



neonatal INTENSIVE CARE

Vol. 21 No. 4
July-August 2008

The Journal of Perinatology-Neonatology

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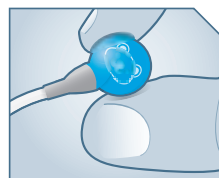
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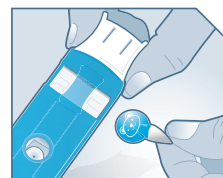
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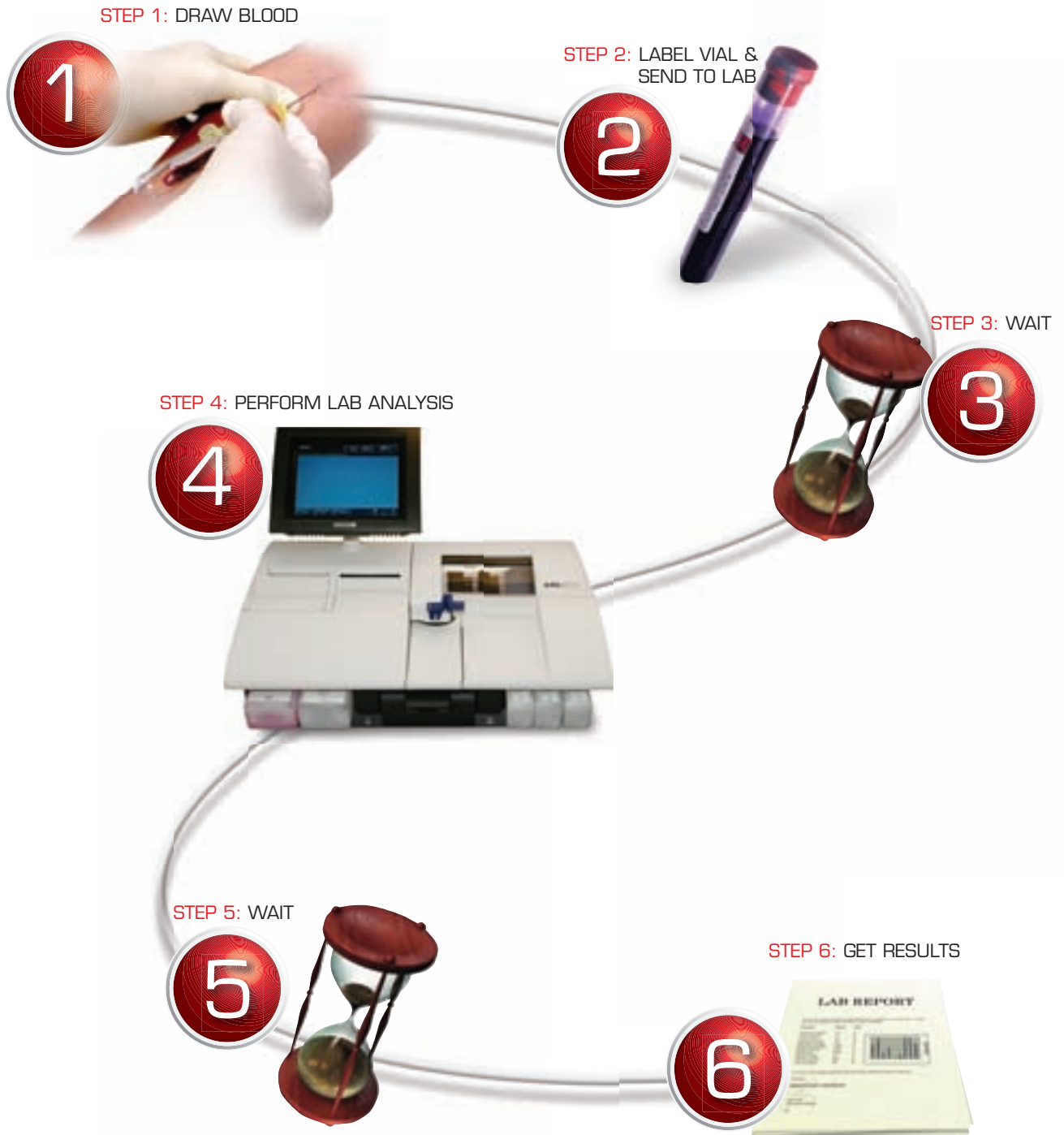
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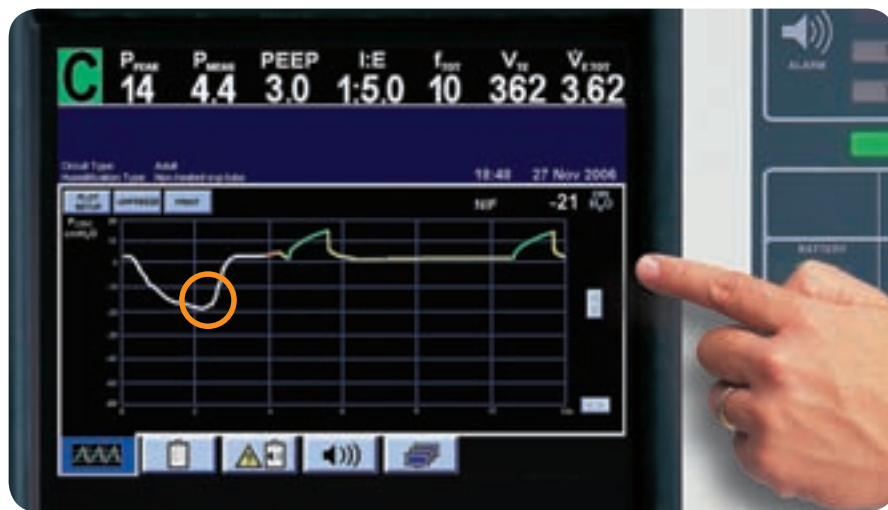
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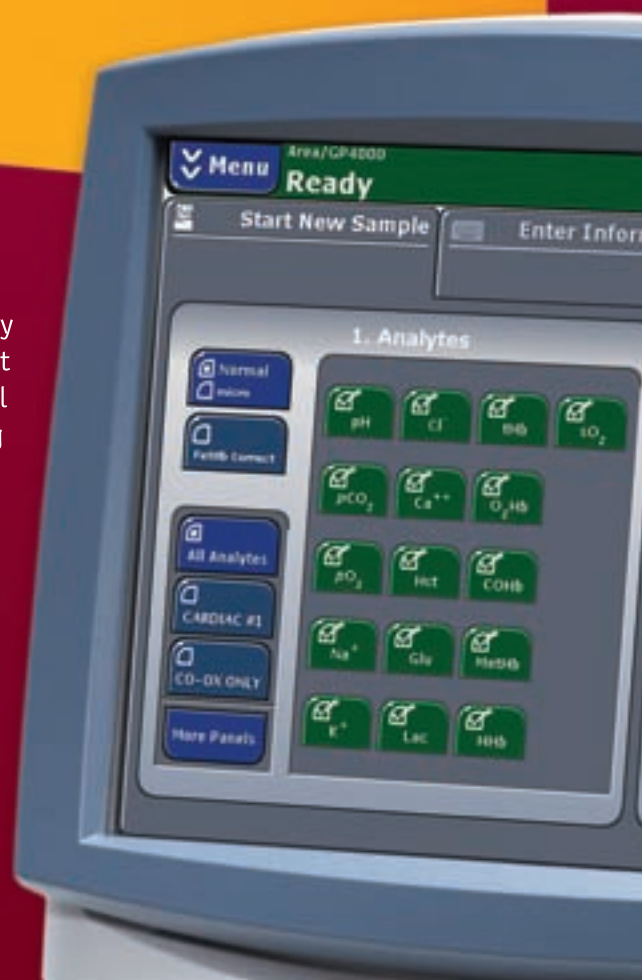
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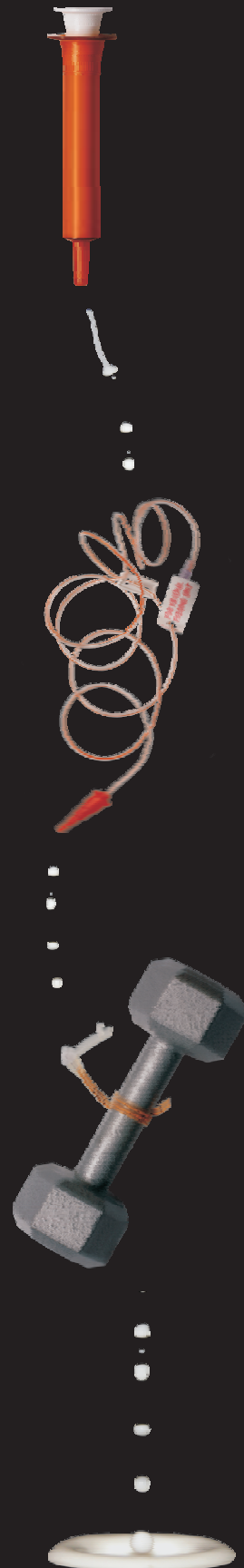
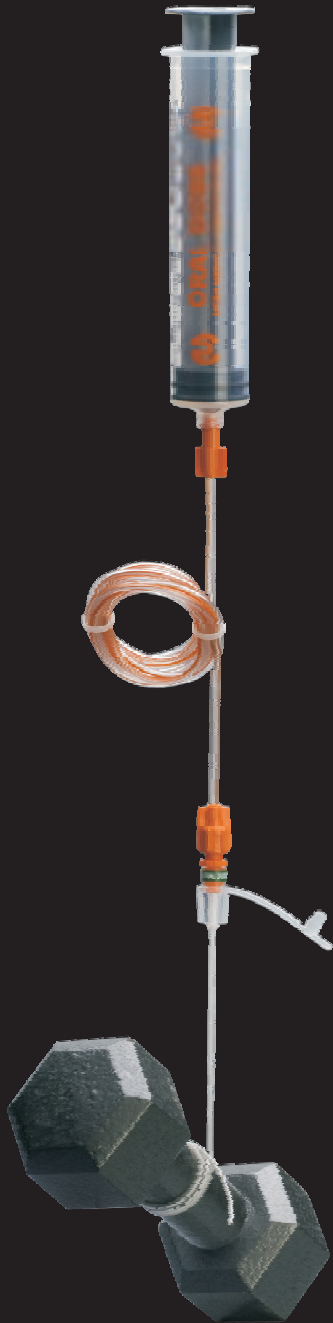
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Bilirubin Encephalopathy (Kernicterus): Have We Prevented This Problem?

Benamanahalli K. Rajegowda, MD; Muhammad Aslam, MD

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Hyperbilirubinemia is the cause of bilirubin encephalopathy in late-term and term infants, who are not closely monitored in the hospital or at home after discharge. Jaundice is the most common clinical sign observed in the immediate newborn period. This will not harm the majority of the newborns except some unfortunate infants who may be susceptible to high levels of serum bilirubin. The serum bilirubin levels depend on the rate at which it is produced, bilirubin binding capacity, unbound free bilirubin in the serum and dissociable factors for bilirubin binding. The unbound bilirubin may play a role in accelerating the risk of kernicterus by crossing the blood brain barrier. Unfortunately the measurement of unbound bilirubin is difficult and not used widely in clinical practice. Instead total and indirect bilirubin levels are measured and an indirect bilirubin level > 20-25 mg/dL is used for full term infants as a marker for kernicterus risk and treatment with either phototherapy or exchange transfusion. A lower level is used for late-term and extreme preterm infants.

Sixty to 70% of newborns are routinely jaundiced from day two to through first week of life. Almost all of them belong to clinically evident physiological jaundice category requiring observation only. Jaundice apparent within 24 hours of life or with rise of serum bilirubin level at about 12.8 mg/dL in 24-48 hours, is not physiologic and warrants a thorough evaluation for etiological factors. In the 1960s and 1970s length of stay for vaginal and cesarean births was 5 days and 7 days respectively. The number of days of stay was reduced to 3 days and 5 days in 1970s and 1980s, and to 2 days and 3 days in 1990s. When infants stayed longer in the hospital nursery, the medical and nursing staff had the opportunity to observe them for jaundice during 3-5 days of life when they were at highest risk for hyperbilirubinemia. The current emphasis of discharging home all well infants on the second day of life does not allow the former practice of observing these infants, particularly for late jaundice. Failed opportunities on follow-up of infants for bilirubin measurement have resulted in an increase in the incidence of reports on kernicterus. Early discharges are economical due to the recent insurance regulations that limit the hospitalization days, laboratory work-up and early follow-up visits to the pediatricians.

Bilirubin encephalopathy is a preventable condition but once clinical signs and symptoms develop, either the infant dies or survives with multiple neurodevelopmental disabilities, including deafness. In the 1990s several case reports of kernicterus were reported due to early discharges from the hospital. Some of these cases have resulted in medical litigation. This condition was alerted by American Academy of Pediatrics (AAP), Center for Disease Control (CDC) and even the Joint Commission on Accreditation of Hospitals (JCAHO) in 1990s. In view of concerns about increasing incidence of bilirubin encephalopathy and related morbidities, Joint Commission issued statements in 2001 and reiterated it in 2006 to all health care organizations stating that kernicterus is "a sentinel event" that threatens healthy newborns, and recommended to the hospitals to review and make improvement to their current patient care practices for the identification and management of jaundice and hyperbilirubinemia. The academy reported reasons and CDC issued guidelines why kernicterus is on the rise including early discharges, unprepared mother and baby going home, inadequate supervision of infant's health after discharge, missed opportunities for jaundice evaluation and breast-feeding assessment, teen age mothers, infection, as well as neglect and abuse.



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AAP and CDC came out with guidelines to assess risk factors for jaundice and kernicterus in late 1990s:

1. Assess and evaluate all newborns for jaundice including blood group, coombs and Rh factor.
2. Pre-discharge bilirubin and use of percentile based bilirubin normograms to predict the risk and follow-up of serum bilirubin. Physical evaluation by looking at the infant's color may be deceptive and measurement of serum bilirubin levels is the best practice.
3. The magnitude of the risk depends on serum bilirubin levels, age of the infant, and gestational age of the infant.
4. Use of non-invasive transcutaneous bilirubin monitoring in the hospital, outpatient clinics and even at home as a screening tool, which will reduce the number of invasive procedures.
5. The measurement of end tidal carbon monoxide (CO) which helps detect an infant with prediction of bilirubin production by measuring exhaled CO. It is used as an end point of bilirubin production to identify risk for hemolysis.
6. The liberal use of guidelines for phototherapy when bilirubin is rising in non-hemolytic cases. This has drastically reduced not only readmission after discharge but also the need for exchange transfusion.
7. Follow-up of all newborns within 3-5 days after discharge by health care staff.
8. Those with risk factors identified should be seen within 24-48 hours with bilirubin evaluation either by transcutaneous bilirubin monitoring or by measuring serum bilirubin in the laboratory. The risk factors that are identified are;
 - a. Infant with ABO and Rh incompatibility with or without positive coombs
 - b. Polycythemia
 - c. Late-term infants
 - d. Previous sibling with jaundice
 - e. Exclusive breast-feeding
 - f. Infant of diabetic mothers
 - g. Extra-collection of blood like cephalhemtoma, ecchymosis, contusion, bruise and swallowed blood
 - h. Serum bilirubin levels of 12.8 mg/dL or above without any incompatibly within 24-48 hrs of life.

In the hospital where we have worked as neonatologists since early 1970s, we have routinely ordered cord blood and mother's blood for group, type and coombs, bilirubin estimation at 48-72 hours of life regardless of clinical jaundice and serological test for syphilis. In addition, infants were examined by resident house staff and for those with jaundice additional serum bilirubin levels were done. Such infants stayed longer in the hospital for close observation until 1994 when discharge home at 24-48 hours of life became routine practice.

At that time there was no Occupational Safety and Health Administration (OSHA) regulation, the infant's blood work drawn by a physician and the bilirubin was estimated at bedside by using a bilirubin spectrophotometer, thereby avoiding discharge of the babies with higher levels; infants with borderline levels were seen on the same or subsequent day in a separate bilirubin clinic without going through registration. Now with the OSHA regulation and insurance control it became impossible to continue the same practice. Parents are given instructions and appointments to go to the clinic to wait in the outpatient for registration, blood drawing and to come back and be seen by the pediatrician, all of which may take 3-4 hours in the hospital. When communication is established well these babies can be managed expeditiously and be admitted for phototherapy when necessary. With our experience we have not seen a case of bilirubin encephalopathy since the early 1980s. It is very important not only to identify infants at risk but also to provide proper education to the mother on jaundice. Follow-up assessment with bilirubin levels, use of phototherapy for those with high levels using AAP guidelines, and very rarely exchange transfusion will definitely prevent this preventable disastrous condition. Even today the most common admission after discharge from the hospital for a newborn is hyperbilirubinemia. With appropriate follow up, the incidence and reporting of kernicterus is very rare and may be a thing of the past. One should follow the AAP guidelines and of course the JCAHO standards for newborns discharged home from the hospital.



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We welcome all electronic submissions, including original papers, works in progress, and guest commentaries, as well product releases, company profiles, and more. See **www.nicmag.ca** for more info.

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News

□ July-August 2008

TAKING YOUR CHANCES

Researchers say they've developed a new way to help doctors and parents make decisions about how much treatment to give extremely low birth weight infants. The New York Times reports that the new method uses an online calculator that factors in traits like birth weight and sex and generating statistics on the chances of the baby's survival and the likelihood of disabilities (see nichd.nih.gov/neonatalestimates). The risk estimate used for the calculation is based on data from similar infants in a large study. ELBW babies with the greatest advantages are singletons or babies whose mothers were given steroids before birth to help the fetal lungs to mature. Girls also have a better chance, though no one knows why. In any case, the above factors were said to be as good as being a week older; that is, a girl at 23 weeks could be as strong as a boy at 24. The study and the calculator were part of an effort to give doctors and parents more solid evidence to make decisions. Plugging numbers into the calculator shows that two infants with the same gestational age, the usual criterion to decide treatment, can have quite different odds of survival and disability. For instance, a 24-week-old two-pound male twin whose mother did not receive steroids has survival odds of 69% and a 50% chance of having a severe impairment. A female twin the same age and weight has survival odds of 86% and a 23% chance of severe impairment. The study included 4,446 infants born at 22 to 25 weeks at 19 hospitals in the Neonatal Research Network; 744, generally the smallest and most premature, did not receive intensive care, and these died. The babies were assessed at birth, and the survivors were examined again shortly before turning two. Overall, half the infants died, half the survivors had neurological impairments, and half the impairments were severe. Many survivors spent months in the hospital, at a typical cost of \$3,400 a day. The researchers estimated that if all babies born at 22 to 23 weeks received intensive care, for every 100 infants treated there would be 1,749 extra hospital days and zero to nine additional survivors, with zero to three having no impairment. Reported in the New York Times, April 17.

HUNGRY HEART

The BBC reports that babies whose mothers develop preeclampsia in pregnancy may be at greater risk of cardiovascular disease in later life, according to a study by the University of Cambridge, which looked at pregnancies at high altitude, where oxygen is restricted. Researchers observed changes in the way the fetus grew when oxygen was restricted, and alterations in the way key systems in the body developed. Oxygen restriction, it was posited, could cause cardiovascular problems later in life. The researchers said their work on animals suggested it may be possible to reverse the damage caused by a lack of oxygen by boosting beneficial nutrients such as Vitamins C and E, selenium and lycopene in the mother's diet, and that this may halt the development of heart disease at its origin. However, the use of antioxidants was discouraged, because it's believed that a small amount of oxidant stress may be necessary for a healthy pregnancy.

BEDLESS

The Vancouver Sun reported that a record number of high-risk, expectant women were being sent across the border to Washington state or to Alberta, CA in the past year because of a shortage of neonatal intensive care beds, doctors and nurses. The government spent \$8 million in a one year period to send 78 women to Washington, where the medical costs are much higher. Another 33 women went to Alberta. The conditions in British Columbia, besides the aforementioned shortages, are said to be exacerbated by the increasing number of preemies and by women delaying childbirth

and relying on fertility drugs to get pregnant, which means they are more likely to have twins or triplets. Other factors putting pressure on the system are medical problems caused by obesity and associated chronic diseases such as diabetes. Adding to the problem is the solution to the problem, in a way: that more babies are surviving at an extremely premature age. Other Canadian regions are also sending their pregnant moms south, at a higher cost to the Canadian healthcare system. The Canadian government spent \$12 million over the past two years on neonatal care in the US. While British Columbia gets a 10% discount from Washington state hospitals, per diem costs in the US are three times as high as in Canada, \$5,400 in the US vs \$1,700 in BC, and air ambulance service costs up to \$10,000 per transfer. Reported by Pamela Fayerman in the Vancouver Sun.

TWO-FACED

A baby was born with two faces in the northern Indian village of Saini, near New Delhi. The baby has two noses, two pairs of lips and two pairs of eyes, but only two ears. Hundreds of pilgrims have visited the baby, who is being worshipped as the reincarnation of a Hindu goddess, and the impoverished parents are accepting donations from people who come to touch the kid's feet. The baby was born with a rare condition called craniofacial duplication. Doctors said she appeared to be in good health, and is leading a normal life with no breathing difficulties. They were initially uncertain whether the baby would have normal functions but say so far she is fine and eating from both of her mouths. She also opens and shuts all four eyes at the same time. Her arrival comes two years after the birth of an eight-limbed girl in Bihar who was supposed to be a reincarnation of the multi-armed god Vishnu. For pictures, see The Daily Mail website of April 9. Reported by The Daily Mail.

NO IMPROVEMENT

A major study in England, Epicure 2, has found no significant improvement in the survival rate for very premature babies over the last 10 years. Babies born above 24 and 25 weeks gestation were more likely to live than in the past, but there was no significant improvement in survival of babies born before 24 weeks. Epicure 2 analyzed all severely premature births in England in 2006 and compared their survival outcomes with those born in 1995. There were 1,300 live births before 26 weeks gestation, of whom 952 babies survived long enough to be admitted into neonatal intensive care. Of this group 52% survived compared with 40% in 1995, with significant improvements above 24 weeks gestation. There has been a statistically significant increase in survival at 24 and 25 weeks, but not at 23 weeks. Forty per cent of babies born at 23 weeks die in the labor ward, the study found. Severely premature babies who do survive very often have long term problems stemming from the lack of lung and brain development. The research said there has been no reduction in the proportion of infants who have such problems over the last decade. Reported by the BBC, via the internet.

INTO THE BREECH

Breech delivery may be an inherited trait, according to a Norway study of more than 2 million birth records spanning 37 years. Men and women who were breech babies were found to be more than twice as likely to have breech babies. Men delivered by breech seem to carry genes for breech delivery that they pass on to their offspring, and women may carry genes for physical characteristics that can lead to breech birth, such as

pelvic size or uterine malformations. As such, the study recommended that healthcare practitioners ask women if they or their spouses were breech births, and pay close attention as the pregnancy progresses.

ENDING HIV

Appropriate treatment can all but eradicate the risk that a pregnant woman with HIV will pass the virus to her child, according to a report by the BBC. Data on 5,151 HIV pregnancies in the UK and Ireland between 2000 and 2006 found an infant infection rate of just 1.2% where preventative steps were taken. Before effective drug therapy, the infant infection rate was over 20%. Researchers at University College London said it was the first time such low rates of infection had been observed at a population level. Most HIV positive women in the UK now take a combination of antiretroviral therapy (ART) drugs during pregnancy. A cesarean section delivery reduces the risk of infection to the child, but the latest study showed that in many cases the drugs are so effective that a normal delivery is possible. Transmission rates for women on ART for at least the last 14 days of pregnancy were 0.8%, regardless of the type of delivery. The researchers said the key to success was that most women in the UK and Ireland now accepted antenatal testing for HIV.

NO CHANGE

The BBC reports that babies born at 23 weeks or earlier are no more likely to survive than they were a decade ago, according to a study at the University of Leicester. The study was published in response to a bid by a British member of parliament to reduce abortion limits. Backers of the reduction claimed that improvements in the treatment available for premature babies mean it shouldn't remain at 24 weeks. The study noted improvement in survival for babies born at 24 and 25 weeks, from 24 to 41% and 52 to 63% respectively. However, at 22 and 23 weeks, 58% died in the delivery room in 1994-9 and 63% in 2000-2005. The study covered 16 hospitals, and covered babies who died on the labor ward as well as in the NICU. The researchers said it appeared that the limits of viability for the survival of premature babies had been reached. The findings are similar to results from the decade-long Epicure 2 study, published last month, which also showed improved survival rates for babies born at 24 and 25 weeks, but not for those born earlier. A government spokesperson noted that this confirmed no evidence of a significant improvement in the survival of preterm infants below 24 weeks gestation in the UK since the upper time limit for abortion was reduced to 24 weeks in 1990.

SAFE OR SUCKERS?

Researchers writing in the journal BJOG said there may be serious risks for babies when mothers who chose a home birth are transferred to hospital. A team at the National Collaborating Centre for Women's and Children's Health looked at data on all home births in England and Wales between 1994 and 2003 and said that while the death rate for births at home was low, if the mother transferred to hospital the risk of losing the baby soared to eight times above average. So what does this really imply? Home birth advocates say the study does not consider women who develop problems in hospital and that the deaths of babies numbered just 65, from 10,752 cases. The death rate among babies whose mothers planned and gave birth at home was lower than the average for all births taken together, including those in a hospital, midwife-led unit, as well as at home. But when complications arose, the risk of losing a baby was nearly

eight times higher than the national average and 12 times higher than had the mother given birth at home. As such, the study's authors said that women will either have a swell outcome or a disaster. However, the authors conceded that the actual data about transfers was taken from a multitude of studies and was inconsistent. "Transfers" did not refer exclusively to women who were rushed to hospital in labor, but included any woman who, having initially chosen a home birth at 12 weeks, ended up giving birth in hospital. The reasons for switching to hospital birth also weren't given. The National Childbirth Trust said the study was flawed, and the Royal College of Midwives noted that of course transfers would inherently result in complications, since that in fact would be the reason for the transfer to a hospital.

HOPELESS HELP

Perinatal hospices can help support families with a terminal prenatal diagnosis, according to a report on MSNBC. In response to the growing number of families struggling with difficult choices after getting the worst news about their baby, about 55 perinatal hospice programs have been set up in the US. (For more contact perinatalhospice.org.) The programs provide medical and emotional support for families with a terminal prenatal diagnosis who decide to continue the pregnancy. Current studies don't follow how many families in the US choose to continue pregnancy after receiving a terminal prenatal diagnosis, but anecdotal evidence says it's about 10-20%. A British study in 2007 found that about 40% of families with a terminal prenatal diagnosis decided to continue the pregnancy when perinatal hospice was offered. Who would make such a choice? According to hospice personnel, some parents say it may be the only time they'll get to be with that child, while other families may have religious reasons. Sometimes parents may hold out a hope that somehow the terminal diagnosis was wrong, and others don't want to be the one who decides when their baby dies. According to a Seattle social worker involved in one project, when the child dies, staff can help parents make their memories tangible by cutting a lock of their baby's hair or making hand impressions. Or, some staff have counseled parents who want to hold their deceased baby that bathing it in warm water can help stave off rigor mortis for a while. Reported by Linda Dahlstrom, MSNBC.com health editor.

COME ON, BABY

A midwife who never formally studied nursing, Ina May Gaskin, of Summertown, TN, has a film in the works for moms who want to consider the midwifery option: a movie called "The Orgasmic Birth." In an Associated Press interview, Gaskin said the term wasn't meant to be a metaphor, and that under the right circumstances, women experience a sort of birth ecstasy. "I mean, it's not a guarantee," she said, "but it's a possibility... It's the only way I can think to market it to this generation." Gaskin has been said to help bring home birth and lay midwifery back from the brink of extinction in the US. In 1975, Gaskin published "Spiritual Midwifery," which included birth stories and a primer on delivering babies. Her book has sold 750,000 copies, has been translated into four languages. She promoted the idea that a woman's state of mind will influence how easy her birth is and encouraged unorthodox ways to improve the woman's experience, like encouraging her to make out with her husband during labor. At the same time, she kept detailed records of each birth, providing her commune, The Farm, with statistics that would prove important in the debate over the

safety of out-of-hospital births. She has tried to widen the reach of her message by airing natural birth videos from The Farm on television, though she noted that TV stations rarely have run them, calling them too graphic. "I started to think I should put them on YouTube," Gaskin said. Information for the above report is © 2007, The Associated Press.

BABY MAMA

The Wall Street Journal reports on surrogacy in light of more media exposure like the movie Baby Mama. The Journal's light, jocular, dismissive, shall we say, elitist-toned editorial, says, basically, that surrogacy is here to stay. Perhaps most revealing in the editorial is that most IPs, or intended parents (a sneaky euphemism not unlike, say, the zombieish expression, the unborn) are in their mid twenties. The reason for surrogacy's popularity, the Journal suggests, is that it's quicker than adoption, and the easier route for gays and lesbians. According to WSJ, The Society for Assisted Reproductive Technology has tracked a 30% increase over the past three years, and "industry experts" – whoever they might be, "estimate that there are as many as 1,000 surrogate births a year." Other advantages to surrogacy: IPs get to choose their "carrier, and get to vicariously enjoy the pregnancy, attending doctor's appointments, shopping for maternity clothes with the carrier, and being present at the birth." But, the Journal piece cautions, "that feeling of control... can be illusory. IPs might hold the checkbook, but the surrogate has the baby." And contracts limiting surrogate behavior may be unenforceable! WSJ concludes, "As entertaining as class war may be, it's the "Mommy Wars" angle that has got the media salivating." So, if you're tired of the "entertaining" class war, as the Journal seems to suggest, you can tune in to the MSM (mainstream media) of your choice to learn all about people with money buying bodies to buy babies. The original article about surrogacy, by Cheryl Miller, appeared on page W11 in the April 25 issue of The Wall Street Journal.

KICKED OUT OF BED

Los Angeles County officials urged parents to avoid sleeping in the same bed as their infant children and, alarmingly, called the practice a "potentially lethal act." [NB: this would, perforce, include *all* acts.] According to the Los Angeles Times, LA County statistics show that 44 infants died after they slept next to an adult in 2006, a 76% increase over the previous year and the county's highest number of deaths associated with co-sleeping. The Times noted that the pronouncement was criticized by those who promote the benefits of co-sleeping, or by those who've actually done it. The American Academy of Pediatrics has said that bed-sharing leaves babies vulnerable to being crushed or suffocated, and may increase their risk of sudden infant death syndrome, and said that the safest place for infants to sleep is in the same room as the mother, but in their own crib. As evidence, LA officials relied on a study in which half of 119 infants who died suddenly and unexpectedly during a four-year period in the St. Louis area did so while sleeping with someone else. A 2000 survey of 8,500 people found that 12.8% of infants regularly shared an adult bed at night. According to Dr Robert Sears, author of "The Baby Sleep Book," as quoted in the Times, "So many babies sleep so much better nestled up to a parent that many parents are doing it to get a better night's sleep. Parents aren't going to stop doing it just because the government tells them what kind of parent they should be." As proof of the danger, a spokesperson for the County's Dept of Children and Family Services noted an instance where "a father sitting on a chair fell asleep with his infant child sleeping on his

chest; he awoke to find that the infant had slipped in between the armrest and seat cushion and died." So there's your solid evidence. Reported in the Los Angeles Times, April 25.

STILL TOO LOW

The rising number of low birthweight babies is still a major problem, according to "Trends in Infancy/Early Childhood and Middle Childhood Well-Being, 1994-2006" from the Foundation for Child Development Child and Youth Well-Being Index (CWI) Project. The project analyzed 25 key national indicators spread across 6 quality of life domains, from 1994 to 2002. Overall improvements occurred across all age groups, but improving health indicators were skewed because they were dragged down by rising obesity rates and the rising number of low birthweight babies. Reasons for low birthweight were posited as women having babies later in life and the increasing use of fertility treatment which increases multiple, lower weight births. The original news item for this summary appears on the website of Medical News Today, © Medical News Today, Catharine Paddock, PhD.

DUMB FROM DIET?

An infant's future mental abilities and susceptibility to mental illness can be permanently altered by dietary changes in early life, according to information presented at the International Symposium on Early Nutrition Programming in Granada, Spain. Evidence suggests that changes in early diet can effect brain structure, verbal IQ, eyesight, appetite regulation and neurodevelopmental outcome.

POOR PERCENTAGES

Only a quarter of 68 countries are reaching a millenium goal of improvements in maternal and child mortality, according to an article in The Lancet. The goals were established by members of the United Nations as a standard to achieve by 2015. Sixteen countries were on track, including China, the largest success story. Maternal mortality was high or very high in 56 of the 68 countries. Immunization and antenatal care had better coverage than emergency care at birth and the care of ill newborns and children. Reported by Anna Sophia McKenney, Medical News Today.

PTERODACTYL PLACENTAS

Researchers at the Stanford University School of Medicine have uncovered the first clues about the anthropology of the placenta. Evidence shows that it evolved from simpler tissue attached to the inside of eggshells and enabled the embryos of birds and reptiles to get oxygen. The placenta is the only organ to develop in adulthood and is the only one with a defined end date, which is what made it of interest to researchers, and a biological curiosity. Recent research shows that it could be a key barrier in preventing or allowing molecules to pass to the unborn baby. The researchers addressed the story of the placenta's evolution by determining which genes are active in its cells throughout pregnancy in mice. The placenta, they discovered, develops in two stages. In the first, from the beginning of pregnancy through mid-gestation, the placental cells activate genes that mammals have in common with birds and reptiles. This suggests that the placenta initially evolved through repurposing genes the early mammals inherited from their immediate ancestors when they arose more than 120 million years ago. In the second stage, cells of the mammalian placenta switch to a new group of species-specific genes. Mice activate newly evolved mouse genes and humans activate

human genes. In other words, mammals develop the kinds of placentas they need, depending on the length of the gestation period. Despite wide variations in placental life-span, so to speak, the placenta tissue is the same. So why is this important? Research demonstrates that the placenta may contribute to triggering the onset of maternal labor, and is suspected to be involved in pre-eclampsia.

CANCER TREATMENT OK

Pregnant breast cancer patients can be treated like non-pregnant patients, according to the results of a study at the University of Frankfurt. Information was collected on 122 pregnant patients diagnosed with breast cancer between over a five year period and analyzed for fetal outcome four weeks after delivery, maternal outcome of pregnancy, stage and biological characteristics of the breast cancer, breast cancer therapy, sensitivity and specificity of diagnostic procedures, outcome of the child five years later, and outcome of the breast cancer five years after diagnosis. Thirty-three percent of the participants received surgery only, 43% were treated by surgery and chemotherapy, 5.4% by chemotherapy alone, and 2.7% had no treatment at all. The median time for delivery was 36 weeks, just slightly earlier than normal. Although there were some health problems among the newborn babies, they were generally minor, and the fetal outcome in babies whose mothers received chemotherapy was not different to those whose mothers did not.

THEY BECOME WHAT YOU EAT

A baby's sex is linked to it's mother's diet around the time of conception, and may explain why fewer boys are born in the industrialized world, according to a study by the Universities of Exeter and Oxford. Researchers found a strong link between the consumption of a high energy diet around the time of conception and giving birth to sons. Researchers investigated the diets of 740 first time mothers living in the UK who did not know the sex of their unborn child. The participants gave information about their eating habits before and around conception and during the early months of their pregnancy. Results revealed that 56% of the women in the highest energy intake group had sons, compared with 45% of the women in the lowest energy intake group. Women who had sons not only had higher energy diets but they were also more likely to have eaten a wider range and higher amount of nutrients such as potassium, calcium, plus vitamins C, E and B12. There was also a strong association between eating breakfast cereals and having sons. Recent studies have shown that average energy intake in the developed world has fallen, and many people are skipping breakfast. For example, 75% of adults in the US ate breakfast in '91, compared to 86% in '65. Another factor is dieting by first world women. It's been long known that many animals produce more sons when resources are abundant or when the mother gets the best food. The above summary is based on an original article by Catharine Paddock, PhD, Medical News Today.

GENES AND BOFS

Researchers at Boston University School of Medicine have discovered that deletions or mutations within the TFAP2A gene result in Branchio-Oculo-Facial syndrome, which is characterized by specific skin anomalies involving the neck and behind the ear, eye abnormalities, a typical facial appearance, and frequently cleft lip and palate. Researchers examined an affected mother and son and two sporadic BOFS cases and

found a small deletion on chromosome 6 in the mother and son. Sequencing of genes revealed mutations clustered in the basic region of the DNA-binding domain of the TFAP2A gene in 4 sporadic BOFS patients. The discovery should lead to more precise diagnostic testing, enable prenatal diagnosis, and suggest directions for new research.

OVERWHELMED AND BUMMED

Moms-to-be may idealize a happy time with their new babies, but wind up feeling depressed and overwhelmed, according to a University of New Hampshire study, "Non-Pharmacological Treatments for Depression in New Mothers." Postpartum depression affects up to 20% of pregnant women and new mothers, and in high-risk populations, that percentage may climb to 40. The monograph suggest alternatives to drugs, which include omega-3 fatty acids, bright light therapy, exercise, social support, psychotherapy, and the use of St John's Wort.

CARD SHARPS

An Austin, TX-based company, AHCO Direct, has been accused by the Texas attorney general's office of selling phony discount health cards to uninsured pregnant women, according to a report in the Austin-American Statesman. The newspaper said that AHCO claimed its MaternityCard was accepted by many healthcare providers and that it covered up to 60% of prenatal care. The lawsuit said the card costs \$199 to enroll and \$99 a month, and it was advertised on Google. According to the lawsuit, members said that when they went to use the card, the providers told them it would not be accepted, and that when the women attempted to cancel the card, they were charged a \$250 cancellation fee. According to the state attorney general's office, 140 people complained to the office and the Better Business Bureau.

BETTER LUCK FOR BABES

Premature infants are more likely to survive and do so without a disability if they're female, from a single birth of a higher birth weight, and if the mom has received steroids, according to a study by the NICHD. Researchers reiterated what's been deemed as fairly common knowledge: that the closer a baby was to the 25th week, the better its chances. But they didn't want to rely on gestational age alone, which isn't always so easy to calculate. They used standardized measures of mental development, vision and hearing to assess the health status of surviving infants when the infants were from 18 to 22 months corrected age, the age they would have been had they been born full term. Twenty-one percent lived and did not have a disability while the remainder died or experienced some degree of disability. The study involved only infants born at level III neonatal intensive care facilities and its findings may not apply to infants born at level I and level II facilities and is said to provide the largest source of information on the survival of extremely low birth-weight infants. The NICHD is making the study's information available to parents and physicians on the NICHD Web site, http://www.nichd.nih.gov/about/org/cdbpm/pp/prog_epbo. Doctors and parents can type certain key characteristics about a particular infant into a form, and a program will provide statistics about survival and disability, based on the experiences of the 4,000 infants in the network.

DRUGS AND MONEY

RSV accounts for up to 125,000 infant hospitalizations, and about 500 infant deaths every year. For lack of a vaccine,

doctors turn to palivizumab (Synagis), the antibody developed by MedImmune, but the cost can be up to \$6,000 for five treatments, and researchers are divided over its use and benefits, according to Laura Landro, writing in the Wall Street Journal. The drug has been shown to reduce hospitalizations by 50%, but doesn't reduce mortality from RSV, and when researchers look strictly at cost-effectiveness, wider use is hard to justify, according to the Journal. The link between RSV and subsequent risk of asthma is also tenuous. Insurance companies limit payments for Synagis to preemies based on guidelines from the American Academy of Pediatrics, guidelines that were made more restrictive five years ago. Some physicians and researchers say there's considerable controversy over how broadly the drug should be used. According to H. Cody Meissner of Tufts Medical Center, quoted in the WSJ, "We have to decide how much we want to spend to reduce hospitalizations by 50% when we don't have enough money in most states to send children to the dentist to get their teeth examined or to pay for vaccines and immunizations." Current AAP guidelines recommend that Synagis be used for infants born at 32 weeks or younger, for most cases. Of about 225,000 infants born annually at 32 to 35 weeks, only about 20% now qualify for Synagis. In many cases insurers won't pay for it because the children don't meet the age and risk guidelines. MedImmune, now AstraZeneca, says the Synagis price reflects the complexity of developing and manufacturing biological products. Recently, the company sought FDA clearance for a newer version of the drug, motavizumab, which may be more effective in preventing disease, though it may have some adverse side effects. Synagis generated \$1.15 billion in sales last year, but revenue growth has slowed, and an easing of the guidelines could sharply increase sales. A company review of 382 pediatricians found that infants born between 32 and 35 weeks who were identified as candidates for Synagis but didn't receive it because of insurance denials had an RSV-infection rate of 8.3%, three times the rate of infants doctors didn't select to receive the drug. The CDC is investigating the parameters of Synagis utilization. Researchers are still saying that without solid evidence about long-term health effects, the benefits for some children are still outweighed by the costs of administering Synagis to all the infants that qualify, even under the current guidelines. Reported in the Wall Street Journal, April 16.

PRODUCTS

SEARCH ME

SearchMedica.com, a search engine for medical professionals, unveiled six new searchable disease categories on its site, including respiratory diseases and pediatrics. Medical professionals can search the site for clinical information and register to receive updates, as well as provide feedback to the site. SearchMedica provides free, open access to its contents, including articles from journals and associations, and it can index select clinical info. Its categories are based on the MeSH library and include cardiovascular, diabetes/endocrine, infectious, musculoskeletal, cancer/hemic, pediatric, mental/nervous system and respiratory disorders. The site was recently acknowledged for its outstanding user experience as a recipient of a 2007 Standard of Excellence WebAward. Contact searchmedica.com.

KEEP IN TOUCH

Children's Medical Ventures (ChMV), a subsidiary of

Respironics, Inc, has introduced two new programs for NICU professionals aimed at improving developmental outcomes for infants and improving communication within caregiving teams. Touch: The Universal Language supports developmentally appropriate handling and parental involvement to promote parent-infant attachment from the time a baby is born through discharge from the hospital. The Looking Glass: Reflections on Culturally Responsive Care focuses on assisting NICU healthcare professionals to communicate with people of all cultures and to understand how backgrounds influence perceptions, attitudes and interaction styles. Touch: The Universal Language offers two different workshops depending on facility needs. Family Attachment through Touch is a half-day program that emphasizes the importance of parent-infant attachment and bonding at the bedside. This workshop focuses on the development and implementation of ideas and strategies, including hand containment, kangaroo care and other routine caregiving opportunities, that support parent confidence and competence as their child develops. Touch: The Art and Science of Infant Handling is a full-day program that emphasizes the importance of the caregiver's role in maximizing opportunities for parents to provide comfort, identify infant behavior cues and understand the infant's developing brain and sensory system. The Looking Glass: Reflections on Culturally Responsive Care is a four-hour workshop that examines how individual perceptions and cultural, ethnic and linguistic heritage influence daily interactions, personal opinions and attitudes when meeting new people. It teaches NICU professionals to identify cultural differences in their unique setting, respond appropriately and positively to patient family members and identify opportunities for culturally responsive enhancement. Touch and The Looking Glass are part of the Education line of products from Children's Medical Ventures that includes Integrating Developmental Care Into Feeding Practice, Jaundice Management: Ensuring Optimal Outcomes, Preemie-for-a-Day, The Technology Dependent Infant, The Wee Care Program, and The Yellow Brick Road: Supporting the Hospitalized Infant and Family Through Their Journey. For additional information on these programs and other staff educational opportunities, visit www.childmed.com.

NEW DISCOVERIES

Discovery Laboratories, Inc announced that new data supporting potential unique properties of its novel KL-4 Surfactant Replacement Technology (SRT) were presented at the Pediatric Academic Societies Annual Meeting. Preclinical studies were presented demonstrating that KL-4 does not induce an immune response known as anaphylaxis and that Surfaxin (lucinactant) displays antimicrobial properties. The Pediatric Academic Societies (PAS) Annual Meeting is internationally recognized as the largest, most relevant medical meeting dedicated to pediatric research. One study assessed the potential for KL-4, a 21 amino acid peptide that is structurally similar to pulmonary surfactant protein B (SP-B), to induce anaphylaxis. In this study, a well-established animal model was used to test whether KL-4 would trigger anaphylaxis. The data showed that KL-4 did not induce active or passive anaphylaxis, even when the immune system was potentiated and sensitized. Another study presented at PAS investigated the antimicrobial properties of Surfaxin. In that study, gram-positive and gram-negative bacterial broth was mixed with Surfaxin and Survanta (beractant), as well as with saline, a negative control, and ciprofloxacin. While both Surfaxin and Survanta suppressed gram-positive bacterial growth, only Surfaxin suppressed gram-negative bacterial growth. Contact discoverylabs.com.

NOT TAKEN FOR GRANTED

Cardinal Health announced grants totaling \$1 million for new and innovative programs at 34 hospitals, health systems and community health clinics across the country. This program is the largest and first of its kind given by a health care company. Grants ranging from \$5,000 to \$50,000 will provide funding for programs that implement creative and replicable methods to improve the quality of patient care. Initiatives that received funding include a regional, collaborative program to reduce Methicillin-Resistant Staphylococcus Aureus in New Mexico, an initiative to create the largest national clinical outcomes database to define, measure and benchmark the highest standards of practice in anesthesiology, and a hospital in New Jersey using pre-labeled and pre-filled insulin pens to reduce errors in insulin administration. More than 700 hospitals applied for the grants. In choosing recipients, Cardinal Health looked for projects that respond to a clearly identified, high priority safety issue; collaborative programs; projects that apply new thinking and approaches to development of solutions; model programs that can be replicated at other organizations and demonstrable and sustainable measures to ensure that improvements last over time. Contact cadinalhealth.com or viasyshe.com.

FULL FEED FORMULA

Nestlé Nutrition is launching Good Start Premature 24, the first and only casein-free, premature infant formula made with 100% whey protein, partially hydrolyzed, designed to help accelerate a premature infant's advancement to full feeds, which is an important step toward going home from the NICU. Specifically created to provide complete nutrition for and to be sensitive to the special needs of the developing digestive tract of premature infants, Good Start Premature 24 formula provides a new feeding alternative for neonatologists. The Good Start nutritional profile formula is based on the recommendations of leading neonatal nutrition panels, and in accordance with the FDA's and Nestlé's own strict standards. The formula has 24 calories per fluid ounce, and has been clinically shown to promote growth in preterm infants. It provides not only complete nutritional support but also a calcium/phosphorous ratio specifically formulated for the needs of premature infants (1.9:1). Furthermore, it is the only preterm infant formula made with 100 percent whey protein, partially hydrolyzed and is designed to minimize curd formation during digestion, promote faster gastric emptying to help reduce the potential residuals available for reflux and spitting up, promote easy digestion, and be well tolerated and promote soft stools. All Good Start milk-based formulas have DHA & ARA to support brain and eye development. Whey protein is inherently a high quality protein, as measured by the biological value and protein efficiency ratio. It is casein-free, which makes it less likely to form curds and is designed to promote faster gastric emptying than intact casein-containing protein formulas. To help facilitate easy digestion, the 100% whey protein in Good Start is partially hydrolyzed to create smaller peptides. As such, the whey proteins are about one-tenth the median molecular weight of proteins in intact, non-hydrolyzed formulas. Contact nestleinfantnutrition.com.

BRIGHT FUTURE

Respironics, Inc and Children's Medical Ventures, a subsidiary of Respironics, Inc, announced the addition of the BiliTx Phototherapy System to its line of jaundice management products for use by clinicians in the NICU, PICU, Pediatrics and Well-Baby Nursery or by parents through home care providers. The BiliTx Phototherapy System features a highly compact

design, multiple therapy configurations and state-of-the-art blue LED photon engine light source that meets the American Association of Pediatrics' phototherapy guidelines. In the clinical setting, the BiliTx Phototherapy System can be configured as an overhead spotlight or connected to a fiber-optic panel in any hospital environment such as a crib or incubator. When used as an overhead spotlight, the unit's energy-efficient blue LED light source does not transfer heat to the baby unlike conventional halogen phototherapy devices that may require cooling fans and constant temperature regulation. The device's small size allows it to fit easily into a caregiver's hand, or into an over-the-shoulder sling while delivering treatment. BiliTx's fiber-optic panel and long cord length make it easy to nurse, hold and even carry the baby without interrupting the phototherapy. The BiliTx Phototherapy System was developed to eliminate the need for bulb replacement and reduce operating and maintenance costs. Its LED photon engine light source can last up to 50,000 hours and carries a warranty of 20,000 hours. By comparison, average halogen bulbs last approximately 285 hours and cost \$33 per bulb. Additionally, BiliTx requires no maintenance and uses approximately 90% less electricity than phototherapy systems utilizing halogen bulbs. The device weighs 2.86 lbs (1.3 kg) and is approximately the size of a beverage can at 6.3 inches tall by 2.9 inches wide. Contact childmed.com.

SIEMENS SAYS

Siemens Healthcare announced the expansion of clinical education offerings with the opening of the Siemens Healthcare Training Center at the University of Utah in Salt Lake City. Through an educational partnership with the University of Utah's Department of Radiology, under the direction of Dr Steve Stevens, Siemens can now offer even more opportunities to expand clinical experience and develop technical skills with Siemens latest imaging technologies. The learning environment at the University blends traditional and alternative learning methods to serve various learning styles and preferences. Imaging professionals can choose from virtual education, onsite and classroom training, workshops, fellowships, and printed self-study programs. In addition to the University of Utah training facility, classroom training is also offered at Siemens training sites. Siemens current portfolio of educational services and offerings can be viewed at medical.siemens.com/education. Donald Quinn has been appointed new head of the Diagnostics division of the Siemens Healthcare Sector. He succeeds Jim Reid-Anderson, who became the new CEO. Prior to his new job, Quinn served as executive vice president and chief customer officer of the Diagnostics division. He has worked for Abbott and Mallinckrodt. In other Siemens news, the company has been selected as the winner of the 2008 VHA Service Excellence Award for Supplier of the Year. VHA Inc is a national healthcare provider alliance of more than 1,400 not-for-profit hospitals and 21,000 non-acute healthcare organizations. Candidates for the award are recommended and selected based upon their sales interactions with VHA members, overall customer satisfaction, and responsiveness to VHA staff and members, as well as contract administration compliance criteria. Contact siemens.com.

CARING CARINA

Draeger Medical Systems, Inc announced that it has received 510(k) clearance from the FDA to market the Carina, Draeger's latest product in its ventilator product line to the US market. The Carina ventilator offers both invasive and noninvasive

capabilities in one device. Its latest technology known as "Synch Plus" will compensate for leakage and provide effective breath delivery. The Carina is well suited for the emergency room, general ward, ICU, or sub-acute facilities as it features an internal battery and can operate independent of a high pressure gas system. For patients who are mechanically ventilated long term, the Carina-home facilitates similar style ventilation technology for chronic patients outside of the hospital. The Carina-home has been in the US marketplace for over a year. For more see draeger.com.

SPOTLIGHT ON MONITORING

WHY USE TWO

Mercury Medical is pleased to introduce the New Improved StatCO₂ and Mini StatCO₂, disposable, colorimetric CO₂ Detectors. Verification with Enhanced economy, reliability, and convenience. StatCO₂ and Mini StatCO₂ provide breath to breath color changes from blue to yellow. The yellow color identifies the presence of CO₂ assisting in verifying proper ET tube placement, initially and throughout transport. The first CO₂ detectors to reliably confirm proper ET tube placement for 24 hours and in 100% humidity are now available with larger viewing windows for improved visibility of vivid color changes. The StatCO₂ or Mini StatCO₂ is conveniently ready for you when and where you need it. Just pull the activation strip. Significantly more economical to use than some other CO₂ detectors. Contact mercurymed.com.

MIGHTY MINI

Radiometer launched a new mini transcutaneous sensor for use in neonates. The new generation of transcutaneous sensors are significantly smaller and lighter than other sensors for neonates available in the market today. The new sensor, TinyTeddy, was developed in cooperation with nurses and physicians. Small, gentle and easy to use, the new sensor sets new standards for transcutaneous monitoring. Designed specially for premature babies, TinyTeddy provides constant monitoring of tcpO₂ and tcpCO₂ values and fast response times, reducing the need for frequent blood sampling. The sensor's small and soft fixation ring enables gentler continuous monitoring, minimizing discomfort for the neonate. The TinyTeddy sensor comes with an improved two-step membranizing tool that allows users to change membranes quickly and effortlessly, reducing the risk of error and saving time. Contact radiometeramerica.com/tinyteddy.

REVOLUTIONARY

The GEM Premier 4000 is the revolutionary whole blood analyzer that delivers immediate, reliable test results to the Neonatal Intensive Care Unit (NICU) and its tiny patients. The analyzer uses capillary-tube sampling to preserve neonatal blood volume. A single, self-contained reagent cartridge includes a broad range of analytes to offer a complete assessment from a single sample, including MethHb and bilirubin (in development). Easy-to-use, touch-screen displays help operators achieve accurate results with minimal effort, giving clinicians the flexibility to make their critical decisions and adjustments. The patented Intelligent Quality Management system, iQM, brings lab-quality results to the NICU, while automating quality control procedures and maintenance. The GEM Premier 4000 makes life easier in the NICU—it saves valuable time while improving patient care. Contact ilww.com.

ENHANCED ANALYSIS

Roche reports its study: Enhanced spectrophotometric analysis of hemoglobin and bilirubin helps ensure accuracy of results.

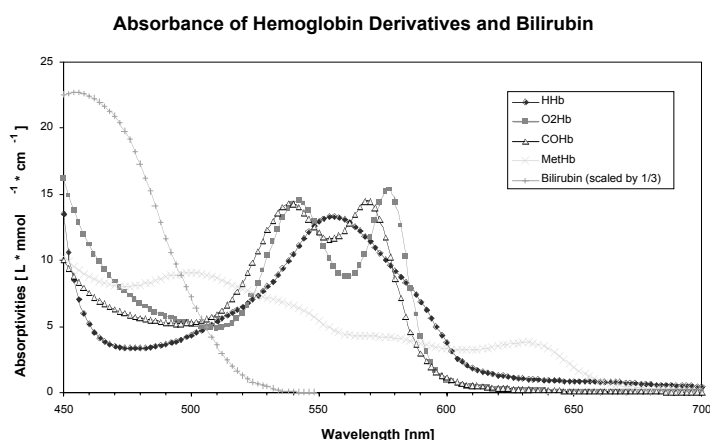
Spectroscopic analysis of hemoglobin and its derivatives (co-oximetry), in combination with blood gas analysis, provides actionable information about oxygen transport in human blood. The accuracy of the hemoglobin and bilirubin results depends on the performance of the co-oximetry technology.

The co-oximetry module of the Roche cobas b 221 blood gas system measures both hemoglobin derivatives and bilirubin spectrophotometrically in the visible spectrum range (460nm to 660nm). Absorbance of the sample is measured at a total of 512 discrete wavelengths. The concentrations of hemoglobin, hemoglobin derivatives and bilirubin are determined by applying an accepted mathematical algorithm.¹ This enables the cobas b 221 system's co-oximetry technology to detect the presence of light-absorbing substances not covered by the reference spectra and to prevent incorrect values due to interfering substances from being reported.³

This advanced co-oximetry design helps improve the accuracy of patient test results, which is demonstrated by a high correlation with results from accepted clinical chemistry test methods.²

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DON'T BE ALARMED

Covidien's SatSeconds alarm management is a proprietary Nellcor feature that allows clinicians to manage true but clinically insignificant oximetry alarms. This tool was designed to reduce nuisance alarms that can consume staff time without jeopardizing patient safety. Unlike an alarm delay, SatSeconds calculates the duration and magnitude of a saturation event. The

clinician chooses from several SatSeconds sensitivity levels based on the patient's condition; the chosen sensitivity level then determines when the monitor will withhold the alarm. SatSeconds provides a safe and practical way to reduce alarms for patients with saturation levels that fluctuate near the alarm threshold. Contact covidien.com.

OVER THE RAINBOW

Masimo Radical-7 is a 3-in-1 (bedside, handheld, transport) Pulse CO-Oximeter featuring Masimo Rainbow SET – the first and only upgradable technology platform that continuously and noninvasively measures hemoglobin (SpHb™) and oxygen content (SpOCTM) (both pending FDA clearance), carboxyhemoglobin (SpCO), methemoglobin (SpMet), oxyhemoglobin (SpO₂), perfusion index, PVITM and pulse rate. Masimo Rainbow SET provides clinicians with the only way to continuously and noninvasively measure hemoglobin – providing clinicians with access to real-time trending and tracking of a patient's total hemoglobin status enabling them to quickly identify conditions of anemia, or blood loss – as well as methemoglobin levels in the blood, making it an appropriate technology to incorporate into neonatal iNO therapies. Future measurements can be added in-the-field with a simple software upgrade. Contact masimo.com.

MAKING CONNECTIONS

Continuously monitor your smallest patients, even in a Kangaroo Care (KC) setting, with the wireless, Avant 4000 tabletop pulse oximeter from Nonin Medical. Integrated with Bluetooth wireless technology, the Avant 4000 eliminates the constraints of cables enabling mother and baby to stay connected, even while ambulatory or in transport. With increased skin-to-skin contact in a KC setting, both parent and baby can experience numerous benefits including, for mom and dad: • Increased bonding • Increased confidence in ability to care for baby • Increased sense of control/freedom • Added privacy during breastfeeding. For baby: • Increased oxygen level • Decreased breathing pauses and apnea • More stable heart rate • Increased comfort/security resulting in deeper sleep states. Nonin Medical has taken oximetry to the next level: cable-free. The integration of Bluetooth wireless technology enables accurate monitoring of a wider selection of patient populations. And with its wide range of applications from pre- and post-op to neonatal monitoring, the Avant 4000 provides a convenient, easy-to-implement solution for vital signs monitoring. Contact nonin.com.

SOUND OFF

Sonicu announced the first fully networked and integrated sound monitoring and advisory system for the Neonatal Intensive Care Unit and other environments where excessive noise levels are a problem. The Sonicu system has its roots in the hospital industry, and was designed in response to evolving standards for noise monitoring and control in NICUs. Studies have shown that babies in the NICU experience physical and developmental stresses when exposed to excessive noise. Implementing the Sonicu system allows NICU staff to monitor and control noise levels; consequently, babies get more rest which enhances their development and recovery timelines. The most visible component of the system is a three-tiered "Sound Level Indicator" device, which can be mounted in a variety of positions. The device displays red, yellow or green signals to provide a visual representation of measured sound levels. A
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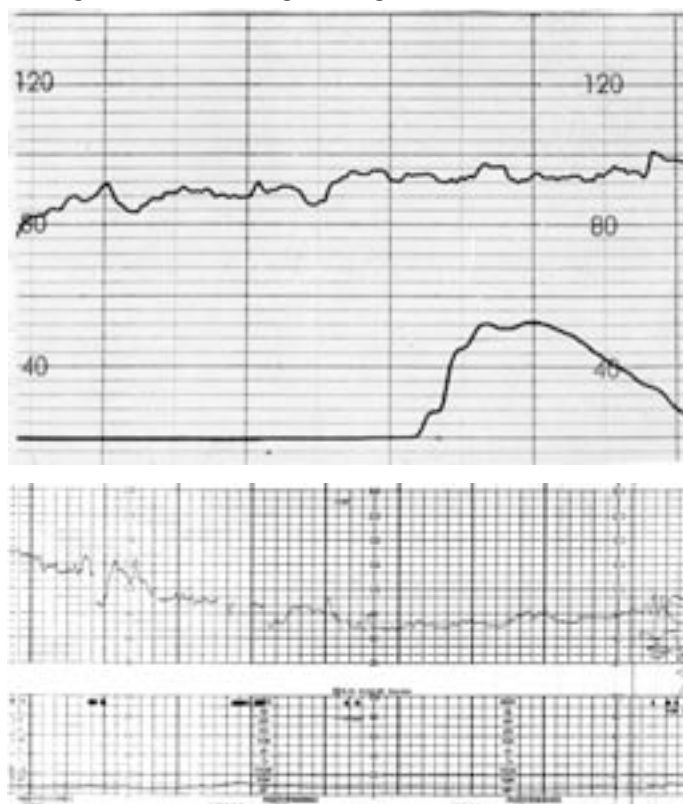
Rare and Unusual Fetal Heart Rate Patterns

Boris M Petrikovsky, MD PhD; Allan Klapper, MD; William Huang, MD; Emil Gurshumov, MD

Within recent years it has become obvious that a major impediment to progress in the evaluation and investigation of FHR monitoring is lack of agreement in definitions and nomenclature of FHR patterns despite numerous publications on the subject. In 1997, the National Institute of Child Health and Human Development (NICHD) published recommendations for standardized definitions of FHR patterns³. Recently, these recommendations have been endorsed by ACOG,⁴ the Association of Women's Health, Obstetrics and Neonatal Nurses (AWHONN), and the American College of Nurse Midwives (ACNM), reflecting unprecedented multidisciplinary consensus regarding standardized FHR terminology. However, no consensus was reached regarding the guidelines for clinical management using FHR patterns.

In July 2004, the Joint Commission on Accreditation of Health Organization (JCAHO) addressed the issue of preventable perinatal injury; identifying poor communication of abnormal FHR patterns as a leading risk factor.² Several patterns are predictive of current or impending fetal compromise. It is imperative that consensus is reached on the definition, clinical significance and management of these patterns to prevent fetal compromise. Of particular concern are FHR patterns that are rarely detected and therefore present a management dilemma. We present our experience with 3 of these rare patterns (prolonged decelerations, sinusoidal pattern and checkmark pattern) including their definition, clinical significance and strategies for management.

Prolonged decelerations (Fig 1 and Fig 2):



The 1997 National Institute of Child Health and Human Development (NICHD) workshop defined a prolonged deceleration as decrease in FHR from baseline of ≥ 15 beats/min, lasting between 2 and 10 minutes from the onset to the return to baseline.

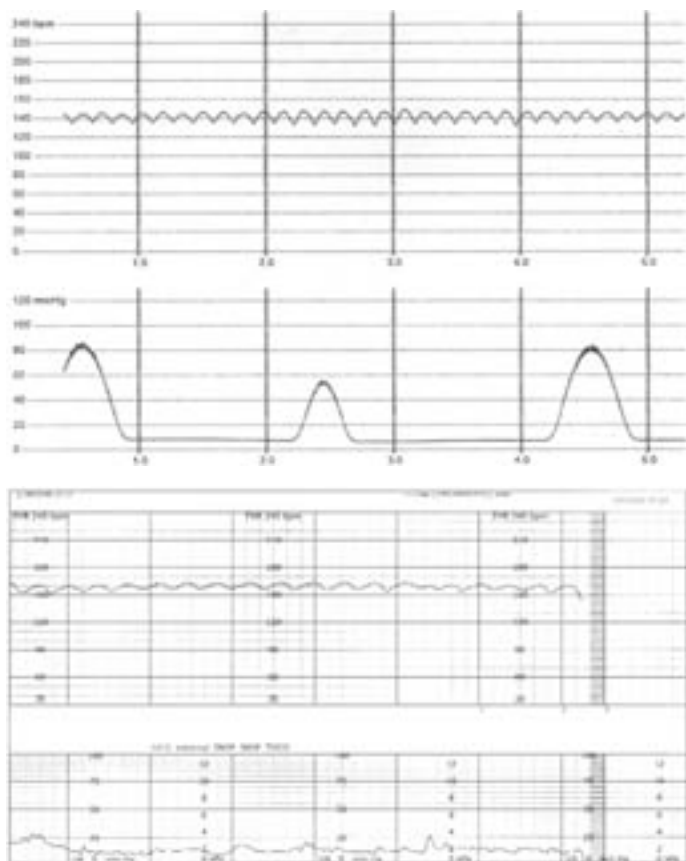
Dildy⁵ put together some causes for prolonged decelerations, including umbilical cord prolapse, placental conditions (abruptio), maternal conditions (uterine overstimulation and rupture) and fetal hemorrhage due to ruptured vasa previa. Benign causes of prolonged decelerations include maternal supine hypotension, valsalva and the effect of a paracervical block. The fetus may also respond to vigorous cervical examination, scalp electrode placement or umbilical blood

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sampling with a prolonged FHR deceleration. Freeman et al¹⁶ advocate avoiding over interpretation, because many such patterns will resolve spontaneously. G. Dildy⁵ suggested a stepwise protocol for managing prolonged decelerations:

1. Examine the cervix
 - a. Check for umbilical cord prolapse
 - b. Check progress of dilation and descent
 - c. Place internal monitor
2. Assess for possible etiologies as noted above
3. Initiate interventions to reverse FHR pattern
 - a. Lateral displacement of the placenta
 - b. Reduce uterine stimulation
 - c. Oxygen supplementation
 - d. Minimize fetal stimulation
4. Preparations for delivery
 - a. Blood type and screen
 - b. Indwelling urinary catheter
 - c. Obtain consent for operative vaginal delivery and cesarean delivery
 - d. Notify appropriate personnel (e.g., anesthesiology, pediatrics)
5. Delivery
 - a. If fetal condition is nonreassuring despite therapies
 - b. If prolonged decelerations recur and spontaneous delivery is remote

Sinusoidal pattern (Fig 3 and Fig 4):



The sinusoidal fetal heart rate is a smooth sine wave-like pattern of regular frequency and amplitude. Modanlou and Murata⁴ presented an extensive review of sinusoidal heart rate patterns grouping these patterns based upon their etiology. The more frequent categories include:

1. True SHR pattern

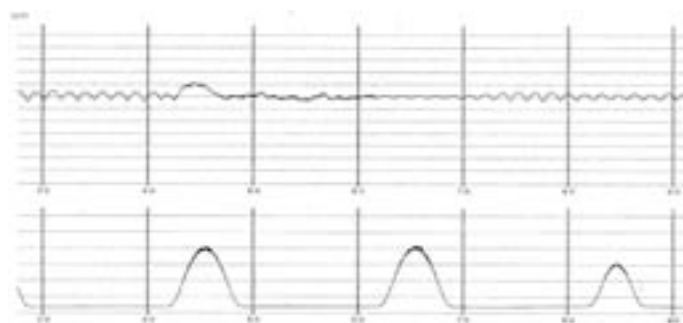
2. Pre-mortem FHR pattern.
3. Physiologic sinusoidal pattern

In addition, sinusoidal FHR patterns may be seen during sleep states, drug induced, or simply as misdiagnosed patterns.

The true sinusoidal pattern is associated with the following conditions: (a) severe fetal anemia,⁸ (b) massive fetomaternal hemorrhage,^{9,10} (c) twin-to-twin transfusion syndrome¹¹ (d) vasa previa with bleeding (e) fetal intracranial hemorrhage and (f) fetal hypoxia. Management should be individualized to these specific etiologies.

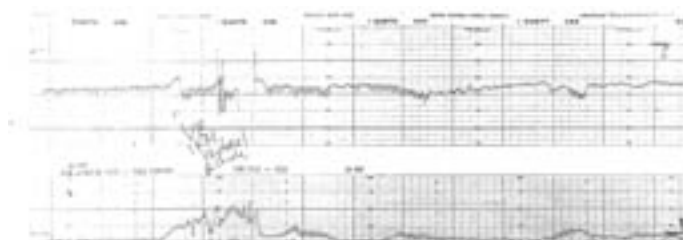
In rare cases of severe fetal hypoxia sinusoidal pattern may appear prior to fetal death. The premortem FHR pattern is similar to the sinusoidal FHR pattern with an undulatory shape but with a higher amplitude. However, the premortem FHR pattern is always preceded by other FHR abnormalities such as loss of variability and/or persistent late decelerations.⁴ Not infrequently, the premortem FHR pattern appears during the second stage of labor associated with severe umbilical cord compression.¹³ Fetuses with this ominous FHR pattern may suffer fetal or neonatal death. The surviving neonates tend to have significant morbidity and long-term neurological sequel.^{7,14}

Physiologic sinusoidal rhythm (Fig 5):



Sinusoidal FHR pattern can also occur during physiologic states such as sucking and breathing movements.¹² This type of pattern is intermittent, benign and is preceded and followed by periods of normal heart rate patterns.

Checkmark FHR pattern (Fig 6):



The checkmark FHR pattern is defined as regular uniform decelerations accompanied by small accelerations. It was originally described by Cruikshank in association with severe fetal hypoxia and neonatal death.¹⁵ Recently, Ikeda et al¹⁶ reported a checkmark pattern in combination with decreased long-term variability in severely asphyxiated fetal lambs with brain damage. However, we reported a similar pattern in a fetus with normal outcome.¹⁷ Our conclusion is supported by the experience of Newman and Green.¹⁸ The fetus in their case showed a baseline FHR rate of 140 to 150 beats per minute with diminished beat-to-beat variability and a checkmark pattern.

The pH of the fetal scalp blood sample was 7.35. A vaginal delivery occurred, and the Apgar scores were 8 and 9 at 1 and 5 minutes respectively.

Conclusion

The lack of uniform definitions and consensus on FHR patterns increases the risk of adverse pregnancy outcome. Several of these patterns are particularly rare and therefore pose a management dilemma. Recognition of these patterns should trigger a thorough work-up and assessment to avoid any adverse outcome.

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green illumination indicates measured sound level is within acceptable parameters. The yellow cautionary light notifies that sound is approaching an excessive decibel level. If the sound level exceeds the programmable excessive decibel limit, the red signal illuminates. The new "Sound Level Indicators" are graduated in height to assure excessive noise (red zone) indication is given greater visual emphasis. One available option even enables overhead lighting in the noisy area to automatically dim, warning parents, family and hospital staff of excessive noise levels. System graphics indicating sound levels and alarm status changes can be viewed by any hospital networked PC having authorized access to the system. The same graphical interface enables parameter changing through the network, as well as real time trending graphs and printouts for unbiased feedback to those causing programmed levels to be exceeded. Contact sonicu.net.

BRAINY

Cardinal Health's Nicolet ICU Monitor is used for continuous monitoring of acutely ill patients at risk for brain damage. The system monitors the brain functions of patients ranging from premature neonates to the elderly. The primary components of the Nicolet ICU Monitor include a touch screen panel PC, state-of-the-art proprietary EEG amplifier and comprehensive proprietary software. Saving and protecting the brain in acutely ill patients is of utmost importance. Minutes and even seconds can mean the difference between life and death and the quality of life after recovery. The Nicolet ICU Monitor allows you to efficiently monitor patients and to make a difference. Contact cardinalhealth.com or viasysnc.com.

Transcutaneous Monitoring: Back to the Future – An important adjunct to care during high frequency oscillatory ventilation

Sherry E. Courtney, MD

High frequency oscillatory ventilation (HFOV) is often used in neonatal intensive care. HFOV has been shown to decrease bronchopulmonary dysplasia^{1,2} in preterm infants and to be very effective in the treatment of persistent pulmonary hypertension of the newborn when used in conjunction with inhaled nitric oxide.³ Other uses include pulmonary hypoplasia, air leak, and ventilation after abdominal surgeries such as gastroschisis closure.

Effective use of HFOV requires close attention to lung volume, with use of an “optimal volume” strategy to open the lung and maintain it open.⁴ Mean airway pressure is adjusted to minimize $\text{FO}_2(\text{I})$ requirement without evidence of under- or overdistention on chest X-ray. Continuous pulse oximetry assists with adjustments of mean airway pressure and $\text{FO}_2(\text{I})$.

Continuous assessment of CO_2 is also very important during HFOV. The oscillator is a powerful machine that can quickly drive arterial CO_2 to unsafe levels. Evidence is accumulating that suggests cerebral damage may result from hypocarbia.^{5,6} In addition, hypercarbia may likewise be damaging to the preterm brain, causing disruption in cerebral autoregulation and increased incidence of intraventricular hemorrhage.^{7,8} Many infants on HFOV have indwelling arterial lines; however, very frequent blood draws may be necessary to appropriately monitor CO_2 changes, leading to increased infection risk and/or anemia. A non-invasive, continuous estimate of pCO_2 during HFOV would be safer and more effective. Transcutaneous monitoring can provide this estimate.

Transcutaneous (tc) monitoring is not new; it has been available for well over twenty years.⁹ Early machines were cumbersome and difficult to use. Accurate tcpO_2 assessment necessitated heating the skin to 43°C , which often led to skin burns in small preterm infants. After the advent of pulse oximetry, use of tc monitoring faded in most NICUs. Unfortunately, this led to “throwing the baby out with the bathwater,” as tcpCO_2

monitoring also dramatically decreased despite the lack of a replacement for CO_2 monitoring such as pulse oximetry.

Currently available tc monitors are small and easy to use. Importantly, they can be used to monitor both tcpO_2 and tcpCO_2 , or either one separately. Even more importantly, use of tcpCO_2 alone can accurately be done at a monitor temperature of 40°C or less, thus not causing skin burns,¹⁰ and site changes can be done as infrequently as every six to eight hours. The machine must simply be calibrated at the appropriate temperature.

The tcpCO_2 will correlate with the pCO_2 (aB)—that is, as one goes up the other goes up; as one goes down the other goes down. The “closeness” of the numbers will depend on the thickness of the skin and the perfusion of the site. The numbers are seldom identical, as they measure different things: one measures the pCO_2 (aB) of arterial blood and the other the CO_2 diffusing from the cutaneous tissue. The numbers, however, will correlate (trend together).

It is important to periodically correlate tcpCO_2 values with arterial blood gas samples or well-done capillary samples. Correlation need not be done with each site change if the tcpCO_2 value is similar to that obtained prior to the site change. However, perfusion will vary somewhat from site to site, and thus the “closeness” of the numbers may also vary. A value widely discrepant from previous values should prompt a blood gas.

A slowly rising or decreasing tcpCO_2 should always be considered a patient problem until proven otherwise. Something often forgotten is that an increasing tcpCO_2 may of and by itself indicate decreasing perfusion in the patient—perhaps sepsis or impending shock. Though the tcpCO_2 will still trend correctly, the tcpCO_2 will be considerably higher than the pCO_2 (aB) in a patient with significant circulatory compromise. In these cases the underlying cause of the problem must be treated. A decreasing tcpCO_2 indicates improving ventilation. Changes to ventilator settings can be easily made based on tcpCO_2 alone; blood gases can be done much less frequently.

“Something is wrong with the machine” is unfortunately often heard before evaluation of the patient has been done. A recent

Sherry Courtney is with the Division of Neonatology, Stony Brook University Medical Center, Stony Brook, NY. Reprinted with permission from www.bloodgas.org, an educational website sponsored by Radiometer.

article, for example, documented the value of a rising tcpCO₂ in alerting staff to a pneumothorax well before acute decompensation of the patient.¹¹ A steadily rising or falling tcpCO₂ should prompt careful attention to reasons for under- or overventilation, not an immediate recalibration of the monitor or, worse, turning a blind eye to the readouts because “the machine is not working.”

Troubleshooting the tc monitor is relatively easy. The calibration cylinder must contain sufficient gas and must be turned on during calibration. The cable must be intact. The sensor must be remembraned as per the manufacturer's recommendations. Sufficient contact fluid must be placed between the skin and the sensor. Recalibration should be done every six to eight hours if only tcpCO₂ is being used. We have found every six hours to be best in this circumstance; towards eight hours the contact fluid tends to evaporate, leading to spurious values. The sensor site should be changed every three to four hours if both tcpO₂ and tcpCO₂ are utilized. Heating of the sensor to 43°C is needed if the tcpO₂ is employed, and the site must be changed more frequently to avoid skin burns. A tcpCO₂ value of 0 or tcpO₂ of about 150 means the sensor has dislodged or an air bubble is under the sensor. These are the values expected for room air. tcpCO₂ values that jump about wildly indicate need for recalibration/remembraning. Steadily rising or falling values reflect patient status.

Though pulse oximetry has largely replaced the need for tcpO₂ monitoring, tcpO₂ monitoring can provide useful and complimentary information should the practitioner choose to use it. High pO₂(aB) should be avoided in most cases.^{12,13} Because of the shape of the oxygen-hemoglobin dissociation curve, an oxygen saturation in an acceptable range could be associated with a pO₂(aB) that is unnecessarily high. By the same token, a low or borderline saturation might be associated with an acceptable pO₂(aB) because of shifts in the oxygen-hemoglobin dissociation curve and varying amounts of fetal hemoglobin. tcpO₂ monitoring can be very useful in titrating the FO₂(I). Use of tcpO₂ monitoring requires more frequent site changes and close attention to the baby's skin to avoid burns. In most cases, however, the “burn” is a reddened area just under the sensor that heals without residua. Occasionally, tiny scars can result if the sensor temperature is too high or the sensor is left on the skin for too long.

For a patient being started on HFOV, the tcpCO₂ monitor should be placed on the patient prior to instituting HFOV. Once the tcpCO₂ is stable and a correlating ABG has been obtained, HFOV can be started and the amplitude adjusted using the tc monitor. Severe hypocapnia, such as can occur with an inadvertently high amplitude or postsurfactant can thus be entirely avoided. Hypercapnia from tube secretions, tube malposition, accidental extubation, pneumothorax or insufficient amplitude can also be quickly noted and appropriate interventions given. The tcpCO₂ monitor is also very valuable as the patient begins to wean, avoiding hypocarbia and allowing the staff to pace the wean appropriately.

In infants, optimal use of HFOV, and in fact any form of full respiratory support, should include concurrent use of tcpCO₂ monitoring to ensure prevention of hypo- and hypercarbia and timely interventions for both complications of therapy and patient weaning.

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Noninvasive Blood Constituent Monitoring in Neonatal Intensive Care

Michael O'Reilly, MD

For newborns in critical condition, blood assessment is a vital component of patient diagnosis and treatment. Historically, blood monitoring has required invasive blood sampling and laboratory analysis, which can create delays in the availability of critical data and is subject to error due to inappropriate handling or processing of the sample. Additionally, invasive blood sampling in this patient population often causes iatrogenic anemia (acquired anemia) because neonates have a very small blood reserve. Noninvasive monitoring of vital blood constituents was once considered an impossible feat, but new technology now makes it possible in the neonatal population.

Introduction to Pulse CO-Oximetry

The invention of Pulse CO-Oximetry technology (Masimo, Irvine, CA) provides noninvasive, immediate, and continuous monitoring of multiple blood constituents—including methemoglobin and total hemoglobin—that once required invasive procedures. These measurements are provided in addition to conventional pulse oximetry measurements of oxyhemoglobin (SpO₂) and pulse rate. In contrast to 2-wavelength pulse oximetry, Pulse CO-Oximetry uses up to 12 wavelengths of light housed in a single, simple-to-apply noninvasive sensor, which provides readily accessible and actionable information to neonatal clinicians. Pulse CO-Oximetry represents a significant advancement for neonatal clinicians because it allows access to the true oxygenation status of their patients, allowing for more informed and timely treatment decisions.

The opportunity for Pulse CO-Oximetry to enable earlier and better clinical decisions, advance patient safety, improve outcomes for patients and decrease costs across patient populations has generated significant interest over the last few years. Today, new research is identifying neonatal conditions in which Pulse CO-Oximetry has important applications that can be of enormous benefit to neonatal clinicians.

Immediate Identification and Tracking of Acquired Methemoglobinemia.

In its first application with significant relevance for neonatal clinicians, Pulse CO-Oximetry measures the level of methemo-

globin (SpMet) in the blood. Methemoglobinemia symptoms are often masked and, therefore, the condition is frequently misdiagnosed. SpMet monitoring has important implications in the monitoring of neonatal patients during inhaled nitric oxide (iNO) therapy for hypoxic respiratory failure associated with pulmonary hypertension,¹ which has been shown to cause methemoglobinemia. This is specifically addressed in the iNO package insert that states “methemoglobinemia is a dose-dependent side effect of inhaled nitric oxide therapy. Therefore, methemoglobin levels should be monitored during iNO administration. Caution should be used when administering iNO with other drugs that may cause methemoglobinemia regardless of their route of administration.”²

It is critical to administer optimal doses of both iNO and oxygen, since high levels of iNO cause toxic risks and low levels result in suboptimal therapeutic doses. However, because the signs and symptoms of methemoglobinemia are ambiguous and nonspecific, detecting it can be problematic without drawing blood for laboratory analysis. The traditional method of detecting methemoglobinemia, by laboratory CO-oximetry, is costly and invasive. A Johns Hopkins study concluded “if CO-oximetry tests had been performed on every blood aliquot sent for arterial blood gas analysis during the 28-month study period, the incurred cost at \$25 per test would have totaled approximately \$9 million.”³

Furthermore, when using conventional pulse oximetry to monitor oxygen saturation, methemoglobinemia “pushes” the SpO₂ value to 85%, clearly misrepresenting a patient’s oxygenation status.^{4,5} In a 2006 Patient Safety Alert from the Veterans Health Administration System, the VA Central Office warns that methemoglobin “renders routine 2-wavelength pulse oximetry unreliable, thus reducing a clinician’s ability to detect a critical level of hypoxia” and instructs VA clinicians to “not rely on routine 2-wavelength pulse oximetry to detect hypoxemia in the presence of MetHb.”⁶

The ability to use SpMet to continuously monitor for methemoglobinemia without having to draw blood makes Pulse CO-Oximetry an ideal complement to managing iNO therapy administration in neonates.

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Real-time Diagnosis and Monitoring of Anemia.

Looking toward the future, new advances in Pulse CO-Oximetry technology have enabled noninvasive total hemoglobin (SpHb) monitoring (pending regulatory clearance). Early clinical studies in adult patients demonstrate that SpHb may reveal conditions of chronic or acute anemia due to blood loss or underproduction of erythrocytes that can threaten both the life and safety of patients. SpHb monitoring may also aid the initial and ongoing decisions necessary to determine when blood transfusions may be indicated to correct anemia and improve oxygenation status.

In neonates, anemia is a frequently occurring problem that can lead to significant morbidity and mortality.⁷ Iatrogenic anemia occurs as a result of repeated blood draws for laboratory analyses. For this reason, the opportunity for Pulse CO-Oximetry to help clinicians in neonatal intensive care units to preserve precious neonatal blood volume by avoiding unnecessary blood draws may make noninvasive assessment a preferable solution. Further study is required in this area, and Masimo does not expect SpHb to be cleared for neonatal use at launch.

Improved Detection of Congenital Heart Defects

In the last few years, multiple studies have documented the failure of routine neonatal physical examinations to detect congenital heart disease (CHD) in babies ⁸⁻¹¹ and that it fails mainly in children with duct-dependent systemic circulation.¹² Failing to diagnose duct-dependent systemic- or pulmonary circulation before discharge has been reported to result in cardiovascular collapse, with 10–30% of deaths occurring in the first year of life.^{8,10,13}

Today, the noninvasive measurement of perfusion index (PI) with Pulse CO-Oximetry technology has been shown to greatly improve the detection of CHD before discharge. In a study of 10,000 newborns, researchers concluded that combined neonatal examination and saturation screening detected only 7 out of 9 babies with CHD. However, when PI was added, 9 out of 9 showed test abnormalities—improving the detection rate for CHD from 78% to 100%. The authors also reported that they had “established reference values for Masimo PI (right hand and foot) in normal newborns between 1 and 120 h of age” and concluded that “including cut-off values for Masimo PI in pulse oximetry screening for duct dependent congenital heart disease is a promising tool for improving the detection of critical congenital heart disease with duct-dependent systemic circulation.”¹⁴

Diagnosis of Congenital Heart Disease (CHD) in Infants¹⁴

	Neonatal Exam & Saturation	Neonatal Exam, Saturation, & Masimo PI
CHD Detection in newborns	78% (7 out of 9)	100% (9 out of 9)

Significant Reduction in Retinopathy of Prematurity (ROP)

ROP, associated with hyperoxic conditions related to the overuse of supplemental oxygen therapy, as well as low birth weight, low gestational age, and genetic factors¹⁵ can be a devastating disease that renders infants partially or completely blind. And, while efforts to lower ROP rates have included

increased education and commitment of bedside care providers, development of guidelines to decrease hyperoxemic periods and implementation of wide changes in oxygenation, none have been as impactful as the advances made in SpO₂ technology through the use of Pulse CO-Oximetry.

Researchers have discovered that the increased accuracy and reliability of Measure-Through-Motion-and-Low-Perfusion pulse oximetry technology can enable a 40% reduction in ROP. In conducting a large, multicenter study of 366 newborns, at birth weights of less than 1.25 kg and managed under the same clinical guidelines for the diagnosis and treatment of ROP, researchers aimed to assess the importance of SpO₂ technology choice in the relative risk reduction of ROP.¹⁶ Their findings over the four-year study period were “significantly more favorable” for the center that switched to Masimo technology, which researchers concluded “further supports the significance of adequate SpO₂ monitors in managing critically-ill infants.”

Reduction in Retinopathy Of Prematurity¹⁶

Center	ROP (Pre-Policy Change without Masimo)	ROP (Post-Policy Change)	% Reduction in ROP
Center #1	11.1%	6% with Masimo SET	40%
Center #2	13%	13% without Masimo SET	0%

Patient Safety Implications

Collectively, the information available through the use of Pulse CO-Oximetry presents a unique patient safety opportunity that may help hospitals to comply with the Joint Commission’s 2008 National Patient Safety Goal #16, which calls for “improved recognition and response to changes in a patient’s condition.”¹⁷

This growing body of clinical evidence suggests that Pulse CO-Oximetry may provide critical opportunities for neonatal intensive care clinicians to advance the care they provide. These noninvasive measurements not only serve to greatly improve monitoring of a neonate’s true oxygenation status, but may aid in the early identification of dangerous conditions such as methemoglobinemia and retinopathy of prematurity. As such, Pulse CO-Oximetry has been viewed by many as a critical component to any “first do no harm” initiatives both inside and outside of the neonatal intensive care unit.

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Fetal Fitness Testing as a Predictor of Fetal Well-Being

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Although the safety of exercise in pregnancy remains controversial, up to 42 percent of pregnant women report exercising during their gestation.¹ While some studies have raised concerns about the effects of exercise-induced hyperthermia causing changes in birth weight, fetal heart rate responses, miscarriage, maternal injury and insufficient maternal weight gain,² others have claimed that exercise-induced hyperthermia may adversely affect closure of the neural tube.³

In contrast, some authors have suggested that the previously alleged concerns over hyperthermia, preterm delivery and decreased birth weight may not be warranted; the short and long term benefits of moderate exercise on a regular basis may, in fact, outweigh the potential risks.⁴⁻⁵ Fetal metabolism produces heat which maintains fetal body temperature at 0.5 to 1.0 degrees (celcius) above maternal body temperatures.⁶ When pregnancy and exercise are combined, the increased metabolic rate results in greater heat production but the upper limit of temperature to ensure normal fetal growth and development is unknown. While some suggested a teratogenic risk with maternal body temperature above 39.2 degrees celcius,⁷⁻⁸ an educational pamphlet by the American College of Obstetricians and Gynecologists recommends that a rectal temperature not exceed 38.3 degrees celcius.⁹ Alternatively, Lindqvist et al has suggested that during sub-maximal exercise, the temperature response seems to provide thermal protection for the embryo and the fetus.¹⁰

Due to the contrasting reports in the literature, no causal relationship between exercise and women's health in pregnancy has been established. Exercise stress tests have been utilized in adult medicine as a screening tool to assess cardiac function and the presence/absence of coronary artery disease. We sought to explore the potential for using maternal exercise in pregnancy to assess fetal status as a comparable evaluation mechanism.

Case 1:

A 40 year old at 36 weeks gestational age presented with dyspnea following a brisk walk. She had a history of mild hypertension. Initial assessment disclosed a pulse rate of 108 beats per minute (bpm), Blood pressure (BP) 140/30 and respiratory rate of 26 breaths per minute. A non-stress test (NST) revealed a fetal heart rate of 168 bpm with persistent late decelerations. After treatment with maternal oxygen by face mask and intravascular fluid replacement, the patient's dyspnea resolved and the fetal late decelerations subsided.

The patient was discharged home and a repeat testing 2 days later revealed a non-reactive NST, non-reassuring biophysical profile (BPP), and positive oxytocin challenge test (OCT). Induction of labor was initiated but resulted in an emergent cesarean delivery for persistent late decelerations. The Apgar scores were 4 and 6 at 1 and 5 minutes, respectively with umbilical cord pH 7.19 at time of delivery. The baby was discharged home on day of life 5 and, to date, is doing well.

Case 2:

A 35 year old professional athlete continued rigorous exercise throughout her pregnancy despite medical advice. She presented to labor and delivery for fetal monitoring at 38 weeks gestational age after completion of a 5-mile marathon. Upon admission her heart rate was 72 bpm, compared to a heart rate of 50 bpm which she maintained throughout pregnancy. Her respiratory rate was 32 breaths per minute and BP 130/70. A NST revealed late decelerations and Tocodynamometer showed irregular contractions, both of which resolved after 30 minutes of bed rest and intravascular fluid resuscitation. Two days later induction of labor was initiated due to non reassuring fetal surveillance resulting in delivery of a growth restricted neonate. The baby did well post partum.

Case 3:

A 29 year old obese patient who had never exercised prior to pregnancy presented at 35 weeks gestation after sprinting in the parking lot and climbing 3 flights of stairs en route to a prenatal visit. Upon arrival she complained of heart palpitations, shortness of breath and "almost passing out." Her heart rate was 128 bpm and BP 140/95. NST was non reactive with fetal heart rate noted to be 170 bpm and decreased variability. Both

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maternal vital signs and NST normalized within 10 minutes. Fetal testing was continued weekly and remained reassuring. The patient delivered a full term neonate with Apgar scores of 8 and 9 at 5 and 10 minutes, respectively.

Comment

The effect of exercise during pregnancy on the fetus remains unclear. Recreational and competitive athletes with uncomplicated pregnancies can remain active throughout pregnancy unless medically indicated.¹¹ Although paucity of data exists on the effect of strenuous exercise in pregnancy, we believe that women who engage in such activities require close medical supervision.

Early studies on the fetal response to maternal exercise revealed that during exercise there is a diversion of blood from the splanchnic area to the skeletal musculature of the legs. Shortly after cessation of exercise there is a rapid reversal back to splanchnic circulation. The decreased uterine blood supply during exercise may be similar to an oxytocin challenge test for the fetus.¹² Other authors reported that maternal exercise had little effect on fetal heart rate patterns in most patients. However, they did state that maternal exercise may decrease uterine blood flow and, hence, put a temporary load on uteroplacental transfer mechanism that may manifest in abnormal heart rate patterns.¹³

Therefore, there may be a role for exercise as a modality for assessing fetal testing. Promerance et al screened mothers for uteroplacental insufficiency with an exercise test performed between 35 to 37 weeks of gestation and found a positive test in 5 of 54 fetuses, 4 of whom subsequently developed fetal distress in labor.¹⁴ In a study studying a similar end point, Artal et al concluded that the healthy fetus can tolerate brief periods of hypoxia, such as those encountered in maternal exercise. Initially the fetus will respond with tachycardia as a protective mechanism to facilitate blood circulation. These authors also stated that fetal monitoring after maternal exercise could aid in identification of fetuses at risk for hypoxia.¹⁵

More recently fetal response to maternal exercise was studied in pregnancies complicated by suspected uteroplacental insufficiency. Sub-maximal exercise revealed transient changes such as development of absent end-diastolic flow velocity and two thirds of these pregnancies subsequently demonstrated fetal growth restriction.¹⁶

The placenta acts as a low resistance shunt in the maternal circulation. At rest the vasculature of the voluntary muscle offers high resistance. During exercise, the resistance is lowered by the large vasculature bed. In essence, a second low resistance shunt is placed in parallel to the placenta. If uteroplacental has not been compromised, cardiac output should adequately supply both of these low resistance vasculature beds. However, if the utero-placental circulation has been compromised, the fetal heart rate changes should theoretically be detected during maternal exercise, much as they are during active labor and delivery. Currently non stress testing (NST) is the most widely used primary testing method for assessment of fetal well being and is also incorporated as one of the parameters of the biophysical profile.¹⁷⁻¹⁸ Based on the promising results of this on-going case report series, we propose to further study the possibility of using maternal exercise to screen for fetuses at risk for hypoxia.

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Elevated Maternal Lipoprotein (a) and Neonatal Renal Vein Thrombosis: A Case Report

Vivek Subbiah; Prabhu Parimi

Abstract

Introduction: Renal vein thrombosis, although rare in adults, is well recognized in neonates and is one of the most common manifestations of neonatal thromboembolic events. The etiology of renal vein thrombosis remains unidentified in the majority of cases. We report a case of renal vein thrombosis in a neonate associated with elevated maternal lipoprotein (a).

Case presentation: A full-term female infant, appropriate for gestational age, was born via spontaneous vaginal delivery to an 18-year-old primigravida. The infant's birth weight was 3680g and the Apgar scores were eight and nine at 1 and 5 minutes respectively. Evaluation of the infant in the newborn nursery revealed a palpable mass in the right lumbar area. Tests revealed hematuria and a high serum creatinine level of 1.5 mg/dl. An abdominal ultrasound Doppler flow study demonstrated an enlarged right kidney, right renal vein thrombosis, and progression of the thrombosis to the inferior vena cava. There was no evidence of sagittal sinus thrombosis. An extensive work-up of parents for hypercoagulable conditions was remarkable for a higher plasma lipoprotein (a) level of 73 mg/dl and an elevated fibrinogen level of 512 mg/dl in the mother. All paternal levels were normal. The plasma lipoprotein (a) level in the neonate was also normal. The neonate was treated with low molecular weight heparin (enoxaparin) at 1.5 mg/kg/day every 12 hours for 2 months, at which time a follow-up ultrasound Doppler flow study showed resolution of the thrombosis in both the renal vein and the inferior vena cava.

Conclusion: There have been no studies to date that have explored the effect of abnormal maternal risk factors on fetal hemostasis. A case-control study is required to investigate whether elevated levels of maternal lipoprotein (a) may be a risk factor for neonatal thrombotic processes. Although infants

with this presentation are typically treated with anticoagulation, there is a lack of evidence-based guidelines. Treatment modalities vary between study and treatment centers which warrants the establishment of a national registry.

Introduction

Renal vein thrombosis (RVT), although rare in adults, is well recognized in neonates and is one of the most common manifestations of neonatal thromboembolic events.¹ The clinical signs of neonatal RVT (NRVT) include an enlarged kidney, hematuria, proteinuria, renal failure, hypertension and/or thrombocytopenia. Long-term consequences of NRVT include hypoplastic kidney, tubular defects, hypertension and renal insufficiency.² We report a case of NRVT associated with elevated maternal lipoprotein (a) [Lp (a)].

Case presentation

A full-term female infant, appropriate for gestational age, was born via spontaneous vaginal delivery, weighing 3680g, to an 18-year-old primigravid Hispanic mother and a 21-year-old African American father. The neonate adapted well to extra-uterine life as evidenced by Apgar scores of eight and nine at 1 and 5 minutes, respectively. The pregnancy had been uneventful, and the maternal screens were all negative. There was no evidence of diabetes or pre-eclampsia during pregnancy. The neonate was transferred to the newborn nursery for routine newborn care. Physical examination in the newborn nursery revealed a palpable mass in the right lumbar area. Significant laboratory findings in the neonate included hematuria, and an elevated serum creatinine level of 1.5 mg/dl prompting transfer to the neonatal intensive care unit. A renal ultrasound evaluation showed an enlarged right kidney (5.56 cm) with loss of corticomedullary distinction. A renal Doppler flow study demonstrated an increased resistive index of the right renal artery with suboptimal wave forms of the right renal vein and a clot in the right renal vein (Figure 1). A Doppler flow study of the left renal artery and vein was normal. The neonate had normal blood pressures throughout the hospital stay.

The neonate and her parents were evaluated for prothrombotic risk factors. The mother's laboratory parameters were remarkable for an elevated level of Lp (a) of 73 mg/dl (normal 0 to 40 mg/dl), and fibrinogen of 512 mg/dl (156 to 400 mg/dl). The

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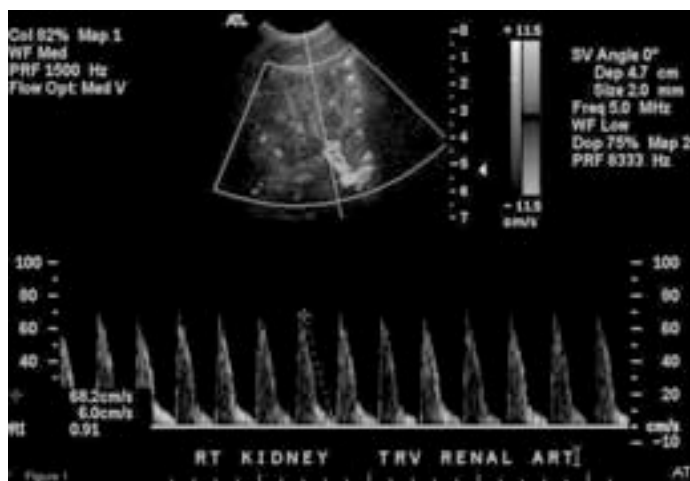


Figure 1

plasma Lp (a) concentration was measured by the enzyme-linked immunosorbent assay (ELISA) technique using mouse monoclonal anti-apo (a) capture antibody and sheep polyclonal anti-apoB detection antibody (COALIZA Lp (a), Chromogenix). The other laboratory tests on the mother were normal: plasma homocysteine 5.3 $\mu\text{mol/l}$; protein C activity greater than 125%; protein S activity greater than 125%; anticardiolipin antibody IgG 6.21gG phospholipid binding units; anticardiolipin IgM 6.41gM phospholipids binding units; beta 2 glycoprotein IgG less than 9 standard IgG antibeta 2 glycoprotein units; beta 2 glycoprotein IGM less than 9 standard IgM antibeta 2 glycoprotein units; lupus anticoagulant negative; Factor VIII A assay 108%; antinuclear antibody (ANA) screening negative; antithrombin III 94%; prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR) normal. DNA analysis showed no point mutation (G20210A) in the 3' untranslated region of the prothrombin gene, no genetic polymorphism (ARG 506/Glu 206) for Factor V Leiden, and no gene mutation (C677T) for 5' 10 methylenetetrahydrofolate reductase (MTHFR). The paternal screens were all normal.

The plasma Lp (a) level in the neonate was 11 mg/dl (0 to 40 mg/dl). This was measured when the maternal Lp (a) results became available, that is, 4 days after the diagnosis of RVT. The plasma homocysteine level was 4.6 $\mu\text{mol/l}$ (4 to 13.7 $\mu\text{mol/l}$). A computed tomography (CT) scan of the head of the neonate was negative for sagittal sinus thrombosis. The neonate was started on low molecular weight heparin (enoxaparin) at 1.5 mg/kg/day every 12 hours, with antifactor Xa monitoring. The antifactor Xa activity measured was 0.741U/ml (less than 0.10IU/ml). The serum creatinine level decreased to 0.5 mg/dl 9 days after initiation of treatment, and urinalysis showed no evidence of hematuria. Renal ultrasound Doppler flow studies were repeated at weekly intervals during the hospital stay. One week after initiation of treatment, an ultrasound demonstrated persistence of RVT and development of a new thrombosis in the inferior vena cava. The neonate was discharged home on enoxaparin and followed by a hematologist, a nephrologists and a primary care physician. A follow-up ultrasound Doppler flow study at 2 months of age showed a normal flow pattern in the aorta, inferior vena cava, right and left renal arteries and veins indicating resolution of the thrombosis (Fig. 2). Enoxaparin was discontinued at 2 months of age. The baby continued to do well



Figure 2

with no evidence of residual renal dysfunction or hypertension of 18 months of age.

Discussion

The etiology of NRVt remains unidentified in the majority of cases. The existence of underlying predisposing factors, such as asphyxia, sepsis, diabetic fetopathy or indwelling intravascular catheters, in combination with inherited prothrombotic risk factors, play a major role in the pathogenesis of NRVt,¹⁻⁴ however their role is not well defined. The association between maternal thrombophilia and thrombotic complications in the neonate is unknown.⁵

Lp (a) consists of phospholipids, cholesterol and apolipoprotein B-100 (low-density lipoprotein), with apolipoprotein (a) attached to the latter at a single point. Recent studies have demonstrated the significance of prothrombotic risk factors, especially the elevation of Lp (a) in the etiology of NRVt. It has been shown that Lp (a) competes with plasminogen for the plasminogen receptor on endothelial cells and initiates thrombosis. It has also been demonstrated that Lp (a) inactivates the 'tissue factor (TF) pathway inhibitor,' which is a major endogenous regulator of TF-mediated coagulation.⁶ Elevated plasma concentration of Lp (a) has been consistently shown to be a risk factor for the development of a variety of thrombotic and atherosclerotic disorders in humans. Lp (a) has been implicated in NRVt1 as well as in cerebral venous thrombosis.⁵ Lp (a) greater than 30 mg/dl has been shown to be a risk factor for the development of venous thromboembolism in children.⁷

There is a paucity of data exploring prothrombotic risk factors in the development of NRVt in neonates. None of the studies reported to date have explored the effect of abnormal maternal risk factors on fetal hemostasis. The mechanism by which an elevated maternal Lp (a) with a normal level in the neonate contributes to the formation of a thrombus was unclear in this case. There is no evidence that Lp (a) crosses the placenta given the large size of this molecule. A higher level of maternal Lp (a) crosses the placenta given the large size of this molecule. A higher level of maternal Lp (a) could be an independent risk factor in neonatal thromboembolic events. A case-control study is required to investigate whether elevated levels of maternal Lp

(a) are a risk factor for neonatal thrombotic processes. In addition to measuring plasma levels of Lp (a) by standardized methods, genetic polymorphisms of Lp (a) should also be explored to identify secretor haplotypes.

Conclusion

The infant reported here is now 18-months old, has normal renal function and has no evidence of hypertension. Although infants with this presentation are typically treated with anticoagulation, there is a lack of evidence-based guidelines. The treatment modalities vary between study and treatment centers which warrants the establishment of a national registry. Screening for prothrombotic risk factors in NRVT remains controversial.^{2,3,8,9} Messinger et al.³ have reported that all neonates with unilateral NRVT treated with heparin and with or without fibrinolytics had either small or atrophic kidneys between 2 and 6.5 years of age, but had normal renal function. This study underscores the importance of long-term follow-up of neonates with NRVT.

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Potential Hazards of Mechanical Ventilation

Melissa Turner, BA, RRT

In the February issue of the SCCM's Critical Connections newsletter, an article by Albert Fantasia¹ addresses some topics that may lead to injury from mechanical ventilation. Those topics are inclusive of mechanical function, communication, evidence-based practice, staffing, and reporting of medical errors. Each of these topics must be carefully scrutinized and addressed in order to make mechanical ventilation safer for all patients.

Ventilator malfunction is certainly an area of concern as this can cause harm to any patient. It is important that ventilators pass their self-check during boot-up as well as a safety check that clinicians must conduct before placing the ventilator on a patient. In a hurry, clinicians sometimes choose to forego the safety check, although it should be a routine and mandatory step in ensuring the safety of the patient. All ventilators have a system of alarms, both audio and visual, to alert clinicians to any potential problems. Clinicians must take the time to set alarms appropriately as the patient's condition warrants. Placement of ventilators in relation to staff location is also important as some locations make it harder for staff to hear alarms. Ventilators that have an adjustable alarm volume are beneficial in this instance. The G5, a new ventilator from Hamilton also incorporates a large alarm lamp on top of the screen that is visible from 360 degrees around the ventilator. This makes it easy to identify an alarm when an alarm condition exists.

The Joint Commission had reported in 2002 that communication breakdown among staff members was a cause of 16 out of 23 ventilator related injuries or deaths. All members of the health care team should understand the care plan for each patient. Many ventilators include trending which can help clinicians to see what happened before they arrived on shift. It is important for staff members to have a clear picture of the direction they are heading based on the individualized care plan.

Evidence based practices are being implemented more than ever today. Doctors are beginning to stick to techniques and methods that have been proven to work and proven safe. For example, evidence based strategies for ARDS ventilator

management today includes using low tidal volumes in the range of 4-6cc/kg of ideal body weight, use of optimal recruitment pressures, and use of plateau pressures limited to less than 30 cm H₂O. Lung protective strategies have been shown to produce more favorable outcomes. Even though the evidence shows that these approaches have better outcomes, they are still not applied routinely.

Applying the ventilator bundle for prevention of VAP has also been shown to have significantly better outcomes when all components, which include elevation of head of bed, daily sedation vacations, peptic ulcer prophylaxis, and DVT prophylaxis, are used together.

Another cause of ventilator induced injury listed by Joint Commission in 2002 was insufficient staffing. Many hospitals today are operating understaffed. Historically, clinicians spent their time with patients based on departmental policy. Generally, each ventilator patient was to receive ventilator checks every 2 hours. In adhering to this type of policy, the sickest patients receive the same amount of clinician time as do the patients who do not have high acuity levels. Fantasia proposed a table to help allocate clinician time more appropriately (See Table 1). Using this table, clinicians are better able to allocate time to patients according to acuity. Combining the use of the ventilator triaging table with closed loop ventilation such as ASV, clinicians can be sure that all patients are being ventilated safely as well as being able to wean when appropriate even though the lower acuity patients are visited less frequently. These patients are able to wean as they are ready and not be held up by a redistribution of clinician time.

Reporting of medical errors was also found to be a factor in mechanical ventilation injury whether due to equipment malfunction or clinician error. Closed loop control systems and new 'clinician friendly' interfaces and graphical presentations of data may help minimize clinician errors. There are less "knobs" or settings to be manipulated with a closed loop system which leaves less room for error. One such aid in the prevention of errors is Hamilton's G5 ventilator through its use of the Ventilation Cockpit. The cockpit allows users to visually identify their patients' status in a matter of seconds through use of graphics such as the Dynamic Lung and the Vent Status Panel.

Melissa Turner is with Hamilton Medical

LEVEL I	LEVEL II	LEVEL III	LEVEL IV
Documentation required once per 8 hour shift	Documentation required twice per 8 hour shift	Documentation required 3 times per 8 hour shift	Documentation required 4 times per 8 hour shift
Floor patient	Stable patient requiring ICU level of care for other than respiratory illness	Patient actively weaning	Patients on unconventional modes of ventilation: <ul style="list-style-type: none"> • Volumetric diffusive respiration • HFOV
Patient whose status has been changed to « comfort measures only »	Patient not actively weaning	Recently intubated (12 hours) and patient has not established severity of illness or level of trauma	Patients with acute unstable disease: <ul style="list-style-type: none"> • ARDS • sepsis • Status asthmaticus • New intubation with hemodynamic instability
ICU or step-down patient who is flagged to floors		Essentially stable patient who may be requiring frequent intervention to establish adequate ABG's	
Patient who is intubated for airway protection (no other medical issues) and not weaning			

Ventilator Triaging Table¹: Using this table, clinicians are better able to allocate time to patients according to acuity.

With the use of these new tools, clinician time is more productive and patient safety is in the forefront.

Reference

1. Fantasia, A. Preventing Injury from Mechanical Ventilation. Crit Conn. 2008; 7(1): 18-19.

Scripps Mercy Hospital, San Diego, CA

Providing excellent patient care is a top priority for Scripps Mercy Hospital, the longest-operating hospital in San Diego, CA. To ensure state-of-the-art care in its respiratory services, the hospital recently replaced its entire fleet of ventilators with SERVO-i ventilators equipped with BiVent.

BiVent is an effective mode of mechanical ventilation similar to Airway Pressure Release Ventilation (APRV), but with additional features. BiVent applies Continuous Positive Airway Pressure (CPAP) to maintain adequate lung volume and promote alveolar recruitment. BiVent also adds a time-cycled release phase to lower set pressure (P-low). In addition, spontaneous breathing can be integrated and is independent of the ventilator cycle.

Current research shows that APRV improves respiratory care in critically ill patients, especially patients with low compliance. In a study in *Critical Care Medicine* in 2005 (Vol. 33, No. 3, S228-240), Nader M. Habashi, MD, FCCP, an assistant professor at the University of Maryland in Baltimore, finds that APRV has distinct clinical advantages for ventilator management of patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). Among them are improvement in cardiac and renal function, decreased use of sedation, and near elimination of neuromuscular blockades. In his study, Habashi notes that some recent research suggests using APRV results in fewer ventilator days and shorter Intensive Care Unit (ICU) stays for many patients. Although randomized controlled trials still are needed, Habashi expects APRV to become the gold standard for patients with ALI or ARDS.

BiVent is an improvement on APRV because it allows pressure support to be set independently. Also, it allows the practitioner to set auto positive-end expiratory pressure (PEEP) when recruiting the lung. "Spontaneous breaths at the P-high improves dependent ventilation through pleural pressure changes, rather than the application of additional applied airways pressure," explains Jodi Brewer, RCP, RRT, an educator and clinical respiratory specialist in the Respiratory Therapy Department at Scripps. "The advantage is the recruited lung requires less pressure than the recruiting lung."

BiVent allows Scripps busy trauma unit to offer leading-edge respiratory care: "Since the arrival of these ventilators," says



Stephen Kaminiski, MD, FACS, a leading trauma service physician at Scripps Mercy, "we have been able to advance our ventilator care and our lung management to match state-of-the-art information."

Scripps Mercy demands state-of-the-art technology because it has one of the busiest emergency departments and trauma centers in San Diego and Chula Vista, the two communities that it has served for 113 years. Last year, the hospital treated more than 50,000 ER patients and 2,200 trauma patients.

Kaminski, who, during his fellowship was trained on APRV, has noticed that his trauma patients are more comfortable on BiVent. Because they are able to breathe on their own, they are not "bucking" the respirator as often happens with conventional ventilation, he explains.

It is widely recognized that the use of sedation makes it more difficult to wean a patient from a ventilator. Because patients on BiVent breathe spontaneously throughout the ventilatory cycle, the mode requires much less sedation and nearly eliminates paralytics.

Thus, Kaminski has found that patients who are on the mode are often easier to wean and may be able to be weaned sooner, lowering the risk of serious complications that are commonly associated with long-term mechanical ventilation.



Jodi Brewer, RCP, RRT, educator and clinical respiratory specialist in the Respiratory Therapy Department, in surgical intensive care unit with Eleanor Vallejos, RCP.



Stephen Kaminski, MD, FACS, leading trauma service physician at Scripps Mercy, has found that patients on BiVent are often easier to wean.

Anecdotally, physicians at Scripps have found that BiVent reduces patient stays in the ICU. The department plans to confirm its anecdotal findings with a retrospective study looking at patients with the same diagnoses before and after it acquired the SERVO-i ventilators.

Kaminski believes so strongly in the benefits of BiVent that he uses it prophylactically on all his trauma patients. The earlier the intervention with BiVent, the better the outcome, he says. The only exception is for those with severe head injuries. "Patients with head injuries might require control of carbon dioxide, and therefore might be better managed by automode," he notes.

BiVent, Kaminski says, works well not only as lung protection strategy but also as a salvage method. "It's good for patients at the risk of ARDS and for patients who are difficult to oxygenate."

When Kaminski introduced BiVent to the five other physicians in his trauma practice, they were eager to incorporate it as well. "They all adapted it with open arms, from our senior docs to our more junior partners," he says.

George Silva, RCP, a lead respiratory therapist, says that as a Level I Trauma Center, Scripps Mercy has always been dedicated to the highest level in trauma care. "So it is the perfect place to use the BiVent mode," he says.

BiVent is proving to be the best mode for acute-care patients at Scripps as well. At Scripps Mercy, BiVent is now not only the mode of choice for trauma patients, but also is becoming so for its critically ill medical/surgical patients.

"It gives us an extra dimension in being able to ventilate our patients, especially the very sick cases," says Julian Lichter, MD, who has been Medical Director of Respiratory Care Services at Scripps Mercy since 2002. The hospital has a total of 32 intensive-care beds, and is among the top hospitals for cancer and cardiac care as well as bariatric surgery. Lichter says that on several occasions, BiVent has proven a lifesaving mode for some patients who are more difficult to ventilate because of their size or other pre-existing health conditions.

"Before we had the BiVent capability, we probably had 20% whom we were not able to oxygenate or who oxygenated very poorly," Lichter says. "Now, we can oxygenate upwards of 95% of patients."



"Thanks to BiVent, we have reduced the need for oscillation." Glenn Tanaka, RRT, RCP, Manager of Respiratory Care Services at Scripps Mercy.



"Now, we can oxygenate upwards of 95 percent of patients." Julian Lichter, MD, Medical Director of Respiratory Care Services at Scripps Mercy.



SERVO-i in BiVent mode.



Members of the Respiratory Therapy Department at Scripps Mercy Hospital.



The nurses station in the medical intensive care unit at Scripps Mercy.

While BiVent requires a change in thinking, it has become standard protocol in difficult cases, Lichter says. “In circumstances where we have patients who are difficult to ventilate, we will always use that mode to see if it helps them.”

One advantage to BiVent, Lichter says, is that it can be used in conjunction with proning, which one small study suggests can improve gas exchange and survival rates among critical care patients. BiVent is easier to employ than proning because it is a matter of changing settings, whereas proning is more nurse-and-technician intense because it requires placing the patient on a special bed to be turned. Once the patients are on the bed and prone, it becomes more difficult to examine them, Lichter says. Also, he says, proning requires special care so tubes and other equipment are not displaced when the patient is turned. Still, he says, proning and BiVent can work well together when ventilating difficult patients.

Another positive feature of BiVent is that it can be used in conjunction with pressure support, says Glenn Tanaka, RRT, RCP, Manager of Respiratory Care Services at Scripps Mercy. The SERVO-i allows the judicious addition of pressures support due to its floating exhalation valve, he explains.

“The idea is to use the tools so you don’t have change to an oscillatory ventilation strategy,” Tanaka says. “Thanks to BiVent, we reduced the need for oscillation.”

Some researchers report success with BiVent in neonatal and pediatric populations as well as adults. For that reason, Scripps Mercy is looking at employing BiVent in its Neonatal Intensive Care Unit.

Physicians, staff anxious to incorporate BiVent and help patients: As an educator, Brewer was pleasantly surprised at how well the staff embraced the new mode and other SERVO-i open-lung capabilities. “To be honest,” she says, “I didn’t expect people to be as enthusiastic as they were because when there is a new theory out there, it is often hard to get everyone thinking it is advantageous.” However, Brewer says, the respiratory therapists were eager to learn BiVent and to assist the physicians in using it in appropriate cases. Brewer is helping the hospital to write protocols for BiVent.

With the support of MAQUET’s clinical applications specialists, a select group of physicians and RTs were trained first and they, in turn, trained others, including the nurses, on the use of BiVent. MAQUET provides continued support as needed. Scripps Mercy believes in collaborative healthcare and thus crosstrains its staff, which was easy to do in this case because the ventilators and BiVent operate with a touch screen, Tanaka notes. “BiVent is very user-friendly,” he says.

The respiratory therapists favored the SERVO-i when the hospital was looking to be able to provide new and more effective ventilation strategies. A committee had narrowed the choices on the recommendations.

“It is very important that the therapists appreciate the ventilator and are comfortable with all its modes because they are very closely involved with the equipment,” Lichter says. The hospital has 70 respiratory therapists on staff.

Tanaka says that like anything new, the physicians and staff had to be convinced that BiVent works, but it did not take long once they saw how easily it could be employed, and how beneficial it could be for their trauma and medical patients.

“Going forward,” Tanaka says, “we want to be able to provide the best care possible for our patients, and we believe that with BiVent, we can do that.”

The views, opinions, and assertions stated by Scripps Mercy staff members in this article are strictly those of the clinicians and administrators, and do not necessarily reflect the views of MAQUET.

Case Report: Status Asthmaticus Refractory to Conventional Treatment

Patricia Dailey, BS, RRT

A 15 year old known asthmatic was admitted to the Emergency Room for an acute exacerbation. Her mother stated that she had been sick with an upper respiratory infection which triggered her asthma. Over the course of her treatment in the ER she developed status asthmaticus that was refractory to standard treatment requiring intubation. She received several hours of continuous nebulized albuterol at a dose of 15 mg per hour via the Airlife Misty Finity nebulizer, and multiple 2.5 mg doses of albuterol instilled down the ET tube. The patient became increasingly difficult to ventilate and required manual ventilation with a resuscitation bag in conjunction with continuous bronchodilator therapy.

The patient was then transferred to PICU and due to the severity of her exacerbation preparations were made to place the patient on heliox therapy through the ventilator. The nebulizer was changed to an Aeroneb Solo and it was placed in-line on the dry side of the ventilator circuit which previously would not have been feasible with a standard nebulizer. Continuous bronchodilator therapy was resumed at the same dosage of 15 mg of albuterol per hour. After two hours of continuous bronchodilator therapy utilizing the Aeroneb® Solo there was a dramatic improvement in her breath sounds and she subsequently did not require heliox therapy. She continued to steadily improve on Q2 hour bronchodilator therapy and the dose was gradually weaned to 5 mg of albuterol over the next 24 hours. She was extubated the next day and continued using the Aeroneb Solo with a mouthpiece until her discharge twenty four hours later.

Our therapists were quick to recognize the benefits provided by micropump nebulizers such as the Aeroneb Solo and they are excited about our patient's demonstrated clinical response. We have seen numerous positive patient outcomes in a variety of patient populations since its introduction. The Aeroneb Solo has provided us with the superior technology necessary to assure optimal outcomes for our patients.



Patricia Dailey is Clinical Educator, BMC, Springfield, MA. This article was provided by Aerogen.

Unreported Births and Deaths, A Severe Obstacle for Improved Neonatal Survival in Low-Income Countries: A Population Based Study

Mats Malqvist, Leif Eriksson, Nguyen Thu Nga, Linn Irene Fagerland, Dinh Phuong Hoa, Lars Wallin, Uwe Ewald and Lars-Åke Persson

Abstract

Background: In order to improve child survival there is a need to target neonatal mortality. In this pursuit, valid local and national statistics on child health are essential. We analyze to what extent births and neonatal deaths are unreported in a low-income country and discuss the consequences at local and international levels for efforts to save newborn lives.

Methods: Information on all births and neonatal deaths in Quang Ninh province in Northern Vietnam in 2005 was ascertained by systematic inventory through group interviews with key informants, questionnaires and examination of health facility records. Health care staff at 187 Community Health Centers (CHC) and 18 hospitals, in addition to 1372 Village Health Workers (VHW), were included in the study. Results were compared with the official reports of the Provincial Health Bureau.

Results: The neonatal mortality rate (NMR) was 16/1000 (284 neonatal deaths/17 519 births), as compared to the official rate of 4.2/1000. The NMR varied between 44/1000 and 10/1000 in the different districts of the province. The under-reporting was

mainly attributable to a dysfunctional reporting system and the fact that families, not the health system, were made responsible to register births and deaths. This under-reporting has severe consequences at local, national and international levels. At a local level, it results in a lack of awareness of the magnitude and differentials in NMR, leading to an indifference towards the problem. At a national and international level the perceived low mortality rate is manifested in a lack of investments in perinatal health programs.

Conclusion: This example of a faulty health information system is reportedly not unique in low and middle income countries where needs for neonatal health reforms are greatest. Improving reporting systems on births and neonatal deaths is a matter of human rights and a prerequisite for reducing neonatal mortality in order to reach the fourth millennium goal.

Background

It is increasingly acknowledged that the neonatal period has been neglected in the pursuit of improved child survival¹ and that deaths in the neonatal period (the first 28 days after delivery) today constitute an increasing proportion of the overall under-5 mortality.² This neglect is not only a matter of withheld interventions, but also very much a question of invisibility of the problem.³ Thousands of newborns are never registered as being born. Within this group, the rate of neonatal deaths is higher than in the rest of the population as many unregistered neonatal deaths die before the registration of birth.⁴ This invisibility of neonatal deaths is a severe obstacle in the pursuit of improved neonatal survival since it precludes adequate planning and measures by local and global actors. In order to reach those in greatest need there has been a call for universal access to skilled birth attendance⁵ and community-based interventions,⁶ which have been shown to be cost-effective and well-suited for scaling up.^{7,8} These interventions can not rely on estimates from national or regional levels, but must be based in the local context. Therefore, there is a need for valid health statistics^{9,10} and data reporting on child births and deaths in order to have a sound basis for design and monitoring of interventions for improved child survival.⁸

Vietnam has reported a low neonatal mortality rate (NMR) in the official statistics for the past couple of years compared to

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Table 1: Births and Neonatal deaths in official statistics and in the present study in Quang Ninh province, Vietnam, 2005

	Births	whereof at home	Neonatal deaths	NMR	95% CI
Official statistics from Provincial Health Bureau	16 551	854	70	4.2	-
Present study	17 519	1461	284	16	14–18

Table 2: Neonatal deaths in Quang Ninh province, Vietnam, 2005, identified by different informants and methods of data collection according to place of death. Row percentages relating to the place of death are not cumulative, since neonatal deaths were identified from over-lapping sources.

Place of Death	Neonatal deaths	Source of information			
		Hospital register	CHC register	CHC staff	VHWs
Regional and provincial hospital	151	129 (85%)	57 (38%)	59 (39%)	94 (62%)
District hospital	60	33 (55%)	22 (37%)	32 (53%)	43 (72%)
Community Health Center	3	0 (0%)	3 (100%)	3 (100%)	2 (67%)
Home or outside health facility	67	3 (4%)	23 (34%)	31 (46%)	60 (90%)
Total	281*	168 (59%)	105 (37%)	126 (44%)	202 (71%)

*Information on place of death was missing in three cases

Table 3: Reasons found for under-reporting births and neonatal deaths in Quang Ninh province, Vietnam, 2005.

Local level

- Poor understanding of the rationale and importance for registering among health staff and families.
- Poor access to registrars.
- Difficulties in defining a neonatal death as opposed to a stillbirth.
- Local health staff having poor access to data due to family seclusion and high mobility in society.
- Reports by Village Health Workers being based on verbal reporting.

Health system level

- Reports being based on aggregates and not on individual data, making cross checking and additions impossible.
- The responsibility of reporting not being clearly communicated within the health system.
- Inadequate report forms.
- Infant mortality, but not neonatal mortality, being used in national statistics and surveys.
- Families and not the health system being ultimately responsible to register a birth or death.

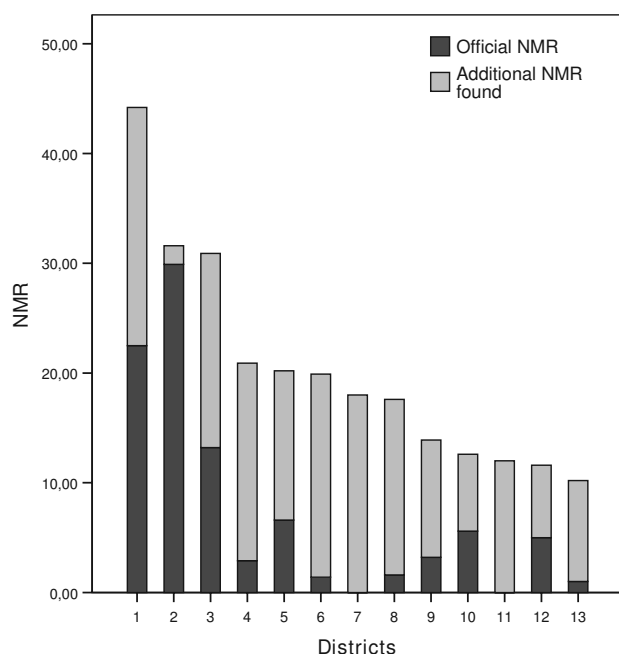


Figure 1: NMR stratified according to districts in Quang Ninh province revealing the extent of invisible neonatal mortality. Due to small size, two districts were merged in the analysis, resulting in 13 sub-entities.

other countries in equivalent socioeconomic situations. According to the Demographic and Health Survey of 2002, Vietnam has a NMR of 12.2/1000,¹¹ a figure used for WHO official statistics as well.¹² If this NMR is correct it will pose questions and hopes about the causes to the relative success in the field of child health of a country in the lower half of the income scale. However, studies indicate that there might be considerable under-reporting of neonatal deaths in the official registers¹³ and difficulties in obtaining correct information on neonatal deaths even in population-based studies. Considering the importance of the official figures at all levels for policy formation, planning and allocation of funds, it is evident that accurate information is needed on the health situation of newborns in low- and middle-income countries. The aim of the present study is to analyse to what extent births and neonatal deaths go unreported in the official statistics in a province in Vietnam, and to discuss the consequences at local and national levels for future efforts to save newborn lives.

Methods

Setting: The study area was Quang Ninh province, one out of 64 provinces in Vietnam. Quang Ninh is situated along the Vietnamese coastline bordering China in the north, with a population reaching just above 1 million, 80% of which live in rural and mountainous areas. Ha Long City, the major city in the

Table 4: Observed consequences of poor registration systems on neonatal health.International and national levels

- The magnitude of neonatal mortality in the country is underestimated, and the flow of resources from major stake-holders is misguided
- The monitoring of indicators for the Millennium Development Goals will be arbitrary without valid information.
- Targeting of interventions to those most in need will be impossible.

Regional and local levels

- Awareness of neonatal mortality as a major health problem will be low, and interventions proved to reduce neonatal mortality will not be implemented.
- If any, measures taken to improve reproductive health will be inadequate since the interventions needed differ substantially between high and low mortality settings.
- At a local level, the perinatal period will not be perceived as a period of increased risk for mother and child, resulting in poor preparations and precautions for pregnancy and delivery.

province, is one of Vietnam's major tourist centres, tourism being the driving force of the present economic boom in Quang Ninh. Within this population, 11% belong to ethnic minorities and 10–15% are considered poor.¹⁴ The province is divided into 14 districts and 184 communes. This division is also the base for the health system, with each district containing one district hospital (DH) and each commune containing at least one community health centre (CHC). At the provincial level there is one provincial hospital (PH) situated in Ha Long city and one regional hospital in Uong Bi Town (UBGH).

The reporting of health statistics follows the structure of the health system, with the CHC being the lowest level at which data is recorded in registers. Births and deaths that occur in a commune should all be registered at the CHC, using information from monthly verbal reports from the Village Health Workers (VHW) of that commune. The information is then sent upwards in the system as aggregates, first to the District Health Bureau (DHB) where the figures for the whole district are compiled and then on to the Provincial Health Bureau (PHB). In our study, the official statistics were collected from the data sent to the Ministry of Health from the PHB.

Aside from the health system there are alternate reporting systems through governmental administrative bodies. When a child is born, the family receives a birth certificate from the health institution where the delivery took place or from the CHC if it was a home delivery. With this certificate, the family should register at the Community's People's Committee, providing an alternate source of official statistics on births. The Vietnamese Government has issued a decree which requires parents to register their child within 30 days of birth (60 days in remote areas).¹⁵ However, even if the child is registered within the prescribed time period it is not necessarily within the neonatal time period, implying that neonatal deaths take place before children need to be registered. When there is a death, there is no death certificate, and the family seldom registers the event at the People's Committee. At the national level, the General Statistics Office (GSO) in Hanoi annually performs a survey, gathering data on infant mortality rate (IMR) and under-5 mortality rate (U5MR) for the whole country. That survey uses a multi-level cluster sampling technique, covering 2% of the population. NMR is not an indicator in that survey.

Study design: Different sources of information were used to collect data on neonatal mortality in Quang Ninh province for the time period between January and December 2005: health registers at hospitals and CHCs, recollections of reproductive health events by health staff, and group interviews with VHWs.

The results were then compared to the official statistics obtained from the Provincial Health Bureau (PHB). Fifteen full-time employed data collectors gathered data from April to June 2006.

At the regional, provincial and district hospitals, registers at the obstetric and pediatric departments were checked in order to find notations about neonatal deaths. The staff was also asked to recollect cases of neonatal death during 2005 that had not been noted in the books. Before collecting data, a meeting in each district with all the midwives working at CHCs was arranged. At these meetings, information about the study was provided and the midwives got a report form to bring back to the CHC, including data on neonatal deaths. These forms were later cross-checked with the registers of the CHCs.

Every commune is divided into a number of villages and each village has an assigned health worker, mainly responsible for health information and reporting. All in all there were 1500 VHWs in Quang Ninh province. Group interviews, with three to six VHWs at a time, were performed by the data collectors. Verbal consent of participation was obtained before the group interviews took place. The VHWs were asked to recollect any neonatal deaths that happened during 2005 and to give details about these cases. This information was later crosschecked with registers and the recollection of CHC staff.

Data analysis: For every neonatal death identified, a separate report form was filled in. The forms were compared in order to find over-lapping information sources and avoid duplicates. Every case of mortality was evaluated according to the WHO definition of neonatal death in order to avoid misclassifications. This process was supervised by the authors.

Results: Information was excerpted from registers at all relevant health facilities in Quang Ninh province ($n = 205$). Questionnaires were received from all midwives at CHCs ($n = 187$) and 427 group interviews were conducted with Village Health Workers (VHW). Out of the 1500 villages in the province, 109 were not represented at group interviews (7.3%).

According to the official statistics gathered from the Provincial Health Bureau there were 16 551 live births in Quang Ninh province during 2005, whereof 854 were born at home. By collecting data from the registers at the different health facilities and adding the information given by the VHWs at group interviews on home deliveries and births taking place outside the province, 17 519 live births in 2005 were found, 1461 of which had occurred outside health facilities (Table 1).

Neonatal deaths

A total number of 284 individual neonatal deaths were found through the different methods used, giving a NMR of 16/1000 (284/17 519), using the number of live births and deaths found in our study. The early neonatal deaths (day 0–6) numbered 229/284 (81%) and 131/284 (46%) died within the first 24 hours, 217 (76%) of the deaths occurred at a health facility. When checking registers at health facilities, notations of 213 neonatal deaths were found, whereas the VHWs and CHC staff knew 225 out of the 284 neonatal death cases. Only two cases were found exclusively at the CHC level, as compared to 57 and 54 cases respectively that were found only in the hospital records and when interviewing the VHWs (Table 2). The official statistics from the PHB reported 70 neonatal deaths during 2005, giving an NMR of 4.2/1000 (70/16 551) for the whole province according to the official records. Due to limitations in the official reports, there was no possibility to identify the individual cases of neonatal death for comparison. However, the distribution of NMR at a district level reveals that only one out of 14 districts reported more than 50% of the neonatal deaths. The accuracy of the official statistics vis-à-vis our results varied considerably between the different districts (Figure 1), indicating a severe malfunction of the official reporting system. Our study also found a considerable incompleteness in the health facility records. Of the newborns that died in a district hospital, 45% (27 of 60) were not noted as dead in the corresponding registers (Table 2). The corresponding figure for third level hospitals (PH and UBGH) was 15%. There seems to be many reasons for this under-reporting of neonatal deaths. One reason noted was the structure of the reporting system, where the responsibility for reporting was shifted away from the health system towards the parents of the newborn. There also seemed to be a poor understanding of the reasons and benefits of reliable statistics at all levels in the health system. In Table 3 we outline some of the reasons found during data collection.

Discussion

We have found a substantial under-reporting of neonatal deaths in a province in Northern Vietnam. The NMR found through the different methods used in this study is four times higher than the officially reported NMR. The distribution of deaths over age is in accordance with international experience. The rule of two thirds apply to our data: that at least two thirds of neonatal deaths occurred in the first week of delivery¹⁶ and that two thirds of the early neonatal deaths happened within the first 24 hours, a proportion that has increased over the past few years.² A tendency to systematically misreport the age of death, with so called “heaping” on day 7 has also been reported and used as a measure of the accuracy of collected data.¹⁷ Our material contained no such heaping.

Nevertheless, our study has limitations, one being that we, in the pursuit of neonatal deaths, many times were depending on the malfunctioning reporting system we were trying to validate. Further, data collectors were dependent on the goodwill of local authorities to be able to get hold of medical records and to talk with health staff. The support from the Ministry of Health was very valuable in this regard. The VHWs were an important source for finding unreported neonatal deaths and the fact that 7% of them did not participate in group interviews implies that the results are not complete. There is also a question of recall bias, since the VHWs were asked to remember events more than a year old. This was dealt with by cross-checking and comparing with other sources whenever possible. However,

correcting the possible errors of our study would only increase the NMR further.

The occurrence of this kind of under-reporting of neonatal deaths is commonly known, but the extent of the problem differs. Our results indicate that this is not an isolated problem and our findings verify earlier research on death reporting from various settings.^{13,18–24}

Reasons for under-reporting: There seems to be various reasons why children are registered late or never (Table 3). In the Vietnamese society the responsibility to register newborns is put on the families, which in many cases have a poor understanding of the necessity to register. Many parents simply do not see an urgent need for the procedure and some in remote areas simply do not have easy access to registrars. Another important aspect, despite being specific to Vietnam, is that Vietnam's family planning law has implemented fines and other penalties for families having more than two children. Consequently, many families try to avoid extra payments and the third and following children go unreported.¹⁵ According to a UNICEF study, less than half of the families had registered their child within the legally prescribed time period.¹⁵ If instead the responsibility to report births and deaths was placed on the institutions where these events occurred, more reliable statistics would be produced. Our study shows that 225 out of the 284 neonatal deaths would have been reported if the deaths that were noted and known of at various institutions had been reported (including 60 neonatal deaths known by VHWs to have happened at home). This means that 79% instead of 25% of the neonatal deaths would have been included in the official statistics. Similar results have been reported elsewhere.¹⁸ However, even if the hospitals were to report directly to the corresponding administrative body, their reports would be based on aggregates and not on individuals, leaving no mechanism for cross checking and adding omitted cases to the official statistics.

Another well-recognised difficulty in the registration of neonatal deaths is the matter of defining early neonatal deaths from stillbirths. To distinguish whether a baby dies intrapartum or shows signs of life right after delivery can be difficult, and establishing the boundary can be a source of confusion.¹⁵ To avoid this, perinatal mortality has often been used as measure, combining the stillbirth rate with the early neonatal mortality rate. Especially in a setting with a large proportion of home deliveries, perinatal mortality has been a widely used indicator, avoiding the troubles of definition. However, considering the differences in etiology between stillbirths and neonatal deaths and the subsequent possible preventive interventions there is an argument for stratifying them.²⁵

The mobility in society also posed a problem for the VHWs and CHC staff to gather information. The antenatal care (ANC) in the province is not centralised or continuous and a pregnant woman can choose many different providers of ANC. The ANC journal also follows the woman and is not kept at a specific health facility. This, together with the habit of many pregnant Vietnamese women to go back to their parents' house in time for delivery, makes it difficult for VHWs and CHC staff to get an overview and follow-up on pregnancy outcomes.

Under-reporting of births and deaths may have severe consequences for policy formation, health planning, research

and resource allocation at all levels in the pursuit of improved neonatal survival (Table 4). As in this example of Vietnam, the country does not qualify among the 60 priority countries set up by the Partnership for Maternal, Newborn and Child Health,²⁶ thereby not receiving the attention given to these countries, despite being in a similar situation.¹ The priority list is based on WHO statistics¹² and with a more accurate reporting system, Vietnam, with its annual 1.6 million births, would be included among the countries in which more than 90% of all child deaths take place. Furthermore, monitoring of indicators for the Millennium Development Goal on child survival (MDG-4) will remain arbitrary as long as figures are based on estimations and extrapolations only and not on locally based reporting systems.

At a national level, there seems to be a general understanding within the Vietnamese health system that the quality of data on births and deaths are poor. Even if there is a structure for a vital registration system in Vietnam, the authorities conduct an annual national survey on births and deaths but without collection of information and reporting on neonatal deaths.²⁷ The lack of accurate information on neonatal mortality results in a situation where health planners and decision-makers at national and regional levels cannot be guided or encouraged to act according to the real situation. Variations between different areas within regions might be very large, as we have found in Quang Ninh province, and without statistics based on the local situation it will be difficult to target interventions that reach those in greatest need.

At a local level, the lack of reliable statistics will be a factor that preserves status quo. Pregnant women will not prepare for or take adequate precautions before delivery since pregnancy may be perceived as a part of life and not as a potentially hazardous situation.²⁸ Initiatives by local actors or NGOs will not be backed up by statistics and local authorities will not act to solve a problem they do not perceive they have. On the contrary, local authorities might even encourage under-reporting in order to gain approval and rewards from higher levels.

To register the death of a newborn is, however, not only a matter of statistics, but also a matter of human rights. The right to birth registration is part of the UN convention on the Rights of the Child²⁹ but despite this fact, newborns that are not reported to have died are often not registered as being born. The implementation and enforcement of human rights depends on civil registration, something that in many parts of the world is not well known or recognized.³⁰ Acknowledging and reporting a neonatal death strengthens the position and rights of the living by acknowledging that every child is a human being from the moment of birth. The UN Millennium Project states that in order to improve the situation of women's and children's health in the world, human rights need to be highlighted and enforced.³¹ Pursuing a true representation of child survival is an integral part of this effort.³²

Conclusion

In order to reach MDG-4 and improve child survival, neonatal mortality must be targeted. One part of that effort is to improve and build trustworthy reporting systems for births and deaths in countries with incomplete official data. Meanwhile, it is recommended that planners and politicians at all levels take the under-reporting into account in order to avoid basing decisions on invalid information. In doing so, the challenges in neonatal health can be recognised and resources may be distributed

according to real needs instead of overly optimistic indicators.

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TIPIT: A Randomized Controlled Trial of Thyroxine in Preterm Infants Under 28 Weeks' Gestation

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Abstract

Background: Infants born at extreme prematurity (below 28 weeks' gestation) are at high risk of developmental disability. A major risk factor for disability is having a low level of thyroid hormone which is recognised to be a frequent phenomenon in these infants. At present it is unclear whether low levels of thyroid hormone are a cause of disability, or a consequence of concurrent adversity.

Methods: We propose an explanatory multi-center double blind randomized controlled trial of thyroid hormone supplementation in babies born below 28 weeks' gestation. All infants will receive either levothyroxine or placebo until 32 weeks' corrected gestational age. The primary outcome will be brain growth. This will be assessed by the width of the subarachnoid space measured using cranial ultrasound and head circumference at 36 weeks' corrected gestational. The secondary outcomes will be (a) thyroid hormone concentrations measured at increasing postnatal age, (b) status of the hypothalamic pituitary axis, (c) auxological data between birth and 36 weeks' corrected gestational age, (d) thyroid gland volume, (e) volumes of brain structures (measured by magnetic resonance imaging), (f) determination of the extent of myelination and white matter integrity (measured by diffusion

weighted MRI) and brain vessel morphology (measured by magnetic resonance angiography) at expected date of delivery and (g) markers of morbidity including duration of mechanical ventilation and chronic lung disease. We will also examine how activity of the hypothalamic-pituitary-adrenal axis modulates the effects of thyroid supplementation. This will contribute to decisions about which confounding variables to assess in large-scale studies.

Background

In the immediate postnatal period of babies born at term, hypothyroidism causes neurodevelopmental disability. This disability can be prevented by giving supplementary thyroid hormone. Infants born at extreme prematurity (ie before 28 weeks' gestation) are at high risk of neurodevelopmental disability, particularly if they are hypothyroid. Some, but not all, forms of thyroid supplementation appear to reduce the incidence of poor neurodevelopmental outcome in infants born at extreme prematurity.

Hypothyroidism in early infancy causes neurodevelopmental disability which can be prevented by giving supplementary thyroid hormone.

In congenital hypothyroidism (CH) early treatment with thyroid replacement reduces severe developmental deficits. Even mild thyroid hormone insufficiency can produce measurable, but preventable, deficits in neuropsychological functions. Magnetic resonance imaging (MRI) and spectroscopy (MRS) have documented brain metabolic changes in untreated CH. The reversal of these abnormalities following replacement therapy is thought to be due to improved myelination. This suggests an important role for thyroid hormone in the developing brain in the early postnatal period.

Infants born before 28 weeks of gestation are at high risk of disability. Advances in neonatal medicine have resulted in an increase in survival of preterm infants below 28 weeks' gestation. Infants born extremely prematurely at this low gestation are at particular risk of neurological abnormalities. The normal development of the brains of these infants is at high risk of disruption with consequent acquired damage especially to the white matter because of multiple facts. These are thought

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Adverse event	Estimated incidence
a) death	20%*
b) necrotising enterocolitis or focal intestinal perforation diagnosed on clinical grounds, or at surgery	15%*
c) intracranial abnormality (parenchymal haemorrhage or focal white matter damage) on cranial ultrasound	15%*
d) requirement for supplementary oxygen 28 days after birth	55%*
e) patent ductus arteriosus requiring medical or surgical management	25%*
f) retinal surgery for retinopathy of prematurity	5%*
g) sustained tachycardia (greater than 220 beats per minute for more than 30 minutes in a 60 minute period)	20%**
h) pulmonary haemorrhage	5%**
i) persistent weight loss after 14 days after birth in the absence of infection.	10%**

Table 1: List of expected serious adverse events

* based on incidence of these complications at Liverpool Women's Hospital

** based on incidences estimated by the investigators

to include hypoxic ischaemia, free radical injury because of low concentrations of antioxidants, undernutrition and sepsis. This period in brain development is important because neuronal migration has only just finished (at about 20 weeks) and synaptogenesis is occurring and therefore the cellular milieu is critical.

Brain MRI studies of survivors of low birth weight, who have subtle cognitive abnormalities have been shown to have diminished volumes of the caudate nucleus hippocampus and these findings have been correlated with lower IQ, learning disorder and attention deficit. Recent brain MRI studies of preterm infants also show that quantitative cerebral structural abnormalities are related to the degree of immaturity at birth and are followed by abnormal neurodevelopmental outcome. Preterm infants assessed at term show reduced myelination when compared to infants born at term.

Evidence of hypothyroidism is common among infants born before 28 weeks of gestation and is associated with an increased risk of disability. Transient hypothyroxinaemia of prematurity as characterized by low blood thyroxine (T4) concentrations with normal or mildly elevated plasma thyroid stimulating hormone (TSH) concentrations is common in infants under 30 weeks' gestation at birth, occurring in up to 69%. The proportion of preterm infants having hypothyroxinaemia increases with decreasing gestational age. A recent large collaborative Scottish study has shown that an extremely premature group of infants of 23-27 weeks' gestation appeared distinctive and were hypothyroxinaemic relative to other groups. The postnatal surge of T4 concentrations described in the term infants was less marked in infants of 31-34 weeks gestation, absent in infants of 28-30 weeks and reversed in infants of 23-27 weeks who had low plasma T4 concentrations.

Low blood thyroid hormone concentrations in the first few weeks of life in preterm infants have been linked with poor neurodevelopment. Reuss et al (n=463) found a 4-fold increased risk of disabling cerebral palsy at 2 years of age associated with hypothyroxinaemia in infants born below 33 weeks gestation. Den Ouden et al (n=563) found a higher incidence of neurological dysfunction at 5 and 9 years of age in associated with lower thyroxine concentrations even after adjustments for other perinatal factors in preterm infants born below 32 weeks. Paul

et al found increased mortality and increased incidence of intraventricular haemorrhage in preterm infants with abnormal thyroid function, whilst Leviton et al reported white matter changes predictive of abnormal neurological outcome on cranial ultrasound of neonates with low T4 blood concentrations. In addition, published data have documented a relationship between maternal thyroid deficiency during pregnancy and problems with neuropsychological development of the offspring. However, the questions of whether this hypothyroidism reflects the adversity leading to brain injury, or whether hypothyroidism is a preventable cause of brain injury can only be answered by randomized controlled clinical trials.

Thyroid supplementation to extreme preterm infants may reduce the risk of disability. A randomized controlled trial of T4 supplementation by Van Wassanaer et al showed an improved Bayley Mental Development Index (MDI) and Psychomotor Development Index (PDI) at 2 years among infants born at extreme prematurity who had received T4 supplementation. However, the babies who appeared to benefit were not the primary target population in this study and the positive result was only evident after subgroup analysis. In the whole sample there was no benefit to long term outcome. The reliability of that trial was limited by a small sample size. In other studies, thyroid hormone replacement has been given to preterm infants with either beneficial effects or no apparent effects. However, the studies which have been done are of small sample size and have not shown rigorous proof of efficacy of such a treatment.

A Cochrane review of thyroid hormone supplementation in premature infants found that none of the available trials provide good evidence for the value of thyroid hormone supplementation in preterm infants. The results of the meta-analysis found no significant difference in overall mortality. Meta-analysis of two studies found no significant difference in Bayley MDI or PDI performed at 7-12 months, death or IQ score at 5.7 years of age. All studies were of small size with the largest by van Wassanaer, which enrolled 200 infants under 30 weeks' gestation. However, the sample size for this post hoc subgroup analysis of infants with gestational age below 27 weeks who benefited from the intervention was small comprising just 46 infants (19 in the treatment arm and 27 in the placebo arm). The review concluded that future trials of sufficient size needed to be undertaken to detect the clinically important differences in



Figure 1: Patient Flow During Trial

neurodevelopmental outcome, particularly enrolling the infants most likely to benefit from thyroid hormone therapy such as extremely preterm infants.

The conclusion from these results is that there is biologically plausible evidence that T4 supplementation for very immature babies may improve their neurological outcome, but that more mature babies are not likely to benefit from this intervention. Studies of triiodothyronine (T3) supplementation have not provided evidence for improved outcome. Animal studies have shown that the postnatal development of brain structures in rats was entirely dependent on local generation of T3 from T4 by type 2 iodothyronine deiodinase. This suggests that normal neurodevelopment requires appropriate T4 supplementation and not T3 supplementation. T3 supplementation appeared to raise plasma free T3 and total T3 concentrations but suppress T4 concentrations. T4 supplementation has been shown to suppress T3 concentrations but raise total and free T4 concentrations (FT4). Van Wassanaer et al examined different T4 dosage scheme and concluded that 8mcg/kg birthweight/day increased T4 and FT4 concentrations most appropriately and prevented transient hypothyroxinaemia during the 6 weeks' treatment. Van Wassanaer also showed that high longitudinal

FT4 concentrations were not associated with worse outcome, while low FT4 concentrations were associated with worse neurodevelopmental outcome at 2 and 5 years of age. In the light of these findings, a trial of T4 supplementation is a strong candidate for intervention.

An important practical issue for intervention studies is the need to classify the thyroid status of individual infants. The blood concentrations used in this classification will determine recruitment to the study and the response to monitoring during the intervention. At present, it remains unclear what cut-off point for T4 or FT4 concentrations constitutes hyperthyroxinaemia or hypothyroxinaemia in these preterm infants, particularly in the weeks just after birth. Normative values for thyroid hormones in cord blood for each gestational age have been published. It has been suggested that these values can provide normative values in the postnatal period by relating concentrations at a particular corrected gestational age to those of infants born at the same gestational age. However, the implications of this strategy have not been explored in treated infants. We will be able to model the implications of this strategy using the results of this trial.

The associations of transient hypothyroidism have not been studied among infants born at extreme prematurity

Following birth, thyroid status changes and these changes are influenced by gestational age at birth. The consequences of these changes have not been reported. Longitudinal measures of thyroid status and neonatal progress will be made during this trial and will allow us to describe how thyroid status in the weeks after birth at extreme prematurity is related to neonatal course.

Thyroid status may affect other organ systems in ways that affect the design of future trials. Thyroid hormones alter metabolic rate. Nutritional and growth implications of hypothyroidism have not been studied. Thyroid supplementation could increase nutritional requirements and reduce extrauterine growth. To date, there is little evidence of this occurring among infants born at extreme prematurity. Given that neurodevelopmental outcome may be confounded by the social environment after discharge, it will be important to include neuroradiological markers of brain development as an intermediate outcome. However, although thyroid hormones are involved in brain development, particularly in myelination, there is a paucity of published data concerning the relationship between thyroid hormone status and brain development in preterm infants. The lack of information about how thyroid status relates to brain size and body growth will hinder clinical trials of thyroid supplementation.

Other factors may be relevant to the effects of thyroid supplementation on outcome. Factors which may contribute to abnormal thyroid function in very preterm infants include: immaturity of the thyroid gland, immaturity of the hypothalamic-pituitary thyroid axis, disruption of maternal transfer of T4 through the placenta, relative immaturity of type 1 deiodothyronine monodeiodinase enzyme systems and reduction in thyroid binding globulin (TBG) due to hepatic immaturity. Iodine is required for renewal of intra-thyroidal T4, but the concentrations of iodine in the thyroid gland of preterm infants are low. This appears to be related to maternal iodine status and effect of inadequate iodine supplementation in parenteral nutrition for preterm infants.

Abnormal thyroid size is often found in disease states, eg goiter. Thyroid size may therefore be a useful marker of thyroid status. However, the only normative study of thyroid size in term infants was limited to 100 infants and did not examine infants born at extreme prematurity.

Blood cortisol concentrations decrease as blood T4 concentrations increase with advancing gestational age. These observations suggest that there may be an interaction between the cortisol and thyroid systems in preterm infants. Since both hormones have been implicated in early brain development, this interaction could contribute to the poor neurological outcome of infants born extremely premature. Activity of the hypothalamic-pituitary-adrenal (HPA) axis is central to normal fetal development and neonatal transition. Extremely premature infants have low basal blood cortisol concentrations and inadequate stimulated cortisol responses to adrenocorticotrophic hormone in the early neonatal period. Cortisol is important for survival during illness and cortisol concentrations are expected to increase during significant stress. In ill adults with low baseline and stimulated cortisol concentrations,

mortality is higher. In the preterm infant population, the physiological significance of lower blood cortisol values remains unclear. Most studies have not consistently correlated blood cortisol concentrations to physiological markers of cortisol effect and outcome in preterm infants. In a recent study, the HPA axis was found to be unresponsive to standard stimulation tests until 11 days of age in preterm baboons indicating HPA axis immaturity. Activation of the HPA axis and increased blood cortisol concentrations may be essential to respond to the many stressors of extra-uterine existence in the extreme preterm infants. This transient inability of the adrenals to maintain cortisol homeostasis in premature newborns in the immediate postnatal period has been described as transient adrenocortical insufficiency of prematurity.

Valerio et al looked at the effect of thyroid hormone supplementation on blood cortisol concentrations in babies born below 28 weeks GA. The sample size was small with only 31 patients. No significant difference was noted in cortisol concentrations and mortality between the groups. The results of the study suggest that hypothyroxinaemia was not involved in the development of hypocortisolism in preterm infants. However, the medium-term effects of the relationships between these two endocrine systems have not been studied. Further understanding of their roles in the outcome of preterm infants is needed.

Possible negative effects of giving T4: Thyroxine is infrequently given to extremely premature babies. The only adverse effect that might be predicated is based on clinical experience of giving the drug to more mature patients, namely a persistent tachycardia. The drug may increase metabolic rate. In the critical paper by van Wassenaer et al, there was no difference in neurodevelopmental outcome as a result of T4 supplementation. However, a post hoc subgroup analysis showed that more mature babies who were given T4 supplementation had a worse neurodevelopmental outcome than those who were unsupplemented. The mechanism for this possible effect is not known.

Levothyroxine pharmacokinetics: There has been no previous work in this patient group on the circulating blood concentrations of thyroid hormones following the administration of levothyroxine. Establishing whether each infant has similar circulating blood concentrations will be an important aspect of the explanatory RCT. We will use population pharmacokinetic techniques. These will allow us to derive information about circulating thyroid hormone concentrations using measurements done on blood samples taken during routine clinical practice.

In summary, the literature indicates that several areas of uncertainty will hamper randomized controlled studies of interventions for hypothyroidism in extremely preterm infants. These areas include: the optimal timing of monitoring, whether it is appropriate to use reference ranges based on cord blood values, the effect of cortisol status on thyroid function and the relationship between thyroid status and HPA axis. None of these issues can be clarified unless infants who receive thyroid supplementation are prospectively compared to infants who do not receive thyroid supplementation.

In the light of the issues outlined above, an explanatory randomized controlled trial of thyroid supplementation is

proposed in infants below 28 weeks' gestation, with an assessment of its effect on short term explanatory outcomes. This study will markedly enhance the design and interpretation of future large-scale studies aimed at determining the effect of such supplementation on long term neurodevelopmental outcome. There is therefore an urgent need for a larger scale study to discover whether thyroid supplementation benefits these very premature babies. This proposed study will examine the effects of one commonly used form of thyroid supplementation on key intermediate outcomes in these infants. We will also extend previous work in this area by exploring perinatal factors which could modulate the effects of thyroid supplementation.

The aim of the study is to determine how treatment with levothyroxine (LT-4) postnatally until 32 weeks corrected gestational age (CGA) modulates brain size and development, the hypothalamic-pituitary-adrenal axis (HPA) and somatic growth in a randomized double blind placebo-controlled trial.

Objectives: Primary Outcome – Effect of levothyroxine therapy on brain size as assessed by the width of the subarachnoid space measured at 36 weeks CGA using cranial ultrasound and serial head circumference as an index of brain weight.

Secondary Outcomes: (a) Serial head circumference as an index of brain weight; (b) Longitudinal thyroid hormone concentrations between birth and expected date of delivery; (c) Cortisol hormone status between birth and expected date of delivery; (d) Auxological data at pre-randomisation, day 14, day 21, day 28 and at 36 weeks' CGA; (e) Thyroid gland size measured by ultrasound imaging; (f) Mortality; (g) The volumes of key brain structures, whole brain volume, extent of myelination of cerebral white matter and white matter integrity and brain vessel morphology using brain MRI examinations at term equivalent; (h) Duration of mechanical ventilation/oxygen requirement; (i) Chronic lung disease requiring home oxygen at discharge.

Methods: Trial Design – A multicenter double blind randomized placebo controlled trial of levothyroxine given postnatally to infants born under 28 weeks' gestation until 32 weeks' CGA. Parents, care providers and outcome assessors will be blind to the allocation of placebo and levothyroxine. For specifics on inclusion criteria and exclusion criteria, randomization, handling of case reports and confidentiality, dosing and placebos, blood investigations, subject withdrawal information, and other detailed trial protocols, please go to the internet, BioMed Central, and type in the full name of this study.

Significance of the Trial

The optimal way to manage transient hypothyroidism in preterm infants under 28 weeks' gestation is unclear. In part, this is because infants born at extreme prematurity have different physiology from older children, preterm delivery leads to some unique complications and infants undergo striking maturational changes during their stay on the intensive care unit. Thus, studies that test whether manipulation of the thyroid system alters outcome need to be based on a refined understanding of how thyroid supplementation relates to premature birth, its complications and subsequent development. Recent guidelines from the National Institute for Clinical Excellence (NICE) emphasise this need for including such children in rigorous studies of interventions rather than treating them on an ad hoc

basis. To date other studies have not reported serious harm as a consequence of T4 therapy in preterm infants. The role of thyroid hormone therapy in preterm infants under 28 weeks gestation will be established or refuted as a consequence of this trial. The information acquired will be of interest to neonatologists, obstetricians, paediatric endocrinologists and a wide circle of general paediatricians in their management of preterm infants. This will help to ensure those who need treatment receive it, and those who do not need treatment will not receive inappropriate therapy.

This study will yield novel data about how supplementation with thyroid hormone of an extreme preterm infant modulates the hypothalamic-pituitary-adrenal axis, somatic growth and brain size at term. It is an explanatory trial designed to provide data that will provide essential underpinning to pragmatic trials of treatment efficacy by clarifying the facts that need to be accounted for in large-scale studies and providing estimates of variability in key confounders.



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