infants will be referred from elevated transcutaneous bilirubin (TcB) screening and enrolled for the definitive TSB estimation. Only infants with significantly elevated TSB levels will qualify for inclusion into the second stage of the study for PT treatment and will be randomly assigned to receive FS-PT or CPT.

Study setting

The study location is Island Maternity Hospital (IMH), Lagos, Nigeria, which is a state-owned hospital. It has a special care baby unit with CPT and other basic neonatal care facilities, including intravenous (IV) fluids, antibiotics, and exchange transfusion. Ventilator support and pumps for giving IV fluids are not available. It is a 180-bed residency teaching hospital with about 300 deliveries per month of which 45 infants (15%) would be expected to qualify for PT. It is possible at this location to give routine care, IV fluids, antibiotics, oxygen, and medications without interrupting PT. The average maximum temperature in Lagos is 32°C (90°F) during the dry season (November to March), with a maximum recorded temperature of 40°C (104°F), making FS-PT possible even with infants unclothed or minimally clothed. In the rainy season it should be possible to maintain satisfactory irradiances in the absence of an excessively overcast sky. This site was chosen for the maiden study to ensure that backup neonatal care services are readily available when required until we have the required safety and efficacy data.

Definition of high-risk threshold

All jaundiced infants with elevated TSB, defined as 3 mg/dl below the level recommended by the American Academy of Pediatrics (AAP) [27] for PT in high-risk infants, will be considered at high risk. The high-risk classification category of the AAP guideline was selected because laboratory evaluation for hemolysis will not be consistently available during the study, and Nigerian infants are known to be at higher risk for severe NNJ secondary to glucose-6-phosphate dehydrogenase (G6PD) deficiency [28]. This TSB level was chosen also because many hospitals begin PT about 2 to 3 mg/dl below the current level in the United States, due to the severity of NNJ and the sub-optimal PT treatment in most locations in Nigeria.

Primary outcome

The primary outcome for the RCT is efficacy of FS-PT compared with CPT.

Evaluation criteria

Change in TSB level per hour of therapy defined as a binary variable. The TSB level will be measured immediately before beginning therapy on a given day and immediately after therapy is completed that day, and the change in bilirubin level in mg/dl per hour of therapy will be calculated. For infants who are less than 72 hours old in the morning, the treatment will be judged efficacious if the bilirubin level rises more slowly than 0.2 mg/dl per hour of therapy that day. For infants who are more than 72 hours old, the treatment will be judged efficacious if the bilirubin level falls. Efficacy will be evaluated only for days in which the treatment was deemed safe (that is, when the infant did not have to be removed from PT due to a need for physician treatment for sunburn or dehydration, persistent temperature instability defined as two or more episodes of temperatures <35.0 or >39.0°C, or failure to return to normothermia (defined as 35.5 to 38.0°C) within 1 hour of being removed from PT). The average efficacy of each type of PT, defined as the proportion of safe days where a given therapy was used in which the therapy was efficacious, will be compared. FS-PT will be considered at least as efficacious as CPT if the average efficacy on days where FS-PT was used is no worse than 10% less than the average efficacy on days where CPT was used.

Secondary outcome

A secondary outcome for this trial is the proportion of enrolled infants who require exchange transfusion. FS-PT will be considered at least as efficacious as CPT if the proportion of infants who require exchange transfusion under FS-PT is no more than 5% greater than the proportion under CPT.

Sample size

The minimum sample size was estimated using the following assumptions: 1) the average efficacy of CPT is 80%; 2) the average efficacy of FS-PT is 80%; 3) there will be the same number of infants assigned to both groups; 4) the delta value is 10% — that is, we want to demonstrate that FS-PT is no more than 10% worse than CPT; and 5) 80% power, one-sided alpha = 0.025.

Under these assumptions, a total of 504 days, or 252 days in each treatment group, will be required. This calculation gives the required number of treatment days that are evaluable for efficacy. Since efficacy will be evaluated only for days in which the treatment was deemed safe, the sample size was increased to account for the possibility that the proportion of safe days might be as low as 90%. Assuming that the safety of both FS-PT and CPT is 90%, a sample size of 560 total days is required. Assuming that a typical course of treatment lasts 1 day, both for FS-PT and CPT, then 560 infants, or 280 infants in each group, will be required. Anticipating up to 10% loss due to rainy days (in the FS-PT group), delisting of infants by parents or guardians, or missing data (in both groups), we will enroll 616 infants, or 308 infants in each group. From our year 1 data in the preceding observational study only 66% of the 826 infants referred for elevated TcB had significant elevated TSB levels, hence 915 infants or more will be enrolled for stage 1 bilirubin estimation until the total requirement of 560 treatment days is reached (Figure 2).

Subject recruitment

Infants born in the hospital will be screened daily from 0 to 14 days of life for elevated TSB using TcB measurements, while in the hospital or, if discharged before 14 days, in the community by nurses sent out from the hospital when possible. Infants from the community will also be screened if within 14 days they choose to come to the study site for screening. The parents will be asked to return with their infants to the hospital if the parent observes new-onset jaundice between 1 and 14 days of life. If the TcB is not elevated during the first 14 days of life, the subject will cease to be eligible for the study. If the TcB is elevated and the other study inclusion and exclusion criteria are met, then the infant will be recruited for the study after informed consent in writing or thumb printing is obtained from a parent or guardian. The infant will then have a TSB measured. Enrolled infants with elevated TSB (defined as 3 mg/dl below the level recommended by the AAP [27] to begin PT in high-risk infants) will be randomly assigned to receive FS-PT or CPT. Enrolled infants with TSB levels that are not elevated as defined above will not be treated with PT. They will continue to be screened for elevated TcB as described above. If their subsequent TcB levels are not elevated during the first 14 days of life, the infant will be withdrawn from the study.

Subject screening

Screening criteria prior to enrolment are shown in Table 1.

Prior and concomitant therapy

All infants who meet the AAP guideline for the initiation of PT will be treated with CPT at night or when it is not possible to use FS-PT, secondary to rain or overcast sky. CPT will be performed per hospital standards. Additionally, since the study physicians only serve as consultants for patients requiring treatment for NNJ, patient management decisions, including the need for and timing of exchange transfusion, administration of antibiotics or other testing, will be at the discretion of the attending physician. AAP guidelines will be used to direct the decision of when to perform exchange transfusion, but the final decision will be that of the attending physician. Generally, exchange transfusion is performed in any term infant in Nigeria whose TSB level is ≥20 mg/dl or in any infant with neurologic signs of ABE, regardless of the recommendations in the AAP guideline.

Inclusion criteria

Subjects will be eligible to participate in the study if all of the following conditions exist:1) at time of birth, infant is ≥35 weeks gestation (or >2.2 kg if gestational age is not available); 2) infant is ≤14 days old at the time of enrollment; 3) at time of enrollment, infant has an elevated TcB defined as 3 mg/dl below the level recommended for high-risk infants per AAP guideline or higher; 4) parent or guardian has given consent for the infant to participate.

Exclusion criteria

Subjects will be excluded from participation in the study if any of the following conditions exist at the time of enrollment:1) infants with a condition requiring referral for treatment not available at the hospital study site and/or CPT unit; 2) infants with a life-expectancy of <24 hours; 3) infants requiring oxygen therapy; 4) infants clinically dehydrated or sunburned; 5) infants with a temperature <35.5°C or >38°C; 6) infants with ABE on clinical examination; 7) infants meeting the criteria for exchange transfusion. Inclusion and exclusion criteria are only applicable at the time of enrollment before randomization to prevent bias of the treatment comparison.

Exit/discontinuation/withdrawal criteria

Subjects will exit the study (will cease to receive FS-PT or CPT) if any of the following conditions occur: 1) persistent temperature instability defined as two or more episodes of temperatures <35.0°C or >39.0°C; 2) failure to return to normothermia (defined as 35.5°C to 38.0°C) within 1 hour of being removed from PT; 3) physician treatment for dehydration or sunburn is required; 4) TSB level reaches exchange transfusion levels; 5) inter-current illness not compatible with PT or needing more care than can be provided in the FS-PT canopy or CPT ward; 6) infants requiring transfer to another hospital; 7) parent request; 8) subject death; 9) subject completes the protocol (TcB or TSB level is no longer elevated); 10) subject's well-being, in the opinion of the Investigator, would be compromised by study continuation; 11) Institutional Review Board (IRB) recommendation; or 12) subject's risk level indicates PT should be stopped.

Infants who have been withdrawn from the study will have a physical examination and a final TcB. Safety data will be analyzed for all days in which the subjects spend any time under either FS-PT or CPT.

Efficacy will be evaluated for all days in which the treatment was deemed safe (that is, when the infant did not have to be removed from PT due to a need for physician treatment for sunburn or dehydration, due to persistent temperature instability defined as two or more episodes of temperatures <35.0 or >39.0°C, or due to failure to return to normothermia (defined as 35.5 to 38.0°C) within 1 hour of being removed from PT).

Randomization scheme

Enrolled infants with elevated TSB (defined as 3 mg/dl below the level recommended by the AAP to begin PT in high-risk infants)

Table 1 Screening criteria prior to enrolment

Test	Screening requirement
Gestational age and/or weight	Greater than or equal to 35 weeks gestation (or >2.2 kg if gestational age is not available). Infant must be ≤14 days old at the time of first PT.
TcB	Screened daily for the first 7 days of life if in hospital and, when possible, in the community if discharged before 7 days of life or if the patient chooses to come in for screening up to14 days of life. If the TcB is elevated (elevated will be defined as a point 3 mg/dl below that recommended by the AAP for PT in high risk infants and above) at any time during the first 14 days of life, a TSB will be done.
Physical examination (dehydration, oxygen use, ABE, life expectancy, sunburn)	Subjects cannot be dehydrated, sunburned, using oxygen, or have ABE or a life expectancy <24 hours at the time of examination by the physician for enrollment in the treatment phase of the protocol.

AAP, American Academy of Pediatrics; ABE, acute bilirubin encephalopathy; PT, phototherapy; TcB, transcutaneous bilirubin; TSB, total serum/plasma bilirubin.

will be randomly assigned to receive FS-PT or CPT. A block randomization procedure with variable block sizes will be used to maximize unpredictability. The randomization assignments of FS-PT or CPT will be printed on sequentially numbered sheets of paper and enclosed in opaque, sealed, sequentially numbered envelopes. The sealed envelopes will be prepared independently by the study statistician based in the USA and transported to Nigeria by the regulatory sponsor. When an enrolled infant's TSB level is obtained and found to be 3 mg/dl or more below the AAP threshold for high-risk infants the study nurse will request the next envelope. The envelope will be opened and both the envelope number and the treatment assignment will be recorded on the case report form. The laboratory technician responsible for measuring the serum bilirubin level will be unaware of the sequence of treatment allocation of either FS-PT or CPT for each eligible infant and will not be involved in administering PT. The study will not be blinded as it is not physically possible to blind either the participating infants or parents, nor the hospital personnel.

Laboratory testing procedures

Glucose-6-phosphate dehydrogenase

Because of the high prevalence of G6PD deficiency in our study population, enrolled infants will be routinely screened for this condition using simple and inexpensive supplies. The method will be based on the fluorescent blood spot originally developed by Beutler and colleagues [29]. This test has been considered a standard method of G6PD screening especially in resource-poor settings, since inexpensive reagents and materials can be used.

Bilirubin

TSB will be estimated using standard methods. Hematocrit testing will be done using standard laboratory methods.

Coombs testing and blood typing

Coombs testing and blood typing will be performed in the blood bank laboratory at IMH.

Specimen collection

Blood specimens for TSB measurements will generally be collected by heel-stick. Specimens for G6PD, blood type and Rh will be drawn by venipuncture.

Clinical procedures

Criteria for admission

Infants born in the hospital will be screened daily from 0 to 14 days of life for elevated TcB while in the hospital or, if discharged before 14 days, in the community by nurses sent out from the hospital when possible. Infants ≤14 days old from the community presenting to the study site will also be screened. The parents will be asked to return with their infant to the hospital if the parent observes new onset jaundice between 1 and 14 days of life.

Screening

During the screening period, information about the baby and the mother will be collected. TcB testing will be done for up to 14 days, using Minolta AirShields Jaundice Meter JM-103 (Draeger Medical Systems, Inc., Telford, PA, USA) either in the hospital or in the community. If the TcB is not elevated during the first 14 days of life, the subject will not be eligible for the study. If at any time during screening the infant's TcB level rises to within 3 mg/dl below the AAP threshold [27] for high-risk infants, inclusion/exclusion criteria will be reviewed. If the infant is eligible, the infant will be recruited for the study. The infant's mother and/or father will be approached to ask if they are interested in participating in the research study. If they are willing, the consent form for the study will be discussed. If informed consent is given to participate, consent will be documented on the consent form in writing or thumb printing.

Pre-treatment (stage 1)

The enrolled infant will then have a TSB drawn (stage 1) using the Advanced Bilirubinometer Stat-Analyzer, Model BR2 (Advanced Instruments, Inc, Norwood, MA, USA) before treatment (stage 2). Enrolled infants with elevated TSB qualify for inclusion into the second stage of the study and will be randomly assigned to receive FS-PT or CPT. Enrolled infants with TSB levels that are not elevated as defined above will not proceed to the second stage to be treated with PT. However, they will continue to be screened for elevated TcB as described above. If their subsequent TcB levels are not elevated during the first 14 days of life, the infant will be withdrawn from the study. All infants who meet the AAP guideline for the initiation of PT will be treated with CPT at night or when it is not possible to use FS-PT, secondary to rain or excessive cloud cover (defined as cloud cover persisting for more than 2 hours). FS-PT will be optimized in all infants by using white cloth lining the bottom and sides of the cot and exposing the infant maximally. CPT will be performed per international standards of practice [27].

Treatment (stage 2)

FS-PT will be started in the morning after the irradiance level inside the canopy is at least 8 μW/cm^2/nm, and will be stopped in the late afternoon when the irradiance level drops below 8 μW/cm^2/nm or at any point during the day during a rainy/cloudy day when the irradiance stays below 8 μW/cm^2/nm. If the irradiance persists below 8 μW/cm^2/nm for more than 1 hour and the infant qualifies for PT per the AAP guideline, CPT will be initiated. If the irradiance again exceeds 8 μW/cm^2/nm then the infant may again be placed in FS-PT.

Treatment canopies

Two FS-PT canopies will be used: one fitted with the Gila Titanium film and the other fitted with the Air Blue 80 film because of concerns about irradiance and heat. The Titanium canopy transmits approximately 33% blue light in the wavelength range 400 to 520 nm with much lower heat and will be used during sunny periods of the day. The Air Blue canopy transmits roughly 79% blue light as well as heat and will be used during cooler overcast periods of the day. The infants will be moved from one canopy to the other as needed during the day, when the weather changes, with the goal of keeping the irradiance level above 8 μW/cm^2/nm. The irradiance will be measured at an infant's abdomen level with a Bili-Blanket Meter II every half hour in infants under FS-PT (if possible, additional measurements may be done) and daily in those infants under CPT.

The proportion of blue light accessible to the subjects under FS-PT canopies is dependent on the location of treatment canopies in relation to surrounding buildings. It is therefore imperative that the treatment canopies be placed in a location with proven day-long sun exposure throughout the year, preferably one also protected from potentially violent wind currents and surface dust generated by traffic. In fact, the single most important reason for replacing films is wind damage. A roof top terrace,

presently in use in our study, has proven to be a very satisfactory location. A courtyard of adequate size surrounded by low buildings could be even more suitable. Finally, perhaps most ideal and practical, will be the construction of a suitable FS-PT room or a small permanent building with a glass or plexiglass roof, in an appropriately "sunny" part of a hospital. This would be a most ideal solution to prevent issues with wind, dust, security, and so forth. However, such a treatment facility may overtax local resources.

Treatment duration

Generally, the infants will be placed under FS-PT/CPT from 9:00 am to 5:00 pm (target minimum duration of 5 hours per day for any infant in the study at 10:00 am, or 65% of total time between start time and 5:00 pm for infants enrolled after 10:00 am). The infants' eyes will be protected with low-cost eye covers made from the elastic tops of any color socks. Bilirubin kinetics will only be calculated for infants who are able to spend at least 5 hours in FS-PT/CPT.

Temperature measurements

Infant temperature will be measured hourly while under FS-PT and CPT and monitored based on World Health Organization guidelines for normothermia, hypothermia, and hyperthermia [30]. For the purpose of this study the normal temperature range of 36.5 to 37.5°C [30] was modified slightly to 35.5 to 38.0°C in consultation with a neonatologist to provide a broader but safe temperature limit for term and near-term infants. In addition, during the prior safety and efficacy observational study in which infants were monitored closely, no untoward effects of temperatures within the chosen range were reported. If the axillary body temperature falls below 35.5°C the infant will be placed skin-to-skin with the mother and/or brought inside until the temperature returns to the normal range of 35.5 to 38.0°C. If the axillary body temperature goes above 38.0°C, the infant will be brought indoors and/or placed in the shade and/or placed on a wet towel until the body temperature returns to normal at which time FS-PT will resume. The time it takes to return to normal will be recorded. Infants who do not return to normothermia within 1 hour will be taken out of FS-PT for that day. If the axillary body temperature falls below 35°C the infant will be placed skin-to-skin with the mother or wrapped well and brought inside until the temperature returns to normal. If the axillary body temperature goes above 39.0°C, the infant will be brought indoors and placed on a wet towel until the body temperature returns to normal at which time FS-PT will resume. The time it takes to return to normal will be recorded. Infants who do not return to normothermia within 1 hour will be taken out of FS-PT for that day. Infants whose axillary body temperature fall below 35°C or exceed 39°C on two occasions will be excluded from the study.

Dehydration

The nurse will also check hourly for clinical signs of dehydration in the form of dry mucus membranes, sunken eyes, dry eyes, and skin tenting. The physician may elect to increase the mother's breastfeeding frequency while continuing with the FS-PT if the diagnosis is mild dehydration. Whenever the diagnosis of moderate or severe dehydration is made, the infant will be withdrawn from the study for treatment. Because both nutrition and hydration are important in the prevention and treatment of severe NNJ, infants will be allowed and encouraged to breastfeed ad lib and often. The FS-PT canopy allows for the mother to stay with the infant and to feed as often as she desires. Mothers will be comfortably seated on custom-made reclined chairs (painted white) and provided with white aprons for breast-feeding or when they need to carry their babies (Figure 1C). If the mother has chosen to use artificial feeds, those will also be allowed and encouraged ad lib. For CPT, the mother will be allowed and encouraged to take the infant out as needed for bathing or feeding.

Sunburn

The nurse will assess for sunburn by looking for the onset of pink skin every hour. Most infants are born relatively light skinned and darken over time. Infants born very dark and for whom it would be difficult to recognize pink skin are also much less likely to become sunburned. Absence of sunburn determined in consultation with a dermatologist is defined as the absence of new-onset pink skin. If the infant has the onset of pink skin, the attending physician will be notified and will verify the finding. If the physician makes the diagnosis of sunburn, the infant will be immediately withdrawn from the study. Mothers will be allowed and encouraged as much as possible to stay with their babies, but will be able to leave as needed to care for themselves or other needs. Study nurses will care for the infants during their mother's absence.

Treatment efficacy

Efficacy will be tested by measuring TSB levels prior to the placement of the infant under PT each morning to establish baseline TSB levels. Infants with morning TSB levels that meet the criteria for PT will be randomized for FS-PT. Repeat TSB levels will be obtained at the end of each day spent under FS-PT and between ~4:00 to 5:00 pm for infants under CPT to estimate the effectiveness of the treatment for the day and to determine if the requirement for night-time PT is met.

Data collection and analysis

Data will be collected on paper case report forms and entered via a web interface into a secure database. The study data will be collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at the University of Minnesota's Academic Health Center. REDCap is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

Demographic data will be summarized and compared between the treatment and control groups using appropriate methods, such as Pearson's chi-square test for categorical variables and two-sample t-tests for continuous variables. The primary objective is to compare the efficacy of FS-PT and CPT. A 95% exact binomial confidence interval for the true difference in efficacy between the FS-PT treated and CPT control groups will be calculated. FS-PT will be deemed non-inferior to CPT if the calculated confidence interval does not extend more than 10% below the equivalence point.

We plan to conduct three distinct analyses: an intent-to-treat analysis based on the assigned treatment for each enrolled infant, an as-treated analysis based on the actual treatment received on a given day and a per-protocol analysis including only enrolled infants who received the assigned treatment on all of their treatment days.

Safety monitoring and adverse events

The Principal Investigator will oversee the safety of the study, including careful assessment and appropriate reporting of adverse events to relevant authorities at IMH. All anticipated adverse events such as sunburn, dehydration, and temperature instability as well as unanticipated adverse events occurring during the study period will be recorded and closely monitored. Medical monitoring will include a regular assessment of the number and type of serious adverse events. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that study treatment or participation is not the cause.

All observed or volunteered adverse effects and abnormal test findings, regardless of treatment group, if applicable, or suspected causal relationship to the investigational device or, if applicable, other study treatment or diagnostic product(s) will be recorded in the subjects' case histories. For all adverse effects, sufficient information will be pursued and/or obtained so as to permit: 1) an adequate determination of the outcome of the effect (that is, whether the effect should be classified as a serious adverse effect); and 2) an assessment of the casual relationship between the adverse effect and the investigational device or, if applicable, the other study treatment or diagnostic product(s).

Ethical considerations

This study was approved by the IRBs/Ethical Committees at the University of Minnesota, Minnesota Medical Research Foundation (Hennepin County Medical Center), and the Lagos State Government. This study is being conducted according to United States and international standards of Good Clinical Practice (21 CFR 812 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures. The parents/guardians of potential subjects for this study will be provided a consent form describing this study and providing sufficient information for the parents/guardians to make an informed decision about their child's participation in this study. The consent form has been submitted with the protocol for review and approval by the relevant IRBs/Ethical Committees for the study. The formal consent of a parent/guardian, using the IRB-approved consent form, will be obtained before the infant is subjected to any study procedure. This consent form will be signed or thumb-printed by the parent/guardian, and the investigator-designated research professional obtaining the consent. A blank copy of the IRB-approved form will be kept on-site and by the sponsor-investigator.

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Neonatal Outcomes After The Transfer of Vitrified Blastocysts: Closed Versus Open Vitrification System

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Abstract

Background: Increasing evidence indicates that closed vitrification has been successfully used in the cryopreservation of human oocytes and embryos. Little information is available regarding the neonatal outcome of closed blastocysts vitrification. The aim of this study was to evaluate the effectiveness and safety of blastocyst vitrification using a high-security closed vitrification system compared with an open vitrification system.

Methods: A total of 332 vitrified-warmed blastocyst transfer cycles between April 2010 and May 2012 were analyzed retrospectively. The post-thaw survival rate, implantation rate, clinical pregnancy rate, live birth rate, and neonatal outcome were recorded.

Results: There were no significant differences between the open vitrification group and the close vitrification group regarding the post-thaw survival rate (98% versus 95.8%), clinical pregnancy rate (47.6% versus 42.2%), implantation rate (42.9% versus 35.6%), and live birth rate (39.8% versus 32.1%). In total, 332 warming cycles produced 131 healthy babies. There were no significant differences in the mean gestational age, the birth weight, and the birth length between the two groups. No adverse neonatal outcomes were observed in the children born after the transfer of closed vitrified blastocysts compared with the transfer of open vitrified blastocysts.

Conclusions: These data suggest that blastocyst vitrification using a closed vitrification device seems safe and effective with results comparable to those obtained through open vitrification.

Background

Vitrification has been widely used for oocyte and embryo cryopreservation in assisted reproduction clinics. Better post-thawing survival rates of vitrification compared with the rates of slow-freezing of blastocysts have been demonstrated [1]. Blastocyst vitrification using open carrier, such as a cryoloop, yields comparable clinical outcomes and congenital defect rates as fresh blastocyst transfer [2]. Since an open vitrification system has a theoretically higher risk of microbiological transmission through liquid nitrogen [3-5], there is a movement towards the use of closed vitrification carriers. One concern with a closed vitrification system is whether the lower cooling rate would have an adverse effect on vitrification. The cooling rate with the open carriers has been reported to be superior to –20,000°C/ min [6,7], whereas the cooling rate with close carrier is below –2000°C/min [8].

A growing body of evidence indicates that closed vitrification using the CBS High Security straw has been successfully used in the cryopreservation of human blastocysts from the early cavitation stage to the expanded blastocyst stage or derived from biopsied embryos [9,10]. The DNA damage in the blastomeres was comparable in mice embryos vitrified on the open Cryoloop and the closed CBS High Security straw [11]. Little information is available concerning the perinatal outcome of closed blastocysts vitrification. The aim of the present study is to evaluate the clinical efficiency and safety of blastocyst vitrification using a closed device (CBS High Security straws; Cryo Bio System) compared with open device (Cryoleaf).

Methods

Study design

The study was approved by the Ethics Committee of the Peking University Third Hospital. A total of 332 blastocysts warming cycles of IVF/ICSI patients performed between April 2010 and May 2012 were analyzed retrospectively.

The patients were <40 years old with a BMI (body mass index) <30 kg/m^2, without previous viral infection (hepatitis B-C, HIV and syphilis). All the patients used long or short protocols for ovarian hyperstimulation. Thirty-six hours after the hCG administration, the oocytes were retrieved and fertilized using conventional IVF or ICSI. Normal fertilization was assessed by the presence of two pronuclei and a second polar body at 16–18 hours after insemination. The zygotes were cultured in cleavage medium (Vitrolife, Sweden) to day 3 and the transfer. The blastocyst vitrification was performed for the patients with the culture of surplus embryos to the blastocyst stage after the fresh day 3 embryo transfer. Only expanded or hatching blastocysts (according to Gardner's grading system [12]) with ICM (Inner Cell Mass) and trophoetoderm type above grade CC were selected for cryopreservation on day 5 or day 6.

Vitrification of blastocysts

Prior to the vitrification, the expanded or hatching blastocysts

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Table 1 Clinical parameters of open and closed vitrification

	Open vitrification (106 cycles)	Closed vitrification (226 cycles)	P value
Patient age at transfer (years)	33.1 ± 4.4	32.5 ± 4.1	0.171
BMI (kg/m²)	23.38 ± 3.3	24.19 ± 4.6	0.105
No. of primary infertility	68 (64.2)	139 (61.5)	0.643
Reason for infertility			
Female factor	59 (55.7)	114 (50.4)	0.375
Male factor	18 (17.0)	46 (20.4)	0.468
Others	29 (27.4)	66 (29.2)	0.729
Method of fertilization			
IVF	64/106 (60.4)	136/226 (60.2)	0.972
ICSI	40/106 (37.7)	86/226 (38.1)	0.956
Half ICSI	2/106 (1.9)	4/226 (1.7)	0.941
Mean number of embryos transferred	1.39 ± 0.52	1.31 ± 0.53	0.193

Values are mean ± SD or n/total (%).

were treated with a laser pulse for the artificial shrinkage of the blastocoelic cavity. The vitrification and warming procedures were similar to those reported by Mukaida T et al. [13]. The solutions were incubated at 37°C for 30 min prior to the vitrification process, and all the steps were conducted at 37°C. The blastocyst was first incubated for 1 min in a droplet of basal medium. The basal medium was Quinns Advantage medium with HEPES (SAGE, Trumbull, CT, USA) supplemented with 20% (v/v) Human Serum Albumin (HSA, Vitrolife, Sweden). The blastocyst was moved to a droplet of equilibration solution composed of 7.5% (v/v) DMSO (Sigma Chemical Co., MO, USA) and 7.5% (v/v) ethylene glycol (Sigma Chemical Co., MO, USA) in basal medium for 2 min. The blastocyst was then transferred into a droplet with vitrification solution containing 15% (v/v) DMSO, 15% (v/v) ethylene glycol and 0.65 mol/L sucrose in a basal medium for 30 s and immediately placed in the McGill Cryoleaf (ORIGIO, Malov, Denmark.) and plunged into liquid nitrogen. As for the closed vitrification, the protocol was similar to that of the open vitrification except for loading the blastocyst onto the closed CBS High Security straws (Cryo BioSystem, Paris, France). The straw was heat sealed and plunged into liquid nitrogen as described previously [9]. The vitrification procedures carried out did not exceed 90 s.

Warming and recovery of blastocysts

The blastocysts were unloaded from the carrier into warming solution 1 containing 0.33 M of sucrose (Sigma Chemical Co., MO, USA) in a basal medium with 20% HSA. After 2 minutes they were transferred into warming solution 2 containing 0.2 M of sucrose for 3 minutes. Finally, the blastocysts were washed in a droplet of washing solution (HEPES-buffered medium supplemented with 20% HSA) for 5 min. All the warming steps were performed at 37°C. The blastocysts were unloaded from the different carriers as follows: (1) Cryoleaf: the blastocysts were recovered by quickly immersing the sheet in warming solution 1. (2) CBS High Security Straw: the straw was held in liquid nitrogen, and the upper end of the outer straw was cut using wire cutters. The inner straw with a gutter was quickly pulled out of the sheath and immersed in warming solution 1 to unload the embryos. After warming, the blastocysts were transferred to a culture dish with blastocyst medium (G-2, Vitrolife, Sweden) to assess their morphological survival and perform assisted

Table 2 Clinical outcomes of open and closed vitrification

	Open vitrification (106 cycles)	Closed vitrification (226 cycles)	P value
Cryosurvival rate	147/150 (98.0)	295/308 (95.8)	0.224
Cancellation rate	3/106 (2.8)	8/226 (3.5)	0.736
Clinical pregnancy rate/transfer	49/103 (47.6)	92/218 (42.2)	0.365
Implantation rate/transferred blastocysts	63/147 (42.9)	105/295 (35.6)	0.138
Pregnancy loss			
Miscarriage rate/pregnancy	8/49 (16.3)	21/92 (22.8)	0.363
Ectopic rate/pregnancy	0	1/92 (1.1)	1.000
Live birth rate/transfer	41/103 (39.8)	70/218 (32.1)	0.176
Complications during pregnancies			
Gestational diabetes	1/103 (0.97)	3/218 (1.3)	0.760
Hypertension	1/103 (0.97)	2/218 (0.92)	0.963
Placenta previa	0	1/218 (0.4)	1.000
Mode of delivery			
Spontaneous vaginal delivery	5/41 (12.2)	10/70 (14.3)	0.756
Cesarean section	36/41 (87.8)	60/70 (85.7)	0.756

Values are n or n/total (%).

hatching using a laser. The blastocysts with good survival (less than half of the blastocysts showing signs of damage) and the re-expanded blastocysts were transferred 2 h after the in vitro culture. The blastocysts with less than 50% damage but showing no signs of expansion were further cultured for an additional period of 24 h. The transfer will be cancelled if no signs of re-expansion were present.

Thawed blastocyst transfer

The thawed blastocyst transfer was performed in natural monitored cycles or in programmed artificial cycles. For the natural monitored cycles, the thawed blastocyst transfer was scheduled for 5 days after ovulation. Luteal support was provided with intramuscular injections of progesterone 20–40 mg from the night of transfer. For the hormone replacement therapy, endometrial development was achieved by daily oral estradiol administration. When the endometrial thickness was suitable, this phase was complemented by the administration of progesterone. The blastocyst transfers were performed on day 5 after the initiation of the progesterone treatment. The serum HCG levels were measured 12 days after the transfer.

Table 3 Neonatal parameters of open and closed vitrification

	Open vitrification	Closed vitrification	P value
Babies born/transferred blastocysts	52/147 (35.4)	80/295 (27.1)	0.074
Male rate	29/52 (55.8)	41/80 (51.3)	0.611
Female rate	23/52 (44.2)	39/80 (48.7)	0.611
Multiple birth rate	11/41 (26.8)	10/70 (14.3)	0.103
Singletons	30	60	
Twins	11	10	
Stillbirth rate /transfer	1/103 (0.97)	0	0.321

Values are n or n/total (%).

Table 4 Neonatal outcome of open and closed vitrification for singletons and twins respectively

	Singletons			Twins		
	Open vitrification (n = 30)	Closed vitrification (n = 60)	P value	Open vitrification (n = 11)	Closed vitrification (n = 10)	P value
Gestational age (wks)	38.3 ± 1.3	37.9 ± 1.5	0.175	37.2 ± 1.4	37.4 ± 1.5	0.844
GA < 37 weeks	2/30 (6.7)	9/60 (15.0)	0.426	4/11 (36.4)	4/10 (40)	1.000
GA ≥ 42 weeks	1/30 (3.3)	2/60 (3.3)	1.000	0	0	
Birth weight (g)	3248 ± 408	3163 ± 481	0.410	2800 ± 380	2598 ± 364	0.091
<2500 g	1/30 (3.3)	5/60 (8.3)	0.654	3/11 (27.3)	4/10 (40)	0.659
≥4000 g	3/30 (10.0)	7/60 (11.7)	0.813	0	0	
Birth length (cm)	49.7 ± 1.6	50.4 ± 1.3	0.086	48.8 ± 1.6	48.9 ± 1.7	0.858

Values are mean ± SD or n/total (%).

Outcome parameters

All of the pregnant women were followed until two months after parturition, and the details of the clinical outcome were obtained from the medical records of our clinic. The blastocyst survival was defined as less than one-half of the blastocysts showing signs of damage. Clinical pregnancy was defined as the presence of gestational sacs observed on an ultrasound scan at least 5 weeks after the embryo transfer. The implantation rate (the number of gestational sacs divided by the number of transferred embryos), the miscarriage rate per clinical pregnancy and the live birth rate per transfer were measured. The neonatal outcomes and minor anomalies. Low birthweight was defined as birth weight <2500 g. high birthweight was defined as birth weight ≥4000 g. Preterm birth was defined as birth before 37 weeks of gestation. Postterm birth was defined as birth after 42 weeks of gestation.

Results

A total of 226 and 106 vitrified-warmed blastocyst transfer cycles were performed for the closed vitrification group and the open vitrification group, respectively. There were no significant differences in maternal age at the time of transfer, BMI, reason for infertility, method of fertilization and average number of transferred embryos between the two groups (P > 0.05, Table 1). Blastocyst survival rate was 98.0% in the open vitrification group and 95.8% in the closed vitrification group. The clinical pregnancy, implantation, miscarriage and live birth rates were similar between the two groups (P > 0.05, Table 2). Three cases of transfers in the closed vitrification group took place 24 hours later, but only one woman became pregnant. The pregnancy complications and spontaneous vaginal delivery rates were comparable between the two groups.

A total of 132 babies (70 males and 62 females) were born from 111 deliveries as the result of vitrified-warmed blastocyst transfers. There were no significant differences in gender rate and multiple-birth rate (P > 0.05, Table 3).

Among the 90 delivered singletons, 30 were derived from the open vitrification group and 60 from the closed vitrification group. Of the 21 women who gave birth to twins after the transfer of two vitrified-warmed blastocysts, 11 were from the open vitrification group and 10 were from the closed vitrification group. For the singleton and twin groups, there were no significant differences in the mean gestational age, the mean birthweight, the mean birth length, the low birthweight rate, and the preterm birth rate between the two vitrification groups (P > 0.05, Table 4).

No significant differences in the rate of post-term birth and high birthweight between singletons in the closed vitrification group and singletons in the open vitrification group. A total of 332 warming cycles produced 131 healthy babies. No birth defects occurred among the newborns, except one baby of twins died from fetal distress in the open vitrification group.

Discussion

These findings demonstrate that a closed human blastocyst vitrification system with artificial shrinkage could be an effective and safe procedure for vitrification.

There have been concerns with the closed system because the slower cooling rate might cause ice crystal formation that could potentially be detrimental to survival. In this study, the closed vitrification protocol, such as the concentration of the cryoprotectants, the temperatures and the exposure times were identical to those described with the open vitrification device. This finding demonstrates that, although a lower cooling rate is a consequence of using a closed vitrification device, it did not affect the vitrification outcome negatively, which might be because of the dominance of the warming rate over the cooling rate in the process of vitrification [14]. In agreement with our data, a recent prospective randomized study that included 432 warming cycles demonstrated that closed or open vitrification with the VitriSafe device rendered comparable clinical results [15]. Although there are no significant differences, most likely because of the small sample size, the indexes of the clinical outcome of open vitrification were most likely better than those of closed vitrification. In this regard, further study is warranted.

Another concern with vitrification is that the risk of detrimental intracellular ice formation is higher in the expanded blastocysts compared with the early blastocysts because of the large fluid-filled cavity. Artificial shrinkage or collapse of the expanded blastocysts by mechanical methods or laser prior to vitrification, as suggested in our study, has been shown to improve survival and increase the clinical pregnancy rates [16]. One published group indicates that the survival rate of full and expanded blastocysts in a closed vitrification system without artificial shrinkage, which was replaced by extended exposure time to the cryoprotectants, is acceptable [9].

Although pregnancies after the transfer of thawed frozen embryos appear to have better obstetric and perinatal outcomes than those after fresh embryos [17,18], the perinatal outcome of vitrified cleavage embryos using the Cryoleaf carrier system yields comparable outcomes with those of the fresh cycles. No significant differences were observed in the

mean gestational age, birth weight, sex ratio, congenital birth defects, and abnormalities [19]. The health of children born after blastocyst vitrification has always been of concern. Most studies of blastocyst vitrification are small cases without data on the neonatal outcomes. Wikland M. et al. demonstrated that children born after the transfer of open vitrified blastocysts (using the cryoloop), compared with fresh blastocysts, yields similar neonatal outcomes [20]. The largest study on vitrified blastocysts that included 147 children showed no differences in the obstetric outcomes for children born after open vitrified blastocysts (using the cryoloop) compared with the children born after fresh blastocysts; however, a low birthweight rate of 43.5% among all the children in the vitrified group was reported [2]. There are very few studies on the follow-up of children after transfer of closed vitrified blastocysts. Wirleitner et al. showed that the length of the storage time of vitrified blastocysts in closed devices that were stored for 6 years in liquid nitrogen had no detected negative effect on the health of the children [21]. In this study, 332 warming cycles produced 131 healthy babies. No adverse outcome was observed in the children born after the transfer of closed vitrified blastocysts compared with the children born after the transfer of open vitrified blastocysts in terms of birth weight, birth length or birth defects. In this regard, it is suggested that closed vitrification has an advantage for the cryopreservation of blastocysts derived from patients with viral infections, such as hepatitis B-C and HIV.

Conclusions

One limitation of this study is its limited size; however, the results are promising. The data suggest that closed blastocyst vitrification seems a safe alternative for open blastocyst vitrification without affecting the efficiency of cryopreservation. Long-term child follow-up studies are needed to investigate open and closed vitrification systems.

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Neonatal Health In Nepal: Analysis of Absolute and Relative Inequalities and Impact of Current Efforts To Reduce Neonatal Mortality

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Abstract

Background: Nepal has made substantial progress in reducing under-five mortality and is on track to achieve Millennium Development Goal 4, but advances in neonatal health are less encouraging. The objectives of this study were to assess relative and absolute inequalities in neonatal mortality over time, and to review experience with major programs to promote neonatal health.

Methods: Using four nationally representative surveys conducted in 1996, 2001, 2006 and 2011, we calculated neonatal mortality rates for Nepal and for population groups based on child sex, geographical and socio-economic variables using a true cohort log probability approach. Inequalities based on different variables and years were assessed using rate differences (rd) and rate ratios (rr); time trends in neonatal mortality were measured using the annual rate of reduction. Through literature searches and expert consultation, information on Nepalese policies and programs implemented since 1990 and directly or indirectly attempting to reduce neonatal mortality was compiled. Data on timeline, coverage and effectiveness were extracted for major programs.

Results: The annual rate of reduction for neonatal mortality between 1996 and 2011 (2.8 percent per annum) greatly lags behind the achievements in under-five and infant mortality, and varies across population groups. For the year 2011, stark absolute and relative inequalities in neonatal mortality exist in relation to wealth status (rd = 21.4, rr = 2.2); these are less pronounced for other measures of socio-economic status, child sex and urban–rural residence, ecological and development region. Among many efforts to promote child and maternal health, three established programs and two pilot programs emerged as particularly relevant to reducing neonatal mortality. While these were designed based on national and international evidence, information about coverage of different population groups and effectiveness is limited.

Conclusion: Neonatal mortality varies greatly by socio-demographic variables. This study clearly shows that much remains to be achieved in terms of reducing neonatal mortality across different socio-economic, ethnic and geographical population groups in Nepal. In moving forward it will be important to scale up programs of proven effectiveness, conduct in-depth evaluation of promising new approaches, target unreached and hard-to-reach populations, and maximize use of financial and personnel resources through integration across programs.

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Background

Insufficient progress in reducing neonatal mortality

While infant and under-five mortality rates in developing countries have declined significantly in the past decades, newborn mortality rates have decreased much more slowly [1]. An estimated 18% to 37% of neonatal deaths, defined as deaths occurring during the first 28 days of life, could be averted through expanded coverage of cost-effective interventions, if delivered through family or community approaches [2].

Nepal is one of the few developing countries considered "on track" to achieve Millennium Development Goal (MDG) 4 to reduce child mortality by two-thirds between 1990 and 2015, [3] with reductions in under-five mortality from 118 to 54 per 1,000 live births (54% reduction) and infant mortality from 79 to 46 per 1,000 live births (41% reduction) between 1996 and 2011 [4-7]. Over the same time period, the neonatal mortality rate decreased by only 34%, from 50 to 33 per 1,000 live births. Socio-economic disparities in neonatal mortality in Nepal have been well documented, for example, neonatal mortality is evidently higher among poor groups and socially disadvantaged castes [8-10]. These are likely to be among the reasons for insufficient progress made to date, as interventions rarely reach all population groups in equitable ways.

Direct and underlying causes of neonatal deaths

Globally, the main direct causes of neonatal death are preterm birth (28%), severe infections (26%), asphyxia (23%), and neonatal tetanus (7%) [11]. Information about the causes of neonatal deaths is limited in Nepal. Verbal autopsy findings of newborn deaths in the 2006 Nepal Demographic and Health Survey showed that major causes of death are infections (39%), birth asphyxia/birth injury (33%), congenital anomalies (8%) and pre-maturity or low birth weight (6%) [5]. Other Nepalese community- and hospital-based data also suggest infections, birth asphyxia, preterm birth and hypothermia as the most

Table 1 Number of households, women of reproductive age and births by survey year

	NFHS 1996	NDHS 2001	NDHS 2006	NDHS 2011
Total households	8,082	8,602	8,707	10,826
Response rate (%)	*99.6*	*99.6*	*99.6*	*99.4*
Total women aged 15–49 years	8,429	8,726	10,793	12,674
Response rate (%)	*98.2*	*98.2*	*98.4*	*98.1*
Total births in last ten years	14,259	14,044	11,531	11,225
Approximate timeframe covered	1986-1995	1991-2000	1996-2005	2001-2010

important causes, [12- 14] largely in agreement with the general picture of the developing world.

In addition to lack of basic prenatal, natal and postnatal healthcare, a range of socio-economic and cultural factors, such as inability to pay for transportation and services, poor knowledge and attitudes in relation to healthcare, and various forms of gender bias negatively affect newborn survival in developing countries [15]. For example, in most of the cultures in rural Nepal, mothers are considered ritually "polluted" until nwaran (the name-giving ceremony on the ninth day) and are restricted to stay at home, preventing access to care during this critical period. Also, newborn bathing immediately after birth and applying oil and turmeric powder to the cord stump are commonly practiced traditions and are known to increase the risk of neonatal infections [16].

Community-level efforts to improve prevention and care

Critical interventions to reduce neonatal mortality include behavior change communication; community mobilization and engagement for improved antenatal, intrapartum, and postnatal care practices; and community-based case management of illness [2]. A major challenge in relation to these is promoting demand for healthcare and meeting this demand through interventions delivered at family and community levels. Indeed, studies from South Asia demonstrate that simple community- and home-based prevention and treatment interventions during pregnancy, birth and the post-natal period can effectively save the lives of newborns [17-19].

Drawing on international, regional and national evidence, the Government of Nepal initiated a series of policies and programs to address neonatal mortality in Nepal with efforts delivered through the governmental health system and its hospitals and peripheral health facilities (i.e. primary health care centres, health posts and sub-health posts) as well as through the strong workforce of 48,000 female community health volunteers. To date, no comprehensive review and analysis of these policies and programs has been undertaken with respect to their implementation and impact on newborn health.

The objectives of this study are to assess relative and absolute socio-economic inequalities in neonatal mortality over time, and to review current experience with programs to promote neonatal health in relation to progress towards achieving MDG 4.

Methods

With respect to the first objective, the study used data from national surveys conducted in 1996 (Nepal Family Health Survey, NFHS) and 2001, 2006 and 2011 (Nepal Demographic and Health Surveys, NDHS). These surveys provide nationally representative data on fertility, health care behaviour and practices, childhood mortality, nutrition, and knowledge of HIV/AIDS that are comparable across different countries and across time. Data are in the public domain and accessible from the MEASURE DHS website (www.measuredhs.com).

The surveys are based on two-stage, systematic cluster random sampling, and are characterized by response rates above 90%. Trained enumerators collect information from households and respondents after obtaining verbal informed consent. Table 1 shows the sample size and response rate for each survey. More details on the sampling methodology are available separately [4-7]. These surveys were reviewed and approved by the Institutional Review Board of the Nepal Health Research Council, Nepal; interviews were conducted after informed consent and the datasets used for this analysis were anonymous.

This paper assesses time trends in neonatal mortality, which is defined as the number of deaths per 1,000 live births occurring during the first 28 days of life. We determined neonatal mortality rate based on a true cohort log probability approach [20] for babies born during the 10 years preceding the survey. In addition to calculating national averages, we disaggregated neonatal mortality by child sex, place of residence (i.e. urban, rural), ecological zone (i.e. mountain, hill, terai or flatland), development region (i.e. Eastern, Central, Western, Mid-Western, Far-Western), maternal education (i.e. no education, primary education, secondary or higher education), wealth quintile, and caste and ethnicity. To assess magnitude and trends in inequalities, we calculated rate differences (highest – lowest) as absolute measures of inequality and rate ratios (highest/lowest) as relative measures of inequality for each of the four survey periods. The rate ratio is unit-less and independent of average levels and scale, whereas the rate difference depends on both average levels and scale [21-23]. These two commonly used measures of inequality are easy to understand, but comparisons are limited to two extreme groups rather than covering the full population spectrum [24]. Reporting both absolute and relative measures of inequality is recommended to increase transparency, reduce systematic reporting biases, and improve the evidence base for policies aimed at reducing health inequalities [25].

The annual rate of change is commonly used to describe trends in increment (e.g. improved coverage) or reduction (e.g. reduced mortality rate), and to make projections of rates into the future. The annual rate of reduction (ARR) in neonatal mortality for this study was calculated as

$$ARR = \frac{LN(NMR_{t1}/NMR_{t0}) \times 100}{(t1-t0)}$$

where LN is the natural logarithm, NMR is the neonatal mortality rate, and t0 and t1 correspond to 1996 and 2011 respectively [26]. Analyses were conducted in Stata Special Edition version 12 [27].

With respect to the second objective, the study compiled information on all policies and programs implemented since 1990

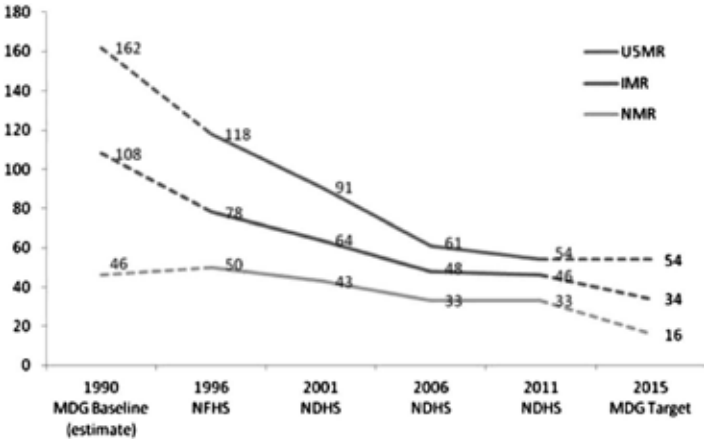

Figure 1. Trend in child, infant and neonatal mortality in Nepal for 1990 to 2011 in relation to the MDG baseline for 1990 and MDG targets for 2015. Note: Estimates of child, infant and neonatal mortality are based on the five-year period preceding the surveys. The MDG baseline is not survey-based but was estimated based on backward extrapolation of trends. Neonatal mortality does not form part of the MDG indicators, and the values for MDG baseline and MDG target are taken from the Nepali national health plan. U5MR: Under five mortality rate; IMR: Infant mortality rate; NMR: Neonatal mortality rate; MDG: Millenium Development Goal; NFHS: Nepal Family Health Survey; NDHS: Nepal Demographic and Health Survey.

that have directly or indirectly attempted to reduce neonatal mortality. We conducted a range of searches in the peer-reviewed literature, using PubMed, and in the grey literature, using the websites and electronic repositories of the Nepal Ministry of Health and Population (e.g. www.mohp.gov.np, www.dohs.gov.np, http://elibrary.mohp.gov.np) and of key donors such as the US Agency for International Development (e.g. http://dec.usaid.gov) and the UK Department for International Development (e.g. www.dfid.gov.uk/r4d), as well as through direct contact with individuals in these and other organizations. Relevant documents identified included scientific publications, annual reports, project reports and technical briefs. These were reviewed to identify existing policies and programs and to select major policies and programs to improve newborn health. For the latter, information was extracted to provide a brief description of activities and to document program timeline, scale and coverage, as well as program effectiveness.

Results

Time trends and socio-economic inequalities in neonatal mortality

The most recent estimates for neonatal, infant and under-five mortality in Nepal are 33, 46 and 54 per 1,000 live births respectively, for the period 2006-2011 [6]. The overall rate of reduction in childhood mortality between 1990 and 2011 is impressive; however, there are stark differences in the annual rate of reduction for under-five, infant and neonatal mortality (5.2, 3.6 and 2.8 percent per annum respectively for the five-year period preceding the survey). As shown in Figure 1, the country had already achieved the MDG 4 target for under- five mortality by 2011, but reductions in infant and neonatal mortality are a must if childhood survival is to improve further.

Table 2 shows inequalities in newborn mortality by child sex, geographical location (as measured by urban–rural residence, ecological region and development region) and socio- economic status (as measured by maternal education, wealth status and caste and ethnicity); these inequalities are evident in all four surveys. Male neonates from rural areas, living in mountain areas and the Far-Western region, born to mothers with no education and into families belonging to the lower wealth quintile and to a marginalized caste or ethnic group (Dalit and Janajati) are dying more frequently than their counterparts.

Annual rate of reduction

The overall average annual rate of reduction in neonatal mortality for the period 1996 to 2011 is 3.3 percent per year. The rate of reduction is greatest for the richest wealth quintile (6.2 percent per annum), and is also substantially above average for the Eastern development region (4.4 percent per annum) and the Mid-Western development region (4.2 percent per annum). Neonates living in the Western development region (2.3 percent per annum), or born into the richer wealth quintile (2.5 percent per annum), into a Janajati family (2.7 percent per annum) or to mothers with no education (2.6 percent per annum) show particularly low average annual rates of reduction.

Absolute inequalities based on rate differences in 2011

In Nepal, differences in neonatal mortality are most pronounced for wealth (21.4 between the wealth quintiles with highest and lowest neonatal mortality rates). Interestingly, neonatal mortality is higher among poorer and middle quintile families than among poorest quintile families. Differences in neonatal mortality rate are also relatively stark for maternal education (14.1 between a child born to a mother with secondary or higher education and a child born to a mother with no education). Differences are moderate for the three geographical indicators (10.9 for urban compared to rural areas, 12.7 for mountain compared to hill areas, 11.6 for the Far-Western compared to Eastern region), as well as caste and ethnicity (11.6 for Brahmins (priests), Chhetris (warriors) and Newars (traditional merchants and traders) compared to others; others include diverse castes and ethnic groups that could not be disaggregated due to small sample sizes). Interestingly, absolute differences in neonatal mortality are not very pronounced for males compared to females (3.8).

Relative inequalities based on rate ratios in 2011

Overall, relative inequalities in neonatal mortality show similar results, with wealth status showing the greatest inequalities (2.2 for the richest wealth quintile compared to the poorer wealth quintile). Maternal education (1.5 for children born to mothers with no education compared to children born to mothers with secondary or higher education), geographical features (1.4 for urban–rural, Far-Western compared to Eastern and mountain compared to hill regions) and caste (1.4 for Brahmins, Chhetris and Newars compared to others) show very similar relative inequalities. Relative inequalities are barely present for male versus female neonates.

Changes over time

No clear and consistent pattern emerges in the reduction of absolute and relative inequalities in neonatal mortality based on the range of variables assessed. For most variables, rate differences and rate ratios are relatively stable with some fluctuation (i.e. urban–rural residence, development region, caste and ethnicity) or stark fluctuation (i.e. ecological region, maternal education) between years. For most comparisons, the groups with the highest and lowest neonatal mortality rates remain the same across comparisons; with caste and ethnicity, there is substantial variation between years. Findings for child sex and wealth status stand out: For child sex, rate differences and rate ratios were much more pronounced in 1996 and have

Table 2 Neonatal mortality rate for the 10-year period preceding the survey, by child sex, geographical location and socio-economic characteristics*

	Neonatal mortality rate				*Annual rate of reduction*
	NFHS 1996	**NDHS 2001**	**NDHS 2006**	**NDHS 2011**	***(1996–2011)***
Child sex					
Male	65.1	51.8	38.6	36.9	3.8
Female	49.6	42.6	36.8	33.1	2.7
Rate difference	*15.5*	*9.2*	*1.8*	*3.8*	*na*
Rate ratio	*1.3*	*1.2*	*1.0*	*1.1*	*na*
Residence					
Urban	43.2	35.9	24.6	25.3	3.6
Rural	58.5	48.1	39.6	36.2	3.2
Rate difference	*15.3*	*12.2*	*15.0*	*10.9*	*na*
Rate ratio	*1.4*	*1.3*	*1.6*	*1.4*	*na*
Ecological region					
Mountain	70.8	63.7	58.9	45.6	2.9
Hill	50.3	41.9	28.6	32.9	2.8
Terai	61.7	49	41.4	35.1	3.8
Rate difference	*20.5*	*21.8*	*30.3*	*12.7*	*na*
Rate ratio	*1.4*	*1.5*	*2.1*	*1.4*	*na*
Development region					
Eastern	56.7	50.1	32.5	29.3	4.4
Central	55.5	47.6	34.8	36.7	2.8
Western	52.0	38.9	34.5	37.0	2.3
Mid-western	63.0	40.3	55.9	33.6	4.2
Far-western	67.0	63.8	39.7	40.9	3.3
Rate difference	*15.0*	*24.9*	*23.4*	*11.6*	*na*
Rate ratio	*1.3*	*1.6*	*1.7*	*1.4*	*na*
Maternal education					
No education	59.5	51.1	43.3	40.3	2.6
Primary	51.6	41.1	34.1	33.6	2.9
Secondary or higher	41.6	24.3	20.3	26.2	3.1
Rate difference	*17.9*	*26.8*	*23.0*	*14.1*	*na*
Rate ratio	*1.4*	*2.1*	*2.1*	*1.5*	*na*
Wealth status					
Poorest	56.4	48.5	42.7	35.6	3.1
Poorer	63.4	56.0	37.6	40.0	3.1
Middle	65.8	46.9	46.9	39.2	3.5
Richer	53.3	47.2	30.4	36.9	2.5
Richest	47.0	32.1	26.3	18.6	6.2
Rate difference	*18.8*	*23.9*	*20.6*	*21.4*	*na*
Rate ratio	*1.4*	*1.7*	*1.8*	*2.2*	*na*
Caste and ethnicity					
Brahmin, Chhetri, Newar	52.6	43.9	33.1	31.0	3.5
Dalits	58.1	51.6	43.9	36.4	3.1
Janajati	51.7	47.9	34.0	34.6	2.7
Other	72.2	49.2	44.5	42.6	3.5
Rate difference	*20.5*	*7.7*	*11.4*	*11.6*	*na*
Rate ratio	*1.4*	*1.2*	*1.3*	*1.4*	*na*
National	**57.5**	**47.2**	**37.7**	**35.1**	**3.3**

*In each survey, the groups with the highest and lowest neonatal mortality were used to calculate rate differences and rate ratios. Please note some fluctuation between years in terms of the groups performing best or worst.

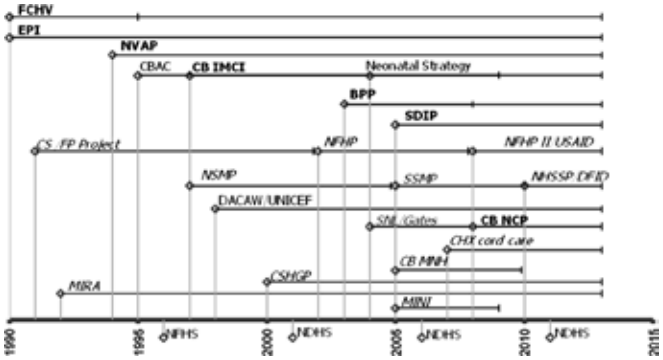

Figure 2. Major maternal, neonatal and child health-related policies, programs and projects in Nepal (1990–2015). FCHV: Female Community Health Volunteer; EPI: Expanded Program on Immunization; NVAP: National Vitamin A Program; CBAC: Community based ARI Control of Diarrheal Diseases program; CB IMCI: Community based Integrated Management of Childhood Illness; BPP: Birth Preparedness Package; SDIP: Safe Delivery Incentive Program; CS/FP Project: Child Survival and Family Planning Project; NFHP: Nepal Family Health Program; USAID: United States Agency for International Development; NSMP: Nepal Safer Motherhood Project; SSMP: Support to Safe Motherhood Program; NHSSP: Nepal Health Sector Support Program; DFID: UK Department of International Development; DACAW: Decentralized Action for Children and Women; UNICEF: United Nations Children's Fund; SNL: Saving Newborn Lives program; CB NCP: Community based Newborn Care Package; CHX Cord Care: Chlorhexidine for Umbilical Cord Care; CB MNH: Community based Maternal Newborn Health program; CSHGP: Child Survival Health and Grant Program; MIRA: Mother and Infant Research Activity; MINI: Morang Innovative Neonatal Intervention; NDHS: Nepal Demographic and Health Survey; NFHS: Nepal Family Health Survey.

shown a steady decline since then. No clear gradient for neonatal mortality emerges across wealth quintiles; the richest wealth quintile performs best across all four surveys but the worst performance is observed for either the poorer or middle wealth quintile rather than the poorest. Overall, rate differences are relatively stable over time whereas the rate ratio increased from 1.4 in 1996 to 2.2 in 2011 between wealth quintiles with the highest and lowest mortality rates.

Major policies and programs to improve neonatal health

Since 1990, Nepal has developed, piloted and gradually scaled-up a broad range of facility- and community-based programs to address maternal, neonatal and child health; many of these have since been integrated with regular public health programs. Figure 2 provides a graphical overview of these programs, distinguishing between national programs (presented in bold) and sub-national programs or pilots (presented in italics) and showing support from external donors. They cover the continuum of maternal and child health and comprise integrated approaches to addressing multiple health concerns among target populations (e.g. community-based Integrated Management of Childhood Illness), highly vertical programs to address specific health conditions (e.g. National Vitamin A program) and interventions to strengthen the health system (e.g. female community health volunteers program). While neonatal health is not an explicit focus in all of these programs, they illustrate the considerable background activity prior to the introduction of focused newborn interventions, with specific components of all programs directly impacting newborn health.

Newborn survival was made a development priority for the country through a major strategic document endorsed by the Ministry of Health and Population, the Nepal Neonatal Health Strategy 2004 [28]. In an effort to develop recommendations towards the implementation of this strategy, a rapid assessment of neonatal health programs in Nepal was conducted in 2007 to analyze the status of ongoing programs and the roles of different partners, and to identify gaps and constraints in the implementation of evidence-based interventions [29]. All recent policy documents, such as the periodic health plans (9th plan, 10th plan and interim plan) and the Nepal Health Sector Plans I (2004–2009) and II (2010–2015) recognized neonatal health as a priority and listed it as a component of essential health care services [30-36]. Some of these policy documents also emphasize improved access for poor and vulnerable groups [33]. Taken together, these policies and strategies provide both a conducive environment and a framework for developing, piloting and implementing newborn programs in the country [37].

Table 3 provides more in-depth information for three established and two more recently initiated programs that are considered to be of critical importance in improving neonatal health based on (i) their explicit focus on delivery and the post-partum and neonatal periods, (ii) their programmatic rather than research orientation, and (iii) their aim for or ongoing national-level implementation. In principle, these were developed and implemented based on available international, regional and national evidence [38,39].

The community-based Integrated Management of Childhood Illness (CB IMCI) represents an established approach and is globally considered one of the best models for integrated delivery of care at family and community level for the most common illnesses (i.e. pneumonia, diarrhoea, malaria, malnutrition) during the first five years of life. The birth preparedness package (BPP) targets pregnant women, helping them and their families to be prepared for a safe delivery and for the arrival of the baby, and to recognize danger signs and seek care from a health provider when needed. It emphasizes the need to be ready for emergencies, such as blood transfusion or caesarean section, and to reduce delays in seeking care for maternal or neonatal illness (in particular newborn asphyxia, postpartum haemorrhage and severe bacterial infections). The main objective of the Safe Delivery Incentives Program (SDIP) is to increase deliveries at health institutions (i.e. hospital, primary health care center or health post and sub-health post with birthing center) and thus to provide better care for mothers and newborns during and immediately after birth. Institutional deliveries or safe home deliveries are expected to contribute to reducing all causes of neonatal mortality, in particular they can prevent newborns from dying due to birth asphyxia and severe bacterial infections. More recent programs include the community-based newborn care package (CB NCP) and the umbilical cord care for newborns (CHX cord care) program; both are in early phases of implementation and roll-out. Based on the experience of implementing these programs and results to date, these programs are being revised to integrate approaches by harmonizing efforts and messages. These changes are expected to create synergies in the delivery of better neonatal health outcomes.

As shown in Table 3 evidence of effectiveness of these programs in Nepal with respect to neonatal health outcomes, as obtained from the scientific publications and documents reviewed, is scarce. Notably, we were unable to quantify coverage of the five programs beyond a general statement about the geographical spread of implementation (i.e. national or various districts); likewise, we were unable to document equity or inequity in program implementation. To date, studies of program impact

on neonatal mortality are rare. We were only able to identify two such studies, where a cluster-randomized controlled trial of a pilot showed large and statistically significant declines in cord infections as a result of applying chlorhexidine [44] and an interrupted time series study in one district failed to demonstrate any impact on neonatal mortality for the implementation of the SDIP program [45]. Current gains in reducing under-five mortality in Nepal can be plausibly linked to CB IMCI [46] but, as of yet, no evidence is available for a measurable impact on neonatal mortality. Instead or in addition to looking at neonatal mortality, several programs measured impact in term of changes in intermediate outcomes, such as birth preparedness (BPP, [43]), institutional or safe home delivery (SDIP, [45]) and case reporting and case severity (CB IMCI, [41,42]).

Discussion

Critical considerations across programs

Based on the data available, Nepal has made very good progress in terms of reducing child and infant mortality [3]. In order to be able to achieve further gains in child survival, the main challenge for the country will be to reduce neonatal mortality. Neonatal mortality varies greatly by wealth status and, to a lesser extent, by maternal education, caste and ethnicity and geographical location. Absolute and relative inequalities in neonatal mortality are relatively stable and interventions to date do not appear to have acted to greatly decrease or increase inequalities. As the annual rate of reduction in neonatal mortality has stagnated in recent years and as inequalities in neonatal mortality persist, labelling a country as "on track" to achieve the MDGs may divert focus and slow the momentum of ongoing efforts. Despite persistent high levels of neonatal mortality, in the last decade Nepal has witnessed a higher rate of decline in neonatal mortality (3.6 percent per annum) compared to the global average (2.1 percent per annum) and compared to progress made in neighbouring countries [47,48]. This achievement can be plausibly linked to the country's progress with respect to family planning, antenatal and delivery care practices as well as significant improvements in infrastructure over the same period.

The Government of Nepal, together with major international donors, has implemented a broad range of programs to address maternal, neonatal and child health problems over the past twenty years. It is difficult to attribute the progress made to date to individual programs, in part because of the broad range of ongoing activities and in part because of insufficient impact data for individual programs. In particular, information on coverage and uptake of the five programs most directly concerned with reducing neonatal mortality and evidence of impact on neonatal mortality rather than intermediate outcomes is limited. Moreover, the available information is rarely disaggregated for different socio-economic groups, although descriptive data suggest that programs do not equitably reach those in greatest need [6]. Given the substantial financial and personnel resources dedicated to these programs, it will be important to carefully evaluate their future performance in terms of coverage and effectiveness.

Other programs covered by Figure 2 but not further considered in Table 3 are also likely to contribute to improved newborn health. Specific interventions, such as tetanus toxoid injections and the safe motherhood program improve coverage and quality of care of obstetric and newborn care services. Other programs are mobilizing communities and their change agents to educate mothers and their families, promoting healthy behaviors for better maternal and newborn health in different parts of the country. With respect to strengthened primary health care, female community health volunteers (FCHV) are a unique and strong cadre for all community-based programs in Nepal and play a crucial role in delivering newborn interventions under the CB NCP and CHX for cord care [49]. Beyond these front-line health workers, Nepal's public health system is suffering from a shortage of health personnel and services, especially in rural areas. For example, many birthing facilities do not offer a 24- hour service seven days a week and, as a result, expectant mothers are often reluctant to deliver at a health facility. Therefore, greater capacity of providers at all levels and broader health system strengthening will also be necessary to improve maternal and newborn health care services further [50].

A further hidden reason behind the limited impact of neonatal health programs to date is the fact that some practices, such as immediate care for newborns and recently delivered women, are greatly affected by existing cultural norms and behaviors. In Nepal and many south-Asian cultures, birth and the postnatal period are considered ritually polluted, and the new mothers often face seclusion which undermines their ability to seek health care when needed for themselves or their babies [51,52]. Their care-seeking behavior is further limited by decision-making authorities in the household, where the ultimate decision to seek care and pay for travel, care or medication usually resides either with the male head of household or older women such as mothers-in-law [53]. As a result, new mothers might not be able to follow recommended newborn care practices due to existing family and social pressures and their inability to negotiate on these matters. Furthermore, issues related to health worker behavior, gender-friendliness in service delivery and perceived quality of care affect service utilization and compliance. In south-Asian cultures, many women do not visit health facilities as most of the providers are male, or because they have not been treated respectfully during previous visits. The design of programs and their delivery will therefore need to pay attention to implementing interventions in socio-culturally appropriate ways, in particular among socio-economically disadvantaged and hard-to-reach population groups.

The strong support from high-level policy makers, as evident in the recognition of neonatal health in the long-term health sector plan and the neonatal health strategy, has been and will be a critical ingredient of making progress. Likewise, effective partnerships between the government and a range of donors have enabled the country to develop and implement neonatal health programs and to scale these up over a relatively short period of time [37,38]. There are, however, some missed opportunities to integrate and harmonize across efforts. Some programs are implemented in a vertical fashion with distinct implementation modalities and information systems, and limited attempts are being made to harmonize messages for behavior change across programs. For example, CHX for cord care is delivered as a stand- alone program even though it clearly fits into the CB NCP and CB IMCI program framework. Similarly, the SDIP could be extended from just focusing on the number of institutional deliveries to expanding quality care for mothers and newborns. This is likely to be particularly relevant for newborn survival as the institutional delivery rate is rapidly increasing and as this early contact between health workers and mothers is an opportunity for timely diagnosis and treatment of newborn illnesses and for the promotion of essential newborn care practices. Most of these programs focus on increasing health

Table 3 Major policies and programs to improve neonatal health

Program	Description	Newborn survival interventions	Evidence of program effectiveness in Nepal	Program timeline and scale
Community Based Integrated Management of Childhood Illness (CB IMCI)	National program, which forms part of the broader WHO/UNICEF IMCI model to improve child health and survival and focuses on treatment of common childhood illness at community level through disease prevention and health promotion, in particular by improving performance of health workers, improving health services, and improving knowledge about the care of children at home and in the community.	• Early identification of newborn illness • Community-based management and referral of sick newborns	• Increased case reporting of diarrhoea and acute respiratory infections (ARI) (0.21 and 0.16 diarrhoea episodes per child per year in areas with and without intervention respectively; 55% and 27% of all under-five children reporting with ARI in areas with and without intervention respectively) [40] • Decreased case severity of diarrhoea and ARI (29% and 35% of all diarrhoea cases with some dehydration in areas with and without intervention respectively; 28% and 38% of ARI cases reported as pneumonia in areas with and without intervention respectively) [41] • Program scalability [42] • Program contribution to overcoming problem of insufficient human resources for health [42]	Initiated: 1997 Nationwide: 2009
Birth preparedness package (BPP)	National package of interventions to encourage pregnant women, their families and communities to plan for normal pregnancies and deliveries as well as for obstetric emergencies, designed to be implemented through female community health volunteers and health workers in primary care facilities.	Education and counselling on: • Preparedness for safe delivery and promoting essential newborn care practices (clean cord, wiping, wrapping, immediate breastfeeding and delayed bathing) • Danger signs during pregnancy, delivery and the postnatal period • Danger signs among newborns • Tetanus toxoid vaccination	• Increase in putting into practice five healthy newborn care practices ranging from 19% to 29% from baseline (42% to 71% for clean cord care, 56% to 75% for immediate wiping, 56% to 79% for immediate wrapping, 21% to 40% for immediate breastfeeding and 12% to 41% for delayed bathing) [43]	Initiated: 2003 Nationwide: 2008
Community-based Newborn Care Package (CB NCP)	A pilot program developed on the basis of CB-IMCI with a new set of interventions to improve the health and survival of newborn babies. The package reflects evolving evidence and national, regional and global experience, taking into account causes of neonatal mortality, suitability of interventions to large-scale implementation and cost. [39]	• Behavior change communication • Promotion of institutional delivery and clean delivery practices at home • Postnatal care • Community-based case management of pneumonia and severe bacterial infections • Care for low birth weight newborns • Prevention and management of hypothermia • Recognition of asphyxia • Initial stimulation and resuscitation of newborns	• Ongoing assessment of the pilot in ten districts through Nepali Ministry of Health and Population with USAID, UNICEF and the Saving Newborn Lives program, and ongoing mixed-method study by Paudel et al. [40] to assess impact of the program on newborn care practices	Initiated: 2008 Ongoing: 35 districts (Dec 2012) [1], preparation for review and national scale-up
Umbilical cord care for newborns (CHX cord care)	A pilot program currently being scaled-up, integrated with other maternal and newborn programs such as BPP and CB-NCP to prevent newborn infections and improve newborn survival by applying chlorohexidine to the umbilical cord stump.	• Use of chlorohexidine for prevention of umbilical cord infections	• 24% reduction in neonatal mortality among those who used chlorohexidine compared to those who practiced dry cord care; even greater 34% reduction among those who applied chlorohexidine within 24 hour after birth [44]	Initiated: 2007 Ongoing: 33 districts (Dec 2012) [2], preparation for national scale-up
Safe Delivery Incentives Program (SDIP) *also described as Maternity Incentives Program or Aama Surakchya Program*	National program to increase utilization of professional care during childbirth. It provides cash to women giving birth in a health facility and an incentive to the health provider for each delivery attended, either at home or in the facility.	• Promotion of institutional delivery and/or home delivery by skilled birth attendant • Care for immediate newborn problems (e.g. birth asphyxia)	• Substantial increase (2.3% points) in probability of deliveries attended by a skilled birth attendant [45] • No impact on neonatal mortality [45]	Initiated: 2005 Nationwide: 2008

[1]Dhankuta, Morang, Palpa, Doti, Bardiya, Dang, Chitwan, Kavre, Parsa, Sunsari, Terathum, Sankhuwasava, Kallali, Myagdi, Bajhang, Banke, Kapilbastu, Arghakhachi, Mohattari, Salyan, Dailekh, Jumla, Nawalparasi, Saptari, Sarlahi, Jajarkot, Lamjung, Humla, Taplejung, Bara, Baglung, Dolpa, Rautahat, Baitadi, Rupandehi.
[2]Banke, Jumla, Bajhang, Parsa, Darchula, Baitadi, Doti, Kallali, Bardiya, Dailekh, Dolpa, Rolpa, Myagdi, Palpa, Rautahat, Mahottari, Saptari, Sankhuwasava, Morang, Sunsari, Dhankuta, Sarlahi, Nawalparasi, Kapilbastu, Arghakhachi, Humla, Kanchanpur, Baglung, Lamjung, Bara, Khotang, Taplejung, Salyan.

workers' knowledge and skills to deliver services to prevent, diagnose and manage newborn illnesses on the one hand, and on improving community behaviors and generating demand for care and services on the other hand. At the same time, efforts should be targeted more towards strengthening health systems to improve the delivery of basic supplies and equipment, such as chlorhexidine for cord care, gentamicine for newborn infections and resuscitation-kits to manage asphyxia, all of which are critically needed to prevent and manage newborn illness.

Nepal has witnessed considerable political unrest and even armed conflict during 1996-2006. Nevertheless the country continued to improve most of its health indicators despite some disruption to health services [54]. During the last two decades, Nepal has also undergone significant socio-economic changes, in particular improved transportation and communication infrastructure and girls' education. International labour migration has been a recent phenomenon leading to young males not being at home to support and care for recently delivered women and their newborns but also generating greater household income due to remittance. The effect of these major societal changes on neonatal and broader health indicators among different population groups has not been yet systematically assessed.

Strengths and limitations

We provided time trends in neonatal mortality and conducted an assessment of absolute and relative differences in neonatal mortality, based on best-available data (Table 2). There are, however, several problems with these data. Due to limited sample size, neonatal mortality was calculated for the last ten years preceding the survey, resulting in sample overlaps between estimates for different points in time. Also, the MDG baseline for 1990 and the MDG targets for 2015 in Figure 1 are estimates provided by the Ministry of Health and are thus not truly comparable to survey data for the years 1996, 2001, 2006 and 2011. Most importantly, NFHS and NDHS data are designed to be representative at the national level but may not necessarily be representative for each of our subgroup analyses, e.g. selected caste and ethnic groups; therefore, the comparison of rate differences and rate ratios and their changes across time must be made with caution.

A major limitation in relation to our review of efforts to reduce neonatal mortality is that information on relevant programs and policies and evidence of their coverage and effectiveness is based on non-systematic literature searches. Through conducting searches of the grey literature as well as the scientific literature and, in particular, through consultation with relevant stakeholders in Nepal, we are confident to have captured all important programs of direct relevance to neonatal health. We are less confident to have unearthed all available evidence on the effectiveness of different programs, especially as much unpublished additional evidence may reside with implementing organizations. Also, we did not conduct any formal quality appraisal for studies of effectiveness and have therefore not examined the evidence in terms of methodological flaws and potential bias due to non-independent evaluations.

Nevertheless, we believe that this study provides an important and much needed overview of key developments in neonatal health in Nepal over the past 20 years, capturing time trends in neonatal mortality in a disaggregated way, examining absolute and relative inequalities and providing an analysis of current experience with policies and programs.

Conclusions

This study clearly shows that much remains to be achieved in terms of reducing neonatal mortality across different socio-economic, ethnic and geographical population groups in Nepal. In moving forward it will be important to (i) strengthen and further increase the reach of those programs that have proven to achieve good results, such as applying chlorhexidine to prevent umbilical cord infections; (ii) put in place in-depth evaluation of the effectiveness and implementation approach of those programs that are promising but whose impact on neonatal mortality has not yet been verified, in particular CB NCP and SDIP; (iii) target hard- to-reach population across the country, customizing interventions as needed to ensure that they are socio-culturally appropriate; and (iv) maximize use of available financial and personnel resources by facilitating interaction between and, where feasible, integration across neonatal health programs as well as broader efforts to promote maternal and child health.

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Magnetic Resonance Spectroscopy as a Prognostic Marker in Neonatal Hypoxic-Ischemic Encephalopathy: A Study Protocol for an Individual Patient Data Meta-Analysis

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Abstract

Background: The prognostic accuracy of 1H (proton) magnetic resonance spectroscopy (MRS) in neonatal hypoxic-ischemic encephalopathy has been assessed by a criticized study-based meta-analysis. An individual patient data meta-analysis may overcome some of the drawbacks encountered in the aggregate data meta-analysis. Moreover, the prognostic marker can be assessed quantitatively and the effect of covariates can be estimated.

Methods: Diagnostic accuracy studies relevant to the study topic were retrieved. The primary authors will be invited to share the raw de-identified study data. These individual patient data will be analyzed using logistic regression analysis. A prediction tool calculating the individualized risk of very adverse outcome will be devised.

Discussion: The proposed individual patient data meta-analysis provides several advantages. Inclusion and exclusion criteria can be applied more uniformly. Furthermore, adjustment is possible for confounding factors and subgroup analyses can be conducted. Our goal is to develop a prediction model for outcome in newborns with hypoxic-ischemic encephalopathy.

Background: Hypoxic-ischemic encephalopathy (HIE) in the newborn is associated with brain energy metabolism disturbances that can be quantified in vivo by ^{1}H (proton) magnetic resonance spectroscopy (MRS)[1,2]. A recent study-level meta-analysis demonstrated that deep gray matter lactate/N-acetyl aspartate (Lac/NAA) peak/area ratio has a better prognostic accuracy than conventional and diffusion-weighted MRI for neurodevelopmental outcome after HIE [3].

The suggestion that Lac/NAA might support early clinical decisions was criticized for several reasons [4]. Although based on available studies, the validity of the meta-analysis and the generalizability of the results were questioned [4]. It was suggested that the spectrum of the included patients was too broad, including very mildly (Sarnat 1) and very severely (Sarnat 3) affected patients; unclear selection criteria could undermine generalizability. In addition, some studies were restricted to surviving infants and the timing of the magnetic resonance (MR) studies varied. Death after HIE frequently follows decisions to withdraw life-sustaining care. Hence death as an adverse outcome may cause incorporation bias. It is conceivable that the outcome assessors were not always blinded to the MR results. Precise definitions of adverse outcome were lacking in studies. Concern was also expressed with respect to the post-hoc choice of 'cut-off values'. Wilkinson [4] concluded: 'It is not possible from published data to assess the usefulness of quantitative markers such as lactate/NAA peak/area ratio for predicting very adverse outcome […] or to look separately at its usefulness for infants with moderate encephalopathy'.

An individual patient data (IPD) meta-analysis, where the raw data from multiple studies are synthesized, may overcome some of the drawbacks encountered in the aggregate data meta-analysis. A prerequisite is that all authors of the original studies are willing to share the individual test results and the patient characteristics to be evaluated. Subgroup analysis based on different HIE Sarnat stage is possible. Infants who died after treatment withdrawal can be excluded from the analysis. An agreed-upon definition of very adverse outcome can be applied uniformly. Finally, logistic regression modeling can be used to derive a prediction tool that calculates the individualized risk of very adverse outcome.

Objectives: The aims of the planned study are to reassess the prognostic performance of MR biomarkers in neonatal HIE and to determine the effect of other patient variables on the outcome using IPD meta-analysis. Logistic regression modeling will be used to develop a clinical risk prediction rule to assess the individual probability for adverse outcome after HIE.

Methods

Identification, selection, and appraisal of relevant studies have already been carried out independently, by two reviewers (PLJD, GJJ). Disagreement was resolved through discussion.

Inclusion criteria for studies

All studies, cohort and case-control studies, evaluating the prognostic accuracy of MRS biomarkers in term and near-term newborns with HIE (Sarnat stages 1, 2 and 3) were considered for review. Case-control studies are prone to spectrum bias [5], and the prevalence affects the predictive value or the post-test probability. Fortunately, in the regression equation:

$$\text{logit}(p)=\beta_0+\beta_1 \cdot x_1+\beta_2 \cdot x_2+\ldots+\beta_n \cdot x_n$$

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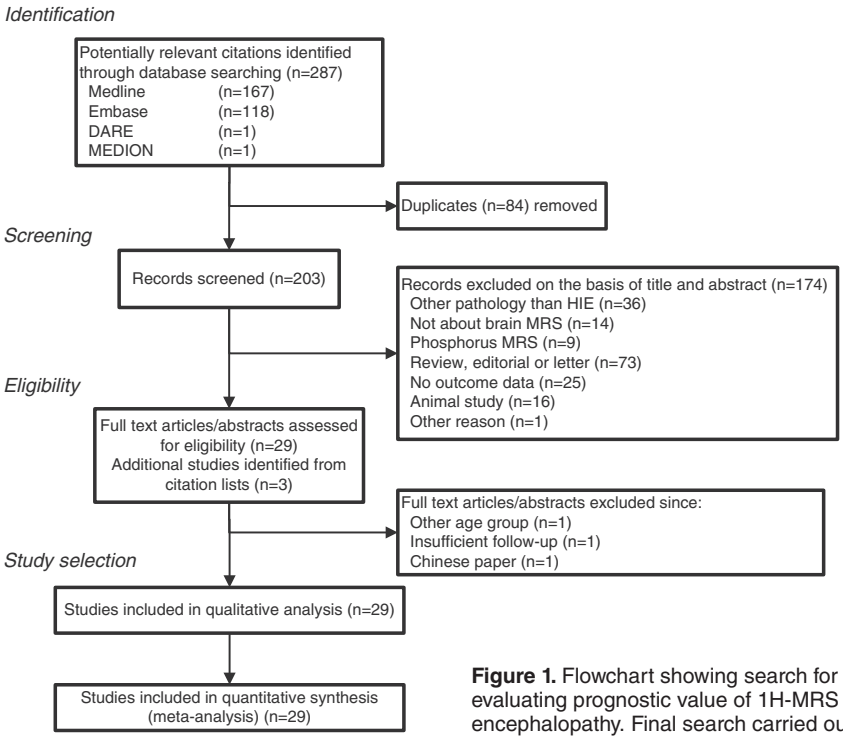

Figure 1. Flowchart showing search for and selection of papers evaluating prognostic value of 1H-MRS in neonatal hypoxic-ischemic encephalopathy. Final search carried out on 14 April 2012.

only β_0 is dependent on the prevalence. This constant β_0 can easily be readjusted to another (disease or) outcome prevalence.

The following data needed to be available for the study to be included in the IPD meta-analysis:

- MR spectroscopy data for Lac/NAA, Lac/creatine (Cr), Lac/choline (Cho), NAA/Cho, NAA/Cr, or Cho/Cr.
- Reliable, quantitative (numerical) neurodevelopmental outcome data at the age of at least 1 year (and preferably 2 years).

Search strategy

A systematic search was performed from inception until 14 April 2012 in MEDLINE (Ovid), EMBASE (Ovid), DARE [6], and Medion [7]. No diagnostic search filter [8,9] or language restrictions were used. Details of the search are given in Additional file 1. Any duplicate articles identified were manually deleted. The reference lists of selected studies were checked for further relevant studies.

After removal of duplicates in our search (see Figure 1), we identified 203 studies of which 174 were excluded on the basis of title or abstract. Another three were excluded after assessment of the full text, and an additional three studies were identified through the reference lists, leaving 29 studies of which the authors will be contacted by email [10-38].

To confirm the thoroughness of our search, the authors will be asked whether they are aware of any untraced but eligible study.

Quality assessment

The quality of the 29 selected studies was assessed using the revised QUADAS tool [39,40]. Since MRS is an objective measurement and outcome is always assessed at a later stage, 3 of the 14 items in the QUADAS tool were omitted: time between index and reference test too long, blinded interpretation of the index test, and availability of clinical data. Two reviewers (PLJD, GJJ) independently answered the 11 remaining questions in the affirmative, in the negative or as being unclear. Figure 2 shows the quality of the 29 selected papers.

Data items to be requested from the authors of the original diagnostic studies

1. Gestational age at birth.
2. Birth weight.
3. Sex.
4. Apgar score at 1, 5, and 10 minutes.
5. Umbilical artery pH and base excess (or first arterial pH and base excess).
6. Sarnat score.
7. Was there an intrapartum sentinel event (for example, uterine rupture, placentalabruption, cord prolapse, and amniotic fluid embolism)?
8. Hypoglycemia: lowest blood (or plasma) glucose in the first 24 hours of life [41].
9. Hyperoxia and hypocarbia: highest arterial pO2 and lowest arterial pCO2 in the first day of life[42,43].
10. Hypothermia (head or whole body cooling).
11. ^{1}H-MRS biomarkers (timing, region of interest (ROI), echo time TE used): peak-area ratios of Lac/NAA, Lac/Cr, Lac/Cho, NAA/Cr, NAA/Cho, Cho/Cr.
12. Outcome (at most recent assessment):
    a. Motor function assessed by the Gross Motor Function Classification System (GMFCS) [44]. This five-level classification system describes the gross motor function of children and youths with cerebral palsy on the basis of their self-initiated movement with particular emphasis on sitting, walking, and wheeled mobility. A criteria list for scoring a child in different languages is available[45].
    b. Early cognitive function as assessed by Griffiths Mental Developmental Scales (general cognitive quotient), scores on the Bayley II Mental Developmental Index or the Bayley III Cognitive Scale, or similar. For comparison, the raw scores will be converted to Z-scores to account

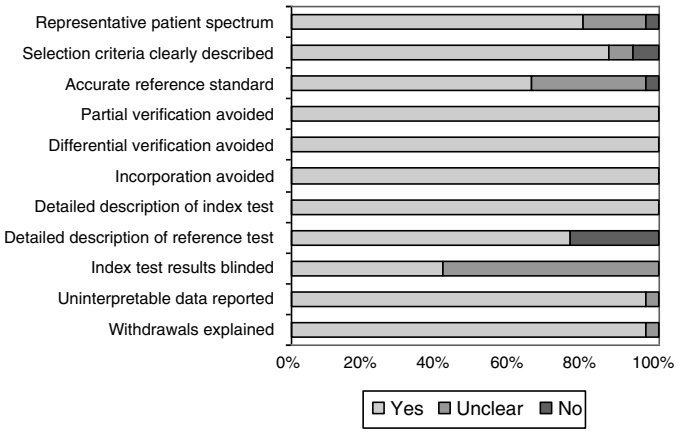

Figure 2. Results of quality assessment using QUADAS tool.

for different standard deviations of the different test result distribution. Children who are too disabled for cognitive testing will be assigned a Z-score of –4. Since early developmental testing is specific but not sensitive for later (school age) impairment [46], cognitive assessment at later age would improve the prognostic accuracy.

c. Visual: bilateral blindness.

d. Auditory: hearing loss requiring bilateral amplification.

13. Was death due to withdrawal of treatment?

The IPD will be delivered by the collaborating researchers using a spreadsheet form for completion in such a way that re-identification is impossible. The data set should not contain personal identifiers such as names, initials, addresses, ZIP code, phone numbers, date of birth or admission, medical record number, social security number, or other unique identifying numbers, characteristics, or codes.

Definition of adverse outcome

Adverse outcome will be defined as the presence of death, substantial motor dysfunction (severe motor impairment) with a level of III or worse on the GMFCS, bilateral blindness (or only light perception), and/or a developmental quotient of less than 3 standard deviations below the norm[47]. Alternative definitions can be used.

Data synthesis and (statistical) analysis

The MRS biomarkers of interest are Lac/NAA, Lac/Cr, Lac/Cho, NAA/Cho, NAA/Cr, and Cho/Cr. The contribution to the adverse prognosis of HIE of these biomarkers (as continuous variables) and the clinical characteristics will be explored using stepwise forward binary logistic regression analysis. The logit and logistic command in Stata/SE 10.1 will be used (Stata Corporation, College Station, TX, USA). An entry probability for each variable will be set at 0.05. A clinical prediction rule will be derived from the final regression model. The predictive accuracy of the logistic regression models will be assessed by computing a cross classification table (lstat command) and by ROC curve analysis or c-statistics (roctab and roccomp command in Stata).

Between-study heterogeneity will be assessed by entering the study as a categorical variable in the logistic regression analysis.

The potential for publication bias will be estimated by using a Deeks' funnel plot. A P value <0.1 was considered statistically significant [48].

Planned sensitivity analyses

The logistic regression analysis will be performed in surviving infants and in survivors plus infants whose decease was not due to a withdrawal decision.

Ethical considerations

The research will be conducted in accordance with the code of conduct for medical research of the Dutch Federation of Biomedical Scientific Societies [49].

The medical ethics committee at Maastricht University Medical Centre did not make an objection to the proposed IPD meta-analysis, but added the express condition that the patient data will be de-identified.

Publication policy

The results of the proposed IPD meta-analysis will be published on behalf of all researchers sharing a usable data set. At least one delegate per study will be proposed as co-author to the journals where the meta-analysis will be submitted. A larger study size may be represented by more authors. Alternatively, the paper will be published under a group name, allowing citation of all contributors in PubMed. The manuscript will be circulated to the collaborators for comments, amendments, and approval before being submitted.

The data provided by the authors will be treated confidentially and will not be copied or distributed elsewhere. Furthermore they will not be used for any other publication without the authors' approval.

Registration

The protocol has not been registered with PROSPERO (the international prospective register of systematic reviews).

Discussion

Strength of the proposed study

Individual participant data meta-analysis has been described as the 'gold standard' for prognostic accuracy studies [50]. In the proposed study, we hope to take advantage of several potential advantages of IPD meta-analysis [51,52]. Inclusion and exclusion criteria can be used more uniformly across studies, and overlapping sets of participants can be identified. Adjustments can be made for confounding factors, subgroup analyses can be conducted, and a prognostic model can be generated.

Important but challenging is the fact that follow-up information on neurodevelopmental outcome can be updated and uniformly described. To increase comparability between the studies, we hope the collaborators will be able to classify the motor outcome using the expanded and revised GMFCS [53]. Updated follow-up information on motor and cognitive developmental status will undoubtedly improve the validity of the prognosis.

Study weaknesses

We are well aware that availability bias is inevitable. No meta-analysis can correct weaknesses in the contributing individual studies, such as diagnostic review bias [54].

Finally, heterogeneity due to different index test methodology (for example, ROI), and especially due to the use of different reference tests is inevitable [55,56], although for the latter problem conversion algorithms exist [57,58]. The modest predictive value of mental development assessment before the

2nd birthday for later cognitive status remains another concern [59].

Summary

Achieving a more uniformly defined outcome across studies, the possibility of obtaining longer-term outcome data, the exploration of interaction between MRS biomarkers and patient-level characteristics, and the possibility of sub-analyses, justify this proposed IPD meta-analysis.

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