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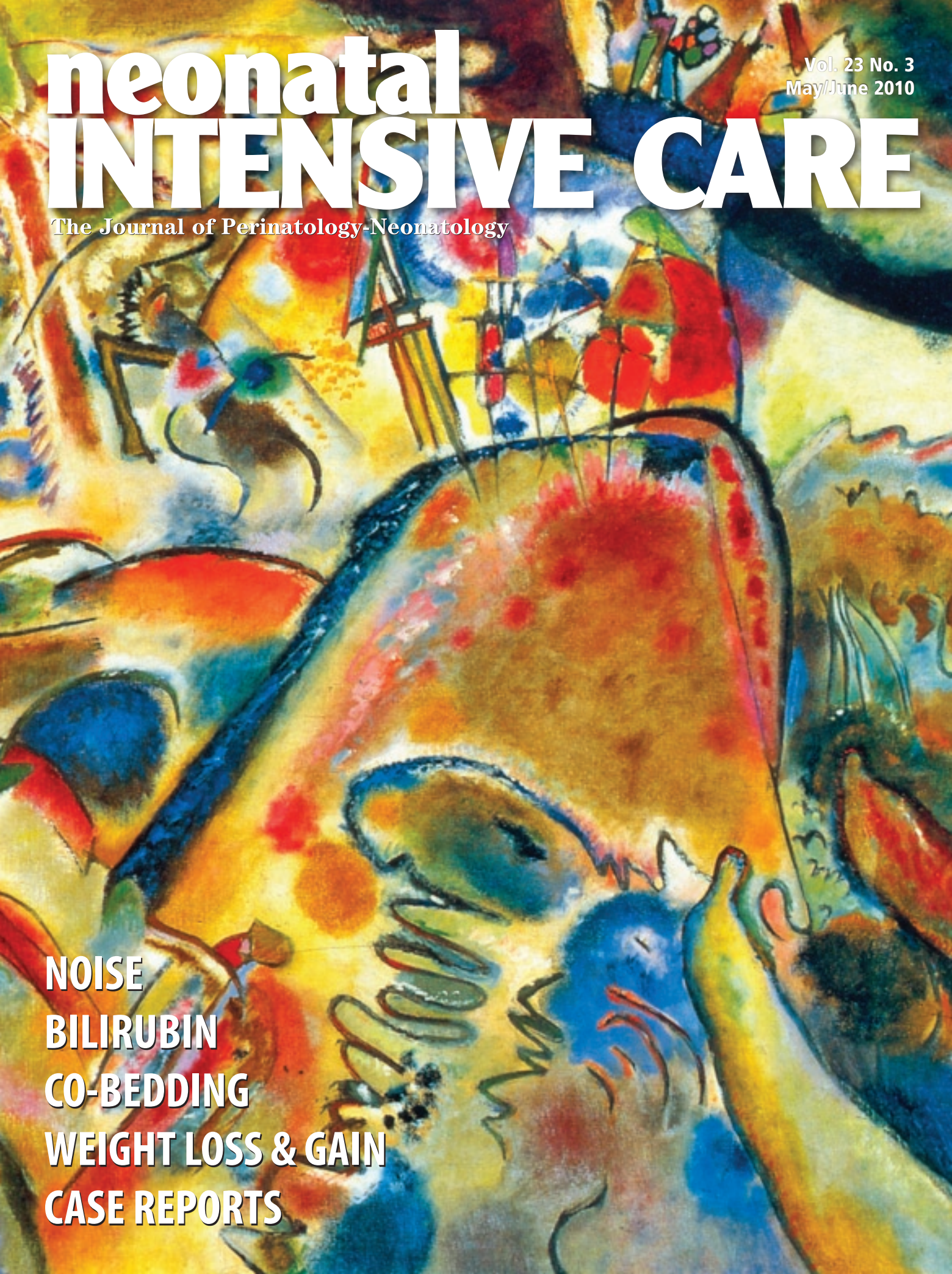
May/June 2010

neonatal INTENSIVE CARE

The Journal of Perinatology-Neonatology



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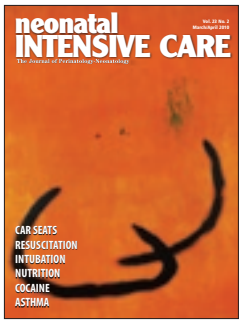

neonatal
INTENSIVE CARE

Vol. 23 No. 3
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Editorial

Chickens and Consequences

"Chickens always come home to roost" meets the "law of unintended consequences." With the limits of viability tested by advances in reproductive technology, admissions to NICUs are certainly not expected to fall any time soon. However, pari passu, the money for such care is certainly not a bottomless fount for our citizenry under our current "healthcare" system, which—regardless of current half-measure fixes, is basically based on a model of greed. Concurrently, with women having, basically, elective childbirth past their prime, and mothers with money opting for a "timed" birth, cesarean sections have increased exponentially. And while women insist on fulfilling their supposedly sacrosanct biological roles, they often wind up making very sick very little babies.

Meanwhile, basic birth-related healthcare for women, that is, good prenatal care, affordable doctor visits, no bums rush from the hospital, and the like, are chimeras for many. This equals more problem births. It's as if we have two competing paradigms: a large group of basically underinsured moms lacking some of the rudimentary basics of prenatal and natal care on the one hand, and on the other, a high-tech, high-octane, big billings sector servicing the affluent and utilizing a disproportionate amount of resources. And, of course, doctors, repaying exorbitant loans for their education, would rather be in the money-making sector. Arguably, medicine always runs up against such moral, ethical, and cultural determinants. You can't have an action without a reaction, and here's where it gets tricky.

Two items from our news section offer cases in point. The consumer group California Watch reports that the mortality rate of the state's women who die from causes related to pregnancy has tripled in the last ten years: "It's more dangerous to give birth in California than it is in Kuwait or Bosnia," the group said. While the comparison is hyperbolic, it is not without foundation. The reasons for the increase in California's mortality rate are morbid obesity, high blood pressure, diabetes, and primarily, hemorrhaging from C-sections. And where did these contributory factors come from? See above.

In a related story, Stephen Latham, writing in The Hastings Center Report, argues that the doctor shortage may be a peculiarly selective one. For example, he writes, "the supply of neonatologists is not greater in regions where newborns have a higher incidence of low birth weight, prematurity, or any other measure of neonatal risk. In fact, studies show that physician supply follows an 'inverse care law,' with supply lowest in high-need regions. What's worse, research also suggests that most newly trained physicians practice precisely in the areas that already have the most physicians." Thus, the projected physician shortage certainly doesn't apply to areas that can afford paying customers, but mainly to underserved areas. More physicians, Latham said, have not, and would not, solve this problem. Additionally, Latham notes, "An increase in the physician supply—particularly if it causes concentrated pockets of oversupply within particular specialties or regions—will result in an increased provision of physician services, not all of it of discernable benefit to patients." In other words, he infers, expansion of supply drives utilization of specialized services.

Any solution or improvement always has unexpected consequences. Neonatologists, at the forefront of basic medicine and high tech care, are, perhaps, in the enviable position of seeing these analytics placed into play every day in the NICU.

Les Plesko, Editor

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When RSV* activity erupts...

More children may be visiting the hospital or your office for help[1,2]

RSV is the leading cause of bronchiolitis and pneumonia in pediatric patients[1,3]

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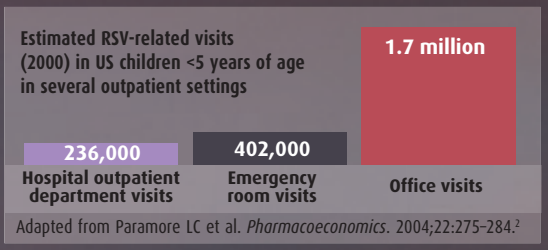

Adapted from Paramore LC et al. *Pharmacoeconomics*. 2004;22:275–284.[2]

Potentially serious long-term consequences

- RSV-related lower respiratory tract illnesses (LRTIs) in infancy may be associated with an increased risk of asthma in the first decade of life[5–7]

Age	Asthma RR† (95% CI‡)
3 years	**21.8** (2.90–163.57)[5]
7 years	**9.23** (2.79–30.55)[6]
13 years	**6.8** (2.7–17.3)[7]

Based on a prospective cohort of 47 (93 control) Scandinavian children <1 year of age in 1989 hospitalized with RSV and followed for 13 years.

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*RSV = respiratory syncytial virus.
†RR = relative risk.
‡CI = confidence interval.

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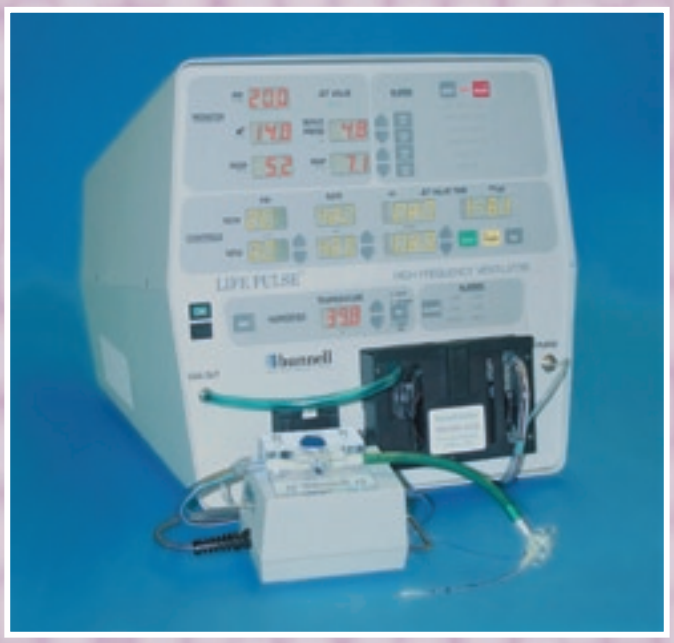

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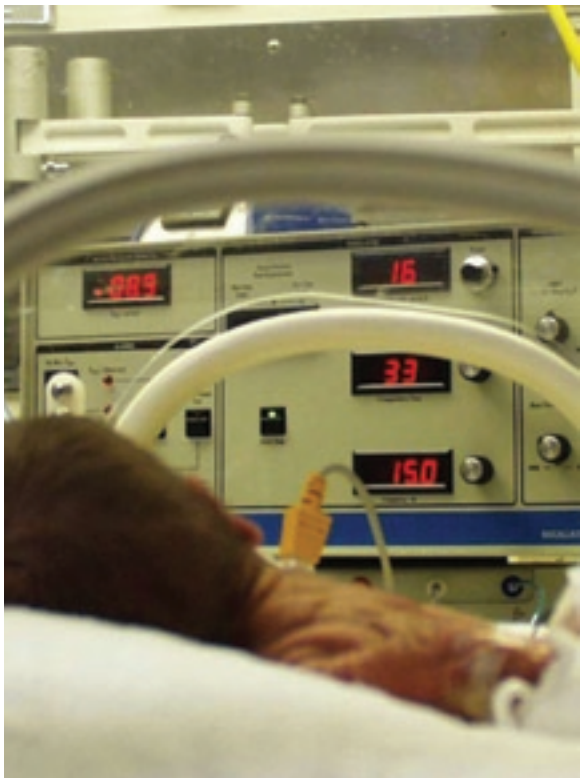

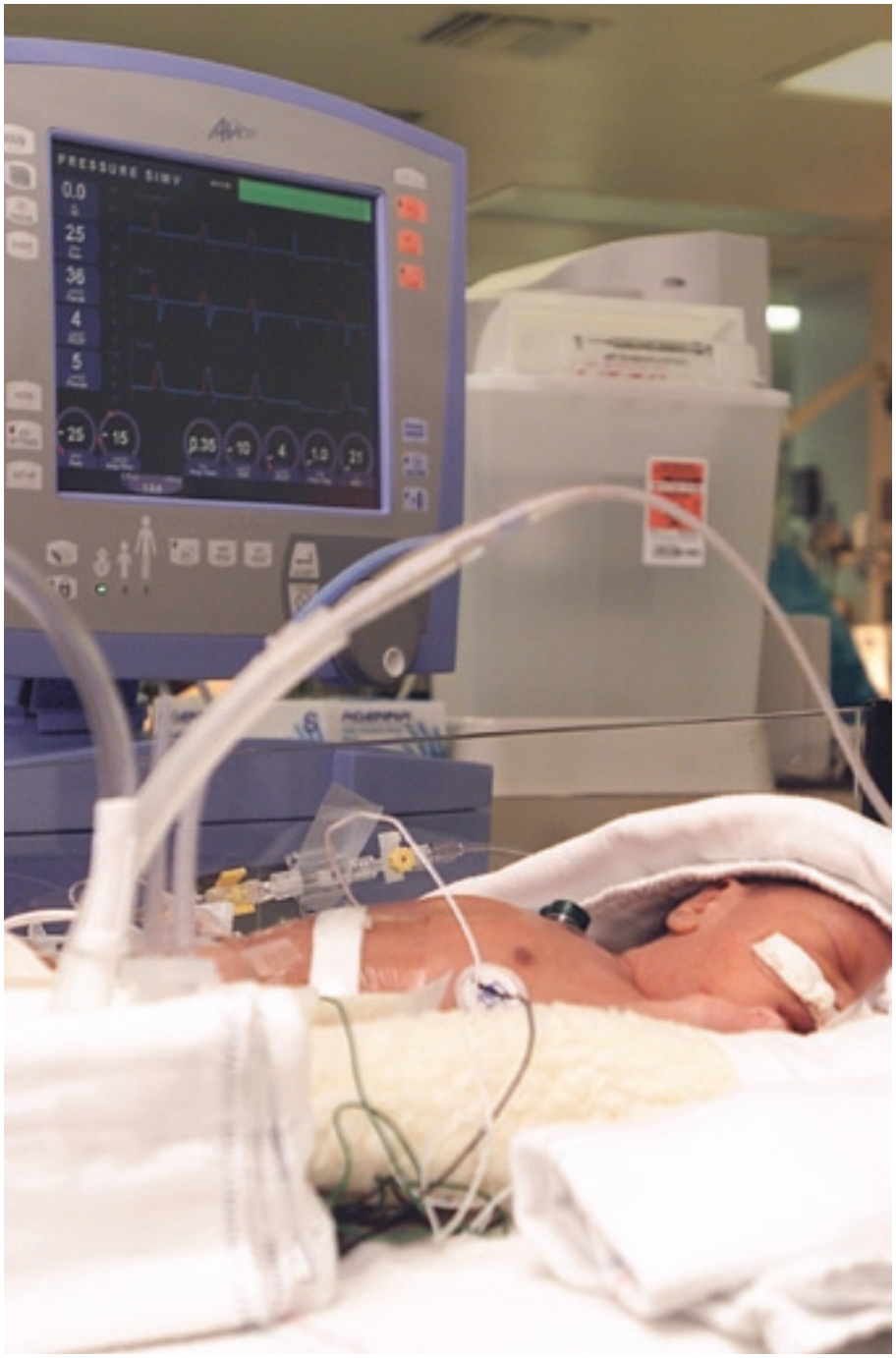

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News

☐ May-June 2010

IN TRAINING

Research at the University of North Carolina at Chapel Hill School of Medicine, performed in the Democratic Republic of Congo, showed that providing training in newborn care and resuscitation to birth attendants significantly increases the likelihood of a baby's survival. Four categories of birth attendant were included in the study: physician, nurse/midwife, traditional birth attendant and a category that included family members and unattended deliveries. Traditional birth attendants, typically non-professional, lay midwives, were by far the most common, attending 40% of deliveries in the entire study and nearly 75% of deliveries in the DRC. Nurse/midwife was the next largest group at 30%, followed by family/unattended/other (17%) and physician (13%). In the study, birth attendants from rural communities in Argentina, the DRC, Guatemala, India, Pakistan and Zambia were trained using the Essential Newborn Care program of the World Health Organization (WHO) and the Neonatal Resuscitation Program of the American Academy of Pediatrics. The Essential Newborn Care course includes training in routine newborn care, resuscitation of babies who have stopped breathing, breastfeeding, keeping the baby warm, kangaroo care, care of the small baby, and common illnesses. The Neonatal Resuscitation Program provides more advanced resuscitation training than the basic training that is part of the Essential Newborn Care course. The results of the study show a statistically significant reduction in stillbirths of about 30%, from 23 stillbirths per 1,000 births before the intervention to 16 after the intervention. Although there was not a reduction in deaths among newborns during the first seven days of life, there was a reduction in the total number of stillbirths and perinatal mortality of about 15%.

TOO MAY OR TOO FEW?

In an article in The Hastings Center Report, Stephen Latham wonders if there really are too few physicians in the US, or in fact, too many. He writes that the Association of American Medical Colleges has long been claiming that a physician shortage is in the offing because of demographic changes that will dramatically increase demand as it curtails supply through physician retirement. Latham writes that, first, there are problems with the data the shortage is premised on. Because the main file of physicians hasn't been updated, physicians are still listed as active when they've already retired. As such, the "future" retirement of physicians has already happened. Another problem, Latham notes, is geographical distribution per the data. For example, he writes, " the supply of neonatologists is not greater in regions where newborns have a higher incidence of low birth weight, prematurity, or any other measure of neonatal risk. In fact, studies show that physician supply follows an 'inverse care law,' with supply lowest in high-need regions. What's worse, research also suggests that most newly trained physicians practice precisely in the areas that already have the most physicians." Thus, the projected physician shortage certainly doesn't apply to areas that can afford paying customers, but mainly to underserved areas. More physicians, Latham said, have not, and would not, solve this problem. Additionally, Latham notes, "An increase in the physician supply—particularly if it causes concentrated pockets of oversupply within particular specialties or regions—will result in an increased provision of physician services, not all of it of discernable benefit to patients." In other words, he infers, expansion of supply drives utilization of specialized services. What's needed, one can infer, is a more equitable spread of general practitioners. But he also adds that new types of caregivers can and do fulfill many GP-type roles, including foreign medical school grads, nurses, physician assistants, and other nonphysician clinicians. Information is quoted and revised from Hastings Center Report, February 2010.

MIS-INFORMATION

Fred Schulte and Emma Schwartz report in the Huffington Post that there is a safety risk to relying exclusively on information technology to manage healthcare. In the past two years, the authors say, the FDA has received reports of six patient deaths and several dozen injuries linked to malfunctions in IT systems. The Huffington Post authors note, "The FDA has been studying the issue for several years. Its latest concerns are surfacing as the government ramps up an ambitious plan to spend as much as $27 billion in stimulus money helping doctors and hospitals across the country purchase electronic medical records systems that rely on digital software rather than paper medical charts… But digital medical systems are not risk-free. Over the past two years, the FDA's voluntary notification system logged a total of 260 reports of 'malfunctions with the potential for patient harm,' including 44 injuries and the six deaths. Among other things, the systems have mixed up patients, put test results in the wrong person's file and lost vital medical information. In one instance, an operating room management system frequently locked up during surgery and lost data had to be re-entered manually in some cases from a nurse's recollection. Another system failed to display a patient's allergies properly because of software errors. In another case, results from lab testing done in a hospital emergency room were returned for the wrong patient." The healthcare-related IT industry is basically unregulated, and US manufacturers have managed to stave off FDA regulation, saying it'll slow down their progress.

BETTER IN BOSNIA

California Watch reports that it's more dangerous to give birth in the Golden State than in Bosnia or Kuwait. Nathanael Johnson reports that the mortality rate of California women who die from causes directly related to pregnancy has nearly tripled in the past decade. The watchdog group said that the state's Department of Public Health had declined to release a report outlining the trend. California Watch spoke with investigators who wrote the report and they confirmed the most significant spike in pregnancy-related deaths since the 1930s. What's alarming is the rapid increase in the rate, and the problem may be occurring nationwide. The Joint Commission issued a Sentinel Event Alert at the beginning of the year suggesting that maternal mortality rates may be increasing and suggested that doctors pay attention to contributing factors like morbid obesity, high blood pressure and diabetes, along with hemorrhaging from

c-sections. (Complications from cesareans have increased 10-fold in the past decade.) Researchers at the state's Department of Public Health conducted a systematic review of every maternal death in California and its initial findings provided the first strong evidence that there is a true increase in deaths, not just the number of reported deaths. It should be noted that in 2006, only 95 California women died from causes directly related to their pregnancies; however, the HHS said that to achieve maternal mortality rate parity with international standards, the number of deaths would have to be closer to 28. California watch reported that when researchers unveiled their initial findings to a conference of the American College of Obstetricians and Gynecologists in 2007, "there were gasps from the audience," according to participants at the San Diego event. "The idea that California was moving backward even in an era of high-tech birthing was implausible to some. Confirmation of the trend was noted in the 2008 report written by 27 doctors and researchers." Besides the reasons above, another reason for the increase in deaths was posited as elective inductions, which are on the rise. As a result, one hospital set a rule: no elective inductions before 41 weeks. The strategy led to fewer NICU admittances, fewer hemorrhages and fewer hysterectomies. However, the hospital lost revenue by reducing c-sections and related procedures. Six of the 10 most commonly billed procedures are maternity related, and a c-section brings in twice the revenue of a vaginal birth.

SMALLER BABIES

Mothers are giving birth to lighter babies in the US, according to a study at Harvard Medical School. Between 1990 and 2005, the birth weight of full-term babies declined two ounces to an average of 7 pounds, 7.54 ounces, a reversal of a trend that had seen birth weights climb steadily since the '50s. Babies were also born 2.5 days earlier on average in 2005 than in 1990. Researchers analyzed 37 million nonmultiple births from a national database. Researchers also found a 2% decrease in the number of babies over the 90th percentile of weight for gestational age. The lower-birth-weight trend couldn't be explained by maternal weight gain, type of birth, the amount of prenatal care, or maternal-health issues. Previously, from the 1950s until the 1980s, birth weights climbed as a result of increases in mothers' weight and in the number of pounds they gained during pregnancy, as well as reduced smoking and older maternal age. From an article by Shirley Wang in the Wall Street Journal.

SHEESH

A baby died in a Brazilian hospital while the two doctors who showed up to perform a cesarean started fighting instead, according to internet news reports. Authorities were investigating if the baby could have been saved had the doctors not been fighting. The mom was in advanced labor when she asked for the doc who provided her prenatal care to deliver the baby. The doctor on duty arrived, and the fistfight began. Said the father, "It was a big fight. They ended up rolling around on the floor." Security guards broke up the fight and sent for a non-fighting doctor who arrived 90 minutes later. The baby was born dead.

IMBALANCE

SIDS may be linked to lower levels of serotonin, according to a study reported by Nicole Ostrow in Bloomberg News. Researchers at Children's Hospital Boston and Harvard found, based on autopsies, that babies who died of SIDS had serotonin

levels that were 26% lower than those who died from other known causes. The researchers said low serotonin levels may impair a baby's response to the risk from breathing in exhaled carbon dioxide when they sleep in a face-down position. The researchers measured levels of serotonin and tryptophan hydroxylase in the brains of 35 infants who died from SIDS. They compared that with five babies who died from identifiable causes and five who died in the hospital of insufficient oxygen supply. Babies who died from SIDS not only had lower serotonin levels but tryptophan hydroxylase levels were 22% lower, as well. Most of the babies who died from SIDS also had one or more external risk factors: sleeping on their stomach or side, sharing a bed or having a trivial illness before death. Information and statements above are from Bloomberg News.

BRAVE NEW WORLD

Prenatal and embryonic genetic testing has resulted in a decline in the number of infants with inheritable diseases, according to various studies, often because parents have chosen abortion or embryo selection based on screening. Many fertility treatments now include embryo screening; there were more than 5,000 in 2006. Testing has proved beneficial for Tay-Sachs, cystic fibrosis, sickle cell, thalassemia, and spinal muscle atrophy. Regarding selective abortion based on genetic testing, for example, a California study by Kaiser Permanente found that from 2006 to 2007, 20 out of 23 couples whose fetuses were shown to have cystic fibrosis opted for abortion. As a reult, the births of infants with the disease declined from 29 in 2000 to 15 in 2006. On the other hand, the availability of genetic testing for Huntington's Disease and sickle cell haven't resulted in drops in those diseases. The above information is from Medical News Today, published by The Advisory Board,

BPA IS AOK

A recent study that exposed pregnant rodents to a range of BPA dietary doses concluded that BPA had no effects on brain development or behavior in rodent offspring exposed to BPA in utero and throughout development. The study, by WIL Research laboratories, follows another low-dose study by the EPA which also found that BPA didn't affect the brain, reproduction or development. See: Developmental Neurotoxicity Study of Dietary Bisphenol A in Sprague-Dawley Rats," (Donald G. Stump, et al).

CUNNING BI-LINGUISTS

Hearing two languages regularly during pregnancy can lead to eventual bilingualism, according to researchers at the University of British Columbia. Two groups of newborns were tested in experiments: English monolinguals (whose mothers spoke only English during pregnancy) and Tagalog-English bilinguals (whose mothers spoke both Tagalog, a language spoken in the Philippines, and English regularly during pregnancy). The researchers used a method called high-amplitude sucking-preference procedure, which capitalizes on the newborns' sucking reflex, wherein increased sucking indicates interest in a stimulus. In the first experiment, infants heard 10 minutes of speech, with every minute alternating between English and Tagalog. English monolingual infants were more interested in English than Tagalog; ie, they exhibited increased sucking behavior on hearing English than when they heard Tagalog being spoken. Bilingual infants had an equal preference for both English and Tagalog. The results suggest that prenatal bilingual exposure may affect infants' language preferences, preparing bilingual infants to listen to and learn about both of their native languages. To test if bilingual infants are able to discriminate between their two languages, they listened to sentences being spoken in one of the languages until they lost interest. Then, they either heard sentences in the other language or heard sentences in the same language, but spoken by a different person. Infants exhibited increased sucking when they heard the other language being spoken, and their sucking did not increase if they heard additional sentences in the same language, which suggest that bilingual infants are able to discriminate between their two languages, and don't get them confused. Ultimately, researchers said their work showed that bilingualism extends to the prenatal period.

BRAINWASHED

The BBC reported on a technique to wash out the brains of preemies as a solution for hydrocephalus. Bristol University studied the technique, used in 77 babies. The therapy takes two days and requires careful monitoring lest the brain pressure get too high. Doctors said the early results were encouraging.

FUTURE & FAT

Researchers at Boston University School of Medicine's (BUSM) Slone Epidemiology Center and Boston University School of Public Health (BUSPH) have found that pre-pregnancy obesity and gestational weight gain can increase the risk of preterm birth. Reserchers compared mothers of more than 1,000 infants born three or more weeks early with mothers of more than 7,000 full-term infants. Among obese women, gestational weight gain within the range recommended by the 2009 Institute of Medicine (IOM) was optimal in reducing risk of preterm birth.

PREGNANCY AND SWINE FLU

Clinicians at the KK Women's and Children's Hospital in Singapore treated 211 confirmed cases of pregnant women with swine flu between May and September 2009. Most of the women had a fever and or acute respiratory illness. They said they had a fever at home but only 62% had one by the time they got to the hosital. Cough was the prevalent symptom, in 90% of the women. Other symptoms were runny nose, sore throat, muscle aches headache, and breathessness. Two women had pneumonia. The time between the onset of acute respiratory illness and presentation at hospital was two days and the average time between onset and commencement of treatment was also two days. The average length of stay in hospital was four days during the containment phase and two in the mitigation phase. Antiviral treatment was given to 208 women and all but one were all treated with Tamiflu. There were few pregnancy complications. Two moms reported severe morning sickenss, three had a first trimester miscarriage, there were two cases of preterm labor, and of hypertension, and one anomalous fetal heart rate. The patients all recovered from their respiratory infection. As such, the researchers noted that the effects of swine flu infection were mild. Because of Singapore's earlier exprience with SARS, it had the infrastructure in place to respond to H1N1 quickly, and the public was aware and responsive. For more see Influenza A/H1N1 (2009) infection in pregnancy—an Asian perspective, M. Lim, et al, BJOG.

MILK AND MS

Drinking milk during pregnancy may help reduce a baby's chances of developing MS as an adult, according to a study by the Harvard School of Public Health. Researchers studied 35,794 nurses whose mothers completed a questionnaire in 2001 about their experiences and diet during pregnancy. Of the nurses

studied, 199 women developed MS over the 16-year study period. The risk of MS was lower among women born to mothers with high milk or dietary vitamin D intake in pregnancy. The risk of MS among daughters whose mothers consumed four glasses of milk per day was 56% lower than daughters whose mothers consumed less than three glasses per month. The risk of MS among daughters whose mothers were in the top 20% of vitamin D intake during pregnancy was 45% lower than daughters whose mothers were in the bottom 20% for vitamin D intake.

SAD = BAD

Children from urban areas whose mothers suffer from depression during pregnancy are more likely than others to show antisocial behavior, including violent behavior, later in life, according to researchers at Cardiff University, King's College and the University of Bristol. Researchers looked at 120 British youth from inner-city areas, and found that mothers who became depressed when pregnant were four times as likely to have children who were violent at 16. This was true for both boys and girls. The mothers' depression, in turn, was predicted by their own aggressive and disruptive behavior as teens. The link between depression in pregnancy and the children's violence couldn't be explained by other factors in the families' environments, such as social class, ethnicity, or family structure; the mothers' age, education, marital status, or IQ; or depression at other times in the children's lives.

GENES AND PREEMIES

Gene variants can cause susceptibility to an inflammatory response to infections inside the uterus, which can increase the risk for a preterm birth, according to a study by the NIH. Researchers in Chile analyzed 190 genes and more than 700 DNA variants from 229 women and 179 preterm infants born before 37 weeks gestation. The genetic material of the preterm group was compared with that of 600 women who delivered at full term. The researchers found DNA variants in the fetus that were associated with the occurrence of premature labor and delivery, and there were genes in the mother that also increase the risk of premature labor and delivery. In infants, the largest gene influence was the interleukin 6 receptor. For women, researchers looked at a gene that affects structures in the cervix and uterus that dissolve at the beginning of labor. If an infection develops, the combination of these two genetic variants raises the risk of preterm labor as the body tries to preserve the health of the woman and fetus. As such, researchers suggested that preterm delivery was an evolutionary mechanism designed to protect the woman and fetus. Reported in Medical News Today,

PREEMIES AND PROGESTERONE

Progesterone can prevent apoptosis in fetal membranes, according to Yale School of Medicine researchers, who were able to demonstrate their findings in a laboratory situation where they stimulated healthy fetal membranes with pro-inflammatory mediators. Researchers also noticed an inhibition of apoptosis under basal conditions without the presence of pro-inflammatory mediators, which suggested that the same mechanism may also be important for the normal onset of labor at term.

FARM FOUL

Researchers at the University of Washington, Seattle, have demonstrated a link between gastroschisis and the agricultural chemical atrazine. Gastroschisis had increased two to four times in the last 30 years. The state of Washington has twice the number of cases than the national average. While most babies survive, they require delivery at tertiary care centers, and need neonatal intervention. Researchers studied all cases of live born infants with gastroschisis during the period of 1987-2006 and matched birth certificates with US Geological Survey databases of agricultural spraying. Of the 805 cases and 3,616 controls in the study, gastroschisis occurred more frequently among infants whose mothers resided less than 25 km from the site of high surface water contamination with atrazine. No risk was associated with the other chemicals reviewed in the study. The risk of gastroschisis also increased for women who conceived in the spring (March through May), when chemical use is more prevalent.

PLAYING TAG

Researchers have used haplotype tagging (hap-tag) single-nucleotide polymorphisms (SNPs) to study the relationship between genetic predispositions, bacterial vaginosis, and

preterm birth. The study collected DNA samples from 744 women, and demographics and outcomes data were recorded. Vaginal smears for Gram-staining were obtained from subjects at 26-28 wk gestation. Researchers studied hap-tag SNPs in five pathways in which >3 SNPs were strongly associated with SPTD at <37 weeks. In the cohort, 68 women experienced SPTD at <37 wk, while 676 women delivered at term; 306 women had asymptomatic BV at 26-28 wk, and BV was not associated with an increased risk of SPTD. Twenty hap-tag SNPs were associated with an increased risk of SPTD in the BV+ group. Researchers noted that chip assays for hap-tag SNPs provide a powerful tool for studying genes related to preterm birth and increase the potential to find groups of SNPs in biologically relevant pathways that might cause preterm birth.

FETAL MEASUREMENT

Measuring the fetal zone of the adrenal gland is a better predictor of preterm birth than measuring cervical length, according to researchers at the University of Maryland and Yale. The researchers worked with moms presenting with preterm labor symptoms and took ultrasound measurement of the cervical length and fetal adrenal gland dimension in 62 singletons with preterm labor at 23-37 weeks. Twenty women had preterm birth at less than seven days (Group A) while 42 (Group B) delivered in seven days or more from initial assessment. While CL was similar, cAGV and d/D were higher in group A. ROC area under the curve was significantly greater for cAGV and d/D than for CL, without any significant differences between adrenal gland measurements. Using ROC derived cutoffs for preterm birth in less than seven days was best predicted by d/D and cAGV but not CL. Researchers noted that measuring the cervical length leads to a high percentage of false positives and also has limited sensitivity, but that the adrenal method would allow for an easy, inexpensive way to identify real preterm deliveries.

VIAGRA AND SHEEP

Bet that got your attention. Researchers have found that Viagra can aid fetal development in sheep, according to researchers at Texas A&M. The study started out as a joke among two Texas AgriLife Research scientists. The study originated in 2003 after the researchers joked that women may also have a use for Viagra. Soon thereafter, Pfizer announced an RFP for just that line of research, and the Texas researchers proposed using pregnant sheep as an animal model for evaluating Viagra's potential role in enhancing fetal growth. The study revealed that Viagra increased the blood supply to the fetus in female sheep, supplying amino acids—a major fuel for fetal growth. Results indicated that long-term use of Viagra enhanced fetal weight in both adequately fed and nutrient-restricted female sheep. Greater concentrations of amino acids and polyamines in fetal blood and placental fluids were found, leading the researchers to suggest that Viagra alters the trafficking of nutrients from the female sheep to the fetus. It was also observed that Viagra did not affect changes in maternal weight, body condition score, maternal liver mass or muscle weight. The Texas researchers plan to continue their Viagra research on pigs, cows, and humans.

AGE AND AUTISM

A 10-year study examining 4.9 million births in the 1990s has found more evidence that there's a link between autism and the mother's age at conception. Researchers at the University of California, Davis examined data from all births in their state for the decade and found that mothers over the age of 40 had 51% higher odds of having children with autism compared with mothers between the ages 25 and 29. The father's age also played a factor, but only when he had a child with a woman under 30. The researchers emphasize that while autism rates have risen 600% in the past two decades, older women having children contributed to only 5% more cases. Some suggest that the cumulative effects of the environment, changes to the autoimmune system, stress and reproductive technology may affect autism risk. Reported by CNN online.

SODA-SIZED

The most premature boy on record was born at 25 weeks in Germany, weighing 9.7 ounces. Doctors kept the news under wraps until they found out if the baby would survive, and it did, getting discharged at 8.2 pounds. The baby was kept on a 24-hour incubation. The most premature girl to survive was born after 21 weeks. Reported by Huffington Post.

MATERNAL FETAL UPDATE

Here's some papers presented at the recent Society for Maternal-Fetal Medicine annual meeting: Ultrasound measurement of fetal adrenal gland a better predictor of preterm birth; statewide initatives to reduce near-term scheduled births; sutures cause fewer complications than staples for c-sections; genes that regulate maternal inflammatory response, bacterial vaginosis and preterm birth are related; waiting for birth is as effective as inducing labor in cases of IUGR; screening for spinal muscular atrophy isn't cost effective; there's an increased risk of stillbirths in women who have fibroids.

SMOKING = SIDS

Researchers at Sweden's Karolinksa Institute found smoke-exposed babies had abnormal surges in blood pressure, even when sleeping undisturbed in their cots, making their hearts pump faster and harder. As such, damage to the circulation may be a factor in SIDS. Researchers studied 36 newborns, 17 with moms who smoked during pregnancy. The babies who'd been exposed to cigarette smoke were clearly affected. At one week of age the smoke-exposed babies showed abnormally large blood pressure rises as they were lifted up from lying down. By the age of one, the babies showed abnormally low blood pressure responses to the same posture change.

READ AND WEEP

According to a report on the Huffington Post, "doctors, nurses and other health care workers are tapping into their inner Tolstoys to better connect with patients. They're meeting in monthly book clubs to discuss medical-themed literature. Humanities courses are now required in many medical schools. A hospital in Bangor, ME, hosted the first program in 1997. The idea has spread over the years to 25 states, including California, Florida, Massachusetts, Missouri, New York, Ohio and Virginia. Said Dr Robin Blake of the University of Missouri, "One hundred years before Kubler-Ross identified the stages of dying, Tolstoy had it,' said Dr Robin Blake, who runs a medical book club. He notes that famous writers Camus, Faulkner, Flannery O'Connor and William Carlos Williams wrote in their fiction about medicine. Williams was a doctor, and O'Connor suffered from lupus. Blake says, in the HuffPost article, "In medical school, there was nothing of this, and I think that was a big omission." A Maine study revealed that participants in a literature program "reported greater empathy for patients and colleagues, higher cultural awareness, increased job satisfaction and improved interpersonal skills." Dr Abraham Verghese, a

novelist and Stanford University professor, has founded the Center for Medical Humanities and Ethics at the University of Texas Health Science Center in San Antonio. He said, "There's a great hunger in clinical practice for discussions and explaining and reconciling the things you're seeing," he said. "It's as much about the physician as it is about the patient." Reported in the Huffington Post. [Editor's note: in my other life, I teach fiction writing at UCLA. As such, here are some book recommendations, not for the faint of heart: The Rise of Life on Earth Joyce by Carol Oates, about a murderous doctor and a victimized nurse (X rated); Louis Ferdinand Celini, Journey to the End of the Night, about a bad doctor in Africa and France; The Benjamenta Institute, by Robert Walser, written by a guy who spent the last 20 years of his life in a mental institution; The Magic Mountain, by Thomas Mann, which takes place in a TB sanatorium; Wit (a play), by Margaret Edson, narrated by a woman with cancer; Do The Windows Open (short stories), by Julie Hecht, linked stories about a woman and her idiosyncratic doctor; and Darwin's Worms: On Life Stories And Death Stories, by Adam Phillips. I would also recommend a subsciption to The Bellevue Literary Review, published by the NYU Langone Medical Center, the only journal of its kind. They also published a book of their "greatest hits." Finally, another excellent journal is Literature and Medicine, published by the Johns Hopkins University Press and also available through Project MUSE.]

PRODUCTS

BLOOD GAS

Siemens RAPIDLab 1200 series of blood gas analyzers offers neonatal bilirubin (nBili) point of care testing with 60 second turnaround time, and detects elevated levels of bilirubin. If undetected, this condition can lead to a variety of health issues in newborn infants, from jaundice to neurological disorders, and in severe cases, brain damage. Siemens neonatal bilirubin (nBili) test requires 100uL sample of whole blood, measuring 2-30 mgdl and does not require any sample preparation, while providing fast and accurate results, and does not increase monthly operating costs. Siemens RAPIDLab systems, nBili testing is conducted as part of a neonatal test panel that includes blood gas, pH, electrolytes, metabolites, total hemoglobin and CO-oximetry, with no additional reagents needed for nBili testing. For additional information, visit usa.siemens.com/bloodgas.

WIPEOUT

Professional Disposables International, Inc (PDI), introduced the Nice 'n Clean Baby Wipes 80-count Solo Soft pak. The new packaging replaces the former tub packaging, offering clinicians easier dispensing while reducing waste. The tissue box-type dispenser allows for single-handed use. Nice 'n Clean Premium Baby Wipes are designed for extra comfort and strength, and include a hypoallergenic formula with aloe and Vitamin E. They were developed for use on a baby's soft and delicate skin and are available in both scented and unscented formulas in a variety of products. Contact pdipdi.com.

GET SMART

Royal Philips Electronics announced its Know How Webinars program, an online learning series for sleep therapy and home respiratory professionals. Know How Webinars are presented live by clinical researchers, physicians, respiratory therapists, or subject matter experts from Philips Respironics and then placed on the Know How website for on-demand viewing. The webinars cover three categories: business, clinical, and products and programs. Business webinars include topics such as reimbursement guidelines, cost-saving strategies, and appropriate equipment selection. Clinical sessions are designed for physicians, respiratory therapists, and sleep technologists and topics include the latest findings on obstructive sleep apnea, the use of noninvasive and invasive ventilation, and trends in the use of home oxygen therapy. Product webinars comprise a review of the latest products and programs from Philips Respironics. All Know How Webinars are offered free of charge. The live Know How Webinars format includes a moderator, presenter, and a question-and-answer session that enables participants to interact with the presenter. On-demand, pre-recorded webinars are available at any time by registering at the Know How Webinars at knowhow.respironics.com.

NEW GENERATION

GE Healthcare's BiliSoft™ LED Phototherapy System is the next generation LED and fiberoptic based technology for treatment of indirect hyperbilirubinemia in newborns. Its increased surface area, high spectral irradiance, and long lasting blue narrow-band LED light are the features that are needed for intensive, efficacious phototherapy as recommended by AAP Guidelines. It is also the only product on the market that supports and promotes developmental care, enables infant-parent bonding and provides healing light where it is needed—in Neonatal ICU, Pediatrics, Well Baby Nursery and at home. The BiliSoft's blue LED light delivers healing phototherapy that meets and exceeds the recommendations of the American Academy of Pediatrics. [American Academy of Pediatrics, clinical practice guideline, subcommittee on hyperbilirubinemia: Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation, 2004; 297-316]. BiliSoft delivers phototherapy anywhere—in the Neonatal ICU, Pediatrics, Well-Baby Nursery or at home. BiliSoft can be used in any environment—in a radiant warmer, incubator, bassinet, crib, or in a caregiver's arms. • BiliSoft's long, lightweight fiberoptic cable and quiet operation make it ideal for in-home application. It's exceptionally easy to set up and use. • BiliSoft is an excellent solution for infants in the Neonatal ICU, where fast, effective treatment can be most critical. • Well Baby Nursery and Pediatrics—baby can be covered or wrapped in a blanket during therapy. • BiliSoft's whisper-quiet operation helps maintain a quiet environment to promote sleep and growth. With BiliSoft, there's no barrier to bonding between infant and parents or caregivers. The baby can be held, fed, even rocked throughout the therapy session. Comfort is the keyword, whichever cover options you select. The flat, cushioned BiliSoft cover lets you swaddle baby and phototherapy pad together. The BiliSoft nest offers sick babies the boundaries and support they need, via a cushy foot-roll and gentle, transparent straps. If a baby cannot be swaddled, positioning aids may be placed under the pad to bring more light to the sides of a baby's body for greater skin surface area exposure to the light. There's no distance factor to diminish treatment intensity. Contact gehealthcare.com.

ACQUISITION

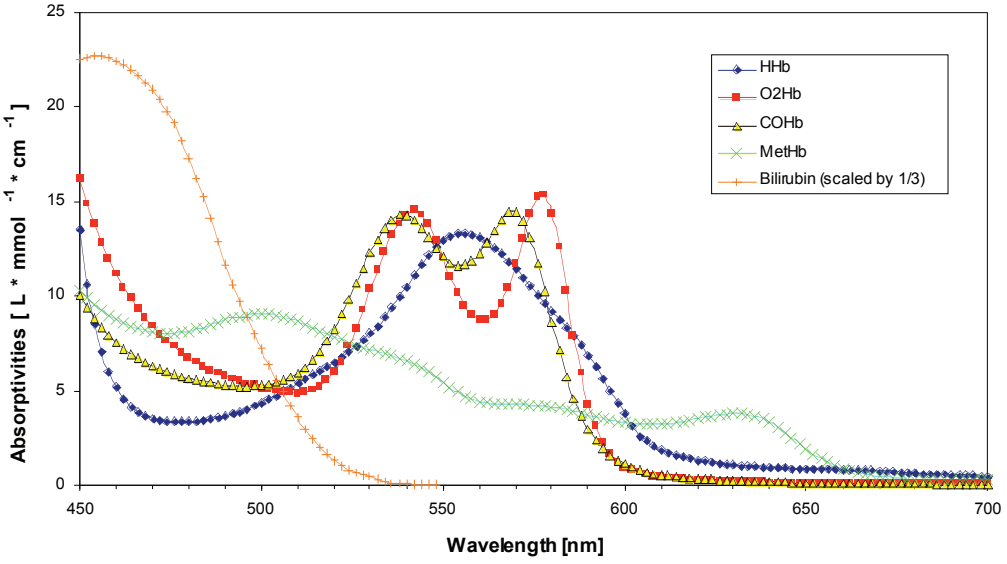
Royal Philips Electronics announced that it has acquired the Somnolyzer 24 x 7 automated scoring solutions business of the Siesta Group in Vienna. This FDA-cleared solution helps improve the productivity of sleep centers and is based on the most advanced and clinically validated automated-scoring technology on the market. The Siesta Group is a research and clinical

Continued on page 62…

Bili Study

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 derivates and bilirubin are determined by applying an accepted mathematical algorthrim.[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] *References: 1. cobas b 221 reference manual version 8.0 pp 20, 21; 2. Bolinski, Boris et al. Evaluation of Total Bilirubin Determination in Neonatal Whole-Blood Samples by Multiwavelength Photometry on the Roche OMNI S Point-of-Care Analyzer. Point of Care, The Journal of Near Patient Testing and Technology; Volume 4, March 2005; 3. Schweiger, Gerd. Technical Aspects: Determination of Bilirubin on the Roche OMNI S, International Evaluation Workshop, October 23, 2003, Deutschlandsberg, Austria; 4. H. Hallemann et al. Technical Aspects of Bilirubin Determination in Whole Blood Care, The Journal of Near Patient Testing and Technology, Volume 4,, March 2005.*

Absorbance of Hemoglobin Derivatives and Bilirubin[4]



The information was provided by Roche Diagnostics.

Is Circumcision Medically Necessary?

Benamanahalli K. Rajegowda, MD; Muhammad Aslam, MD

Circumcision for male infants is the most frequently performed elective surgical procedure in the United States and the world. More than one million American male infants are circumcised each year. According to the CDC 2003 US Hospital Survey report, more than 55.9% of all boys are circumcised. The procedure is to excise the skin that covers the glans penis. Why the skin is removed in male infants is always debatable. For some the choice is very simple because it is based on religion and method of faith, whereas in others it varies from families to families. In the Jewish religion it is a matter of faith; circumcision ("Brit milah") is ritual by cutting off the foreskin, symbolizing the "covenant" between God and the Jewish people. Cutting of foreskin is called "Chituch" and to uncover the flush or glands under the foreskin is called "Priah." The ritual circumcision is performed by a ritual circumciser called "Mohel" who traditionally sucks the blood by mouth from the circumcision area during the ritual called "Metzizah." This has now been replaced by using a glass tube to suck the baby's blood after several case reports of morbidity and mortality from herpetic infection. The procedure to suck the blood is called "Briss," and is used to remove impurities. In Islamic tradition, it is religious to have all the boys be circumcised. "Khitān" or "Khatna" is the term for male circumcision carried out as an Islamic rite and is also referred to by the term "Taharah" (an Arabic word for purity). Ritual circumcision is not mandated by the Quran, but serves to introduce males into the Islamic faith. Muslims are currently the largest single religious group to practice widespread circumcision. However, it is not a condition for converting to Islam or carrying out religious duties. In Christianity there is no prohibition of circumcision, and it is practiced by Coptic Christians.

Circumcision is also an individual preference based on several varied reasons. The question is if there is a medical necessity for advising it. The foreskin which covers and protects the head of the penis is easily retractable and it does not interfere with any function. However there was some anecdotal non-scientific evidence of health benefits from circumcision. It includes good genital hygiene, less chances of phimosis, paraphimosis, balanitis, dribbling of urine, and urinary tract infections. There has been a recent report by WHO of decreased incidence of STDs among circumcised males in Africa. Also there are reports of lesser incidence of penile and cervical cancers. The routine circumcision costs an average of $150-250 dollars for the procedure and probably more if there are complications (rare, but it does occur in less than 0.5% of the cases). Review of the scientific literature from several medical societies including AAP, ACOG, AMA, and AAFP signify some benefits but also associated risks with circumcision. The evidence-based medical data do not have sufficient information to recommend routine neonatal circumcision in the US. However, they do not oppose the circumcision and they leave the decision to the parents and the families and the providers with the ultimate goal being the best interest of the child and the family. The provider must explain in detail the risks and the benefits of circumcision for the parents by giving individualized unbiased information. It should be a well informed consented procedure done at the request of the parents by a trained physician under suitable analgesia. One should be careful to explain the contraindications to circumcision that include penile deformities like epispadias, hypospadias, micropenis and ambiguous genitalia, family history of bleeding diathesis and unstable infants. All obstetricians and pediatricians who provide care to the mothers and the infants must inform them that the current medical indication of circumcision is debatable. They should also emphasize the genital hygiene of uncircumcised male infants issued by the AAP.

In our institution (Rajegowda, BK: Lincoln Medical and Mental Health Center) we do not advertise or recommend circumcision. However, if the parents wish to have their male infant circumcised, the procedure is performed by obstetricians under analgesia after an informed consent with risks, benefits and contraindications disclosed in detail. Our pediatric residents are also trained in circumcision procedure. Following circumcision, the infant is observed for bleeding, swelling and any retention of urine for at least 4-6 hours before discharge home. A detailed instruction sheet is provided to the parents on the care of circumcised infant at home.

Given the available data and lack of clear understanding whether circumcision is medically indicated, in our opinion the decision should rest with the families at present and one should always respect the religious and non-religious views the families have for the procedure. Further data will delineate if there are any medical reasons for the procedure and will help establish guidelines, but religious circumcision is going to be a continued norm.

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Neonatal Bilirubin Method Evaluation: Whole Blood on RAPIDLab® 1200 versus Plasma on VITROS® 950 Chemistry System

T. Hotaling, J. Brunelle, K. Mullert

Abstract

Objective: To provide an assessment of whole blood neonatal bilirubin measurement derived optically compared with a reagent-based chemistry method utilizing plasma.

Relevance: As a diagnostic tool, bilirubin is measured in the neonate as an indicator of jaundice and for assessing the risk of kernicterus.

Method: We describe a performance evaluation of a new neonatal bilirubin assay on the Siemens RAPIDLab® 1200 Model 1245 and 1265 blood gas analyzers using unhemolyzed whole blood neonate specimens. The reference method was the Ortho-Clinical Diagnostics VITROS® 950 chemistry system (using plasma from the same specimens). The evaluation occurred in three studies, incorporating 28 test days across four RAPIDLab 1200 instruments and two chemistry analyzers.

Results: During the development of an unhemolyzed whole blood bilirubin assay, we determined that the hemoglobin type could profoundly affect the result. A significant bias was initially observed with clinical neonate specimens compared to internal contrived adult samples. Although the presence of scatter and fetal hemoglobin (fetalHb) had already been accounted for in the determination of total hemoglobin (tHb) and CO-oximetry fractions, it was not satisfactory for the determination of bilirubin specifically in neonates. Further compensation for native fetalHb was required. The graph below (Figure 1) presents neonatal bilirubin values as determined by the RAPIDLab 1200 using additional fetal compensation versus the VITROS assay method. This example demonstrates excellent bilirubin correlation between the two methods on neonate patients with 2-20 mg/dL bilirubin at native tHb levels. Bilirubin-spiked cord blood (containing native fetalHb) and spiked adult blood (without fetalHb) were evaluated.

Conclusions: We conclude that the accuracy of the RAPIDLab 1200 whole blood bilirubin method is comparable to that of the VITROS plasma chemistry method. The absence of a statistically significant difference in bias between spiked cord and spiked adult samples indicates the effectiveness of the fetalHb compensation algorithm.

The authors are with Siemens Healthcare Diagnostics Inc., Norwood, MA.

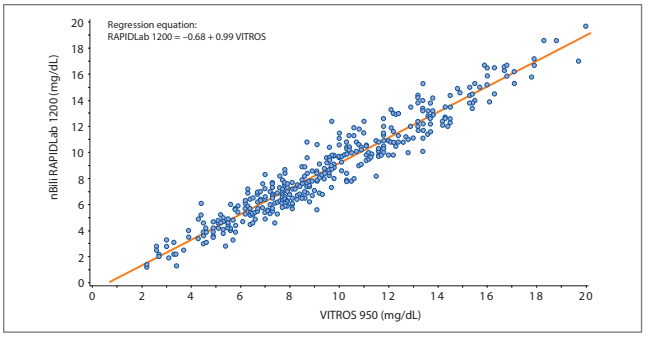

Figure 1. Neonatal bilirubin concentration on the RAPIDLab 1200 vs the VITROS 950 (all three studies, combined).

Background

Bilirubin, the main bile pigment in the liver, is a major end product of hemoglobin decomposition as aged or damaged red blood cells are routinely destroyed. Hemoglobin degradation results in the formation of unconjugated bilirubin. As the unconjugated bilirubin is lipid-soluble, it cannot be excreted until it is bound to albumin and carried to the liver, where it is made water-soluble by conjugation and passed in the urine. For the clinician, bilirubin is considered an index of liver function, as it reflects the liver's ability to take up, process, and secrete bilirubin. Impaired conjugation of bilirubin in the liver can result in elevated bilirubin levels in the blood. An increased level of bilirubin in the blood (hyperbilirubinemia) causes jaundice, resulting in discoloration of body tissues.

Jaundice in newborns is usually harmless, a consequence of immature hepatic function and the normal breakdown of fetal hemoglobin as it is replaced with adult hemoglobin. Severe neonatal jaundice, however, may indicate more serious conditions, including erythrocyte hemolysis (erythroblastosis fetalis) generally caused by blood incompatibilities between baby and mother. Newborn bilirubin levels should be closely monitored, as extremely high levels of bilirubin in infants may cause a form of brain damage (bilirubin encephalopathy or kernicterus).

The Siemens RAPIDLab 1200 blood gas systems are designed to measure pH, pO_2, pCO_2, Na+, K+, Ca++, Cl-, glucose and lactate on unhemolyzed whole blood. Direct multiple wavelength spectrophotometry technology measuring light transmission through the same specimen is also applied to determine concentrations of total hemoglobin and its derivatives (tHb, FO_2Hb, FCOHb, FMetHb, FHHb).

The option to additionally report total bilirubin on neonatal whole blood specimens (nBili) has recently been introduced on the RAPIDLab 1245 and RAPIDLab 1265 models of the RAPIDLab 1200 blood gas series.

The RAPIDLab 1245 and RAPIDLab 1265 analyzers assess neonatal bilirubin concurrently with tHb and CO-oximetry on whole blood using direct spectrophotometry. Raw bilirubin values are determined by iterative least-squares analysis and further adjustments made to produce the reported nBili results. The VITROS analyzer, on the other hand, first employs a caffeine and sodium benzoate reactive chemistry step on plasma (or serum) matrix. After a fixed incubation period, endpoint colorimetric dual-wavelength analysis is made to determine the concentrations of unconjugated and conjugated bilirubin fractions which, when added together, are used to derive the reported total neonatal bilirubin (NBIL) value.

Assessments of neonatal total bilirubin were conducted to determine the comparability of the two methods which utilize different sample matrixes.

Materials and Methods

All samples were obtained from clinical patients and evaluated in the core chemistry lab at the hospital site during three separate studies across 28 test days, incorporating four different RAPIDLab 1245 units and two VITROS instruments.

As bilirubin is light sensitive, care was taken to keep the test samples protected from light exposure prior to testing. The majority of samples tested were from neonatal patients. Gender was equally distributed, and the neonate ethnic profile was reflective of the demographic mixture of the region's population. The neonatal patients' ages ranged from less than 1 through 14 days, with the majority being ≤5 days old. In addition, remnant arterial and/or venous whole blood taken immediately from umbilical cords was tested. A small number of remnant whole blood samples from adult patients were also evaluated as described below.

Neonatal samples were collected as whole blood in amber-colored microtainers (plasma separator tubes with heparin; Becton Dickinson). For each neonate test sample, a small volume was removed via glass capillary and measured on a RAPIDLab 1245 blood gas analyzer. The volume remaining in the microtainers was spun in a centrifuge. The resulting plasma was poured off into plastic cups and measured using the NBIL assay on either of two VITROS chemistry analyzers resident in the core chemistry lab. For each neonate test specimen, the whole blood RAPIDLab 1245 nBili value was compared to the corresponding plasma VITROS NBIL result, in mg/dL.

In similar fashion, portions of remnant adult and cord whole blood samples were measured on a RAPIDLab 1245 and compared to the corresponding plasma matrix measured on the VITROS. Prior to testing, some of these remnant specimens were doped with varying amounts of concentrated bilirubin spiking solution (100 mg/dL unconjugated in 0.85% HSA, pH adjusted) to artificially elevate the bilirubin concentration detailed later in this report.

Results

Described below is a neonatal bilirubin performance evaluation of the new RAPIDLab 1200 blood gas system bilirubin measurement, using whole blood, compared to the VITROS as the plasma chemistry reference method.

Early development of the whole blood nBili measurement on the RAPIDLab 1200 series indicated a pronounced inverse relationship of tHb/hematocrit versus raw bilirubin results; as tHb increases, the raw bilirubin results decreases. To compensate for this relationship, a mathematical hematocrit correction was applied to the raw nBili results. An effective hematocrit correction is of importance as the tHb/hematocrit distribution may be different and/or more diverse among various sample source populations. Figure 2 illustrates the tHb distribution of the test samples at the clinical site differentiated by sample source (adult, cord, and neonate). The bilirubin determination for the neonatal population (in blue), overall displaying a wide spread and overall larger tHb values (mean=18.2 g/dL), would be inversely affected by a poor or no hematocrit correction. The adult population (in light green), overall has a lower average tHb (mean=13.8 g/dL). The tHb distribution for cord specimens (in orange) falls slightly less than midway (mean=15.5 g/dL) between the neonatal and adult peaks.

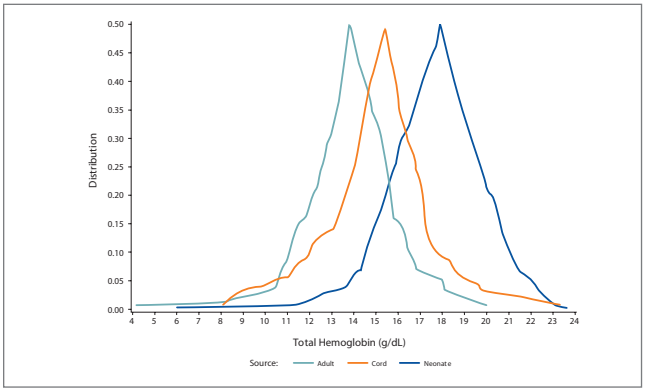

Figure 2. Mountain plot showing distribution of total (native) hemoglobin in adults (light green), neonates (blue), and cord blood (orange).

Despite the application of a RAPIDLab 1200 nBili hematocrit correction, significant bilirubin underrecovery and imprecision was observed on the RAPIDLab 1200 versus the VITROS reference on neonatal samples (Figure 3).

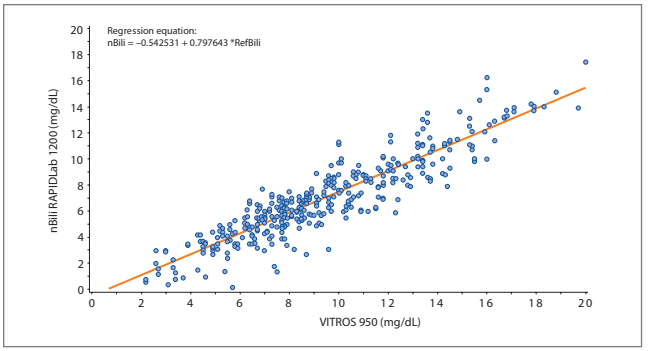

Figure 3. Interim method comparison of bilirubin measurement on the RAPIDLab 1200 versus the VITROS on neonatal specimens (with RAPIDLab 1200 nBili software using only hematocrit correction).

This underrecovery was not observed during internal developmental testing where adult whole blood samples adjusted for tHb and doped with various amounts of prepared unconjugated bilirubin spiking solution were used. An

adjustment for the presence of fetal hemoglobin was already being applied in determining the concentration of tHb and the CO-oximetry fractions on the RAPIDLab 1200. However, the original fetalHb compensation was determined to be inadequate for bilirubin determination.

Whole blood from adult and cord sources was spiked with varying concentrations of the same lot of prepared bilirubin. Cord whole blood, unlike adult, contains elevated levels of native fetalHb. Therefore, the significant difference in the specimens is not the bilirubin source (native versus artificial), but the presence of fetal hemoglobin. Figure 4 exhibits method comparison of RAPIDLab 1200 bilirubin results versus the VITROS for spiked adult and cord samples using the refined fetalHb correction vector.

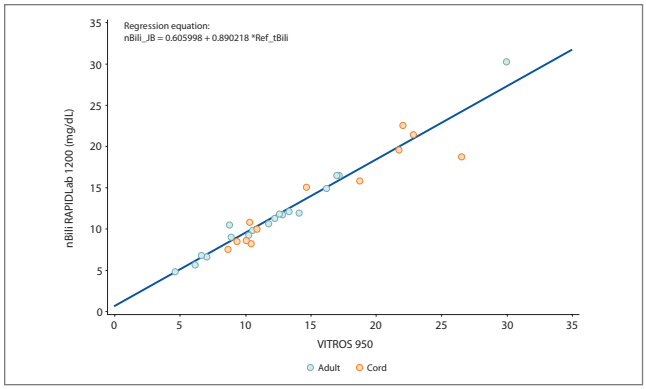

Figure 4. Bilirubin recovery of spiked adult and cord samples: RAPIDLab 1200 vs. VITROS.

On the basis of t-test analysis of the RAPIDLab 1200 mean bilirubin bias against the VITROS for spiked cord and spiked adult samples, the two populations are statistically equivalent (i.e., there is not enough evidence to conclude with 95% confidence that the two populations are different; Table 1). This supports the use of the additional fetalHb compensation and minimizes the difference seen between contrived and natural specimens.

Spiked Cord Samples			Spiked Adult Samples			t-Test		Reject
N	mean bias	SD	N	mean bias	SD	t Stat	Pr > t	Null?
12	–1.55	2.26	18	–0.44	0.83	1.62	0.13	No

Table 1. Statistical comparison of bias (RAPIDLab 1200–VITROS) for bilirubin-spiked samples.

Once this correction for native fetalHb was applied to the clinical neonatal data set utilized in Figure 3, the final method comparison of bilirubin on the RAPIDLab 1200 versus the VITROS chemistry system demonstrated good correlation. Both bias and precision showed observable improvement (Figure 5).

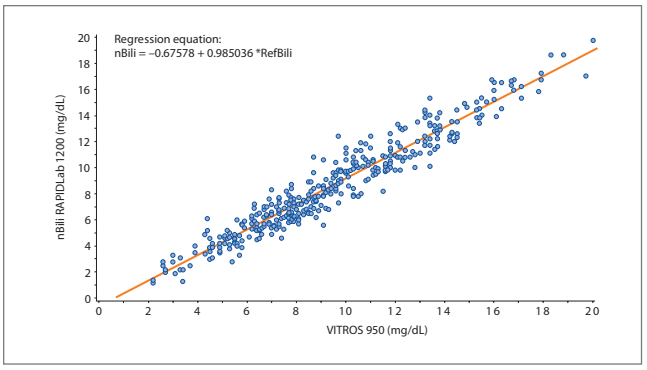

Figure 5. Final method comparison of RAPIDLab 1200 versus VITROS on neonatal specimens (with final RAPIDLab 1200 nBili software using hematocrit and fetalHb corrections).

Despite the differences between the technology and the sample matrix, RAPIDLab 1200 nBili versus VITROS NBIL shows excellent correlation. Linear regression comparison of the clinical neonate specimens using pre- versus post-fetalHb correction (RMSE=root mean square, r2=correlation coefficient) is outlined in Table 2.

Figure	RAPIDLab 1200 Software	N	Intercept	Slope	RMSE	r^2
3	Interim (no fetalHb correction)	379	–0.54	0.80	1.258	0.832
5	Final (with fetalHb correction)	378	–0.68	0.99	0.966	0.928

Table 2. Comparison of linear regression analysis of method comparison of RAPIDLab 1200 pre- or post-fetalHb correction vs VITROS.

Conclusions

A feature of the RAPIDLab 1200 series of blood gas analyzers is the ability to quantify and report patient results for blood gases, pH, electrolytes, metabolites and CO-oximetry. Neonatal total bilirubin is now available on the same analyzers from the same single whole blood sample, eliminating the need for an additional draw.

The testing concludes that the accuracy of the RAPIDLab 1200 whole blood bilirubin method is comparable to that of the VITROS 950 plasma chemistry method. The absence of a statistically significant difference in bias between spiked cord and spiked adult samples indicates the effectiveness of the fetalHb compensation algorithm.

The new RAPIDLab 1200 neonatal total bilirubin measurement provides an alternative method to conventional chemistry analyzers. Using direct spectrophotometry, it provides results in only 60 seconds on whole blood neonatal specimens. RAPIDLab 1200 neonatal bilirubin results are comparable to those obtained with the VITROS chemistry system, which uses a combination of reagent and optical technology on samples requiring separation into plasma and a 5-minute incubation period.

Noise in the NICU

Laszlo Sandor

There was a time when neonatal caregivers didn't give a thought to noise, before it was known that noise is bad for health.

The interest in the impact of noise levels, not only in the NICU but throughout the hospital environment, can perhaps be attributed, counter-intuitively, to the specialization and sophistication of healthcare delivery. Likely as a reaction to the increasing complexity of care, and to the specific focus of specialists, who might have tended, like the blind men, to "see" only one part of the elephant, caregivers realized they'd have to re-focus on a more holistic approach, revitalizing the concept of treating the entire patient, not just dealing with a specific pathology.

Noise Environment

Of course, the patient, while in the hospital, is in a particular and yet all-encompassing environment, and that environment, logically, would have an effect on the patient. And part of that environment is its soundscape.

Some of the earliest studies on the effects of noise were performed by environmental and architectural specialists, with some of early noise studies performed in general-patient environments, typically involving mechanically ventilated patients.

Studies over 24-hour periods that recorded acoustic and physiological data and correlated the results, have demonstrated that arousal from noise on the ward can lead to cardiovascular reactions in adult intensive care patients; sound also affects the staff.[1]

In one study, seven ventilated and six non-ventilated patients were recorded by 24-hour polysomnography. In the course of the studied event, sound levels rose 36.5 times every hour and caused 21 awakenings. The healthy subjects got through this fine, and slept well in the ICU environment, and slept even better in a noise-reduced environment. However, actual patients experienced poorer sleep quality, more awakenings, and shorter sleep time. Slow-wave sleep was lower in patients, who spent half their sleep-time during the day, while healthy non-ventilated participants slept mostly during the night.[2]

According to the Journal of Advanced Nursing, nurse researchers have provided evidence that hospital critical care unit noise may put patients at risk for sleep problems: "Technological advances in this setting have been described as contributing to this problem. Although data on the negative effects of CCU noise on physiological sleep are available, less attention has been given to self-reports of the subjective quality of sleep following exposure to this stressor." The journal's study hypothesized that subjects exposed to CCU sound levels would report poorer subjective sleep than subjects in a quieter environment. Sixty female subjects, attempting to sleep overnight in a laboratory, were randomly assigned to an experimental group, where they heard an audiotape recording of CCU sounds throughout the night, or to a quiet group where the audiotape recording of CCU sounds was withheld. The noise condition subjects reported taking longer to fall asleep, less time sleeping, more awakenings, poorer quality of sleep compared to home, as well as fewer positive and more negative adjectives descriptive of sleep. Self-reports of the time spent sleeping and the number of negative adjectives descriptive of sleep yielded the greatest number of significant correlations with scores for the other measures of sleep, indicating that these measures may be more accurate. The results provide support for the hypothesis that CCU sound levels impact negatively on subjective sleep.[3]

In an Argentine study, fluctuating and impulsive noises were recorded from incubators (67 dB), normal daily environmental noise (71 dB), cleaning noises (83 dB), noise from putting objects in the incubator (102 dB), involultary disturbances, ie knocks and such (110 dB), alarms (89 dB) and access gate use (103 dB). A more general analysis broke down the noise levels as a band-width of dB as follows: exterior background noise – 45-67 dB; instrumental noise – 68-77 dB; environmental cleaning noise – 65-98 dB; tubing and auxiliary gates – 79-85 dB.

The primary causes of incubator equipment noise were squeaky, wheezy, poorly lubricated motors, worn out rollings, and unbalanced turbines. Interestingly, the loudest noises, of up to 130 dB, were from the opening and closing of access portals to the incubator.[4]

Noise In The NICU

Subsequently, soundscape analyses were used to document sound levels in the NICU. Typically, comprehensive analyses comprised sounds heard through several work shifts, as well as for specific activities. Ideally, the analyses' conclusions would then be implemented in the design of the NICU.[5]

The American Academy of Pediatrics reported that noise can

Laszlo Sandor is associate editor of Neonatal Intensive Care.

result in the reduction of infant listening ability and directly affects development of a baby's central nervous system. This is even more likely for preemies in an NICU, because their nervous systems are likely to be immature. Excessive noise is demonstrably related to the loss of infant hearing capacity, chronic stress, sleep disorders, fluctuations of arterial pressure, and hypoxia.

Noise reduction is a subset of the integrated care approach in the NICU. One of the most comrpehensive studies of noise levels, their implications for NICU infants, and what to do about them, was published last year in Neonatal Network.[6]

According to this thorough and comprehensive article by Gemma Brown, there had been a limited amount of current research on the effects of noise on the preterm infant, with most studies dating back to the 60s, and there had not been much objective information about the effects of sound on preemies, and especially VLBW infants. However, other effects of noise have been posited as sensorineural hearing loss, and brain-effects that may be linked to ADHD.

The most recent sound level recommendations come from the Committee to Establish Recommended Standards for Newborn ICU Design, which advises that the combination of all sounds should not exceed an evarage noise level of 45 dB. Despite these recommendations, Brown noted, noise levels commonly exceed these limits. Early studies reported routine sound levels ranging from 70 dB to 117 dB. Other studies showed sound levels that were lower but still frequently above the recommended levels, from 54 dB to 117 dB. Nasal CPAP had been shown to produce noise intensities reaching mean levels of 102 dB. (NB: Conversational speech is about 60 dB, heavy traffic is 75 to 85 dB, and a jet taking off is 125 dB.)

Noise-induced physiologic changes, according to the study, include apnea, bradycardia, alterations in sleep-wake states, and fluctuations in heart rate, respiratory rate, blood pressure, and oxygen saturation. Elevated respiratory and heart rates increase oxygen consumption and caloric requirements, so an acutely ill infant who is subject to environmental stress gets fewer calories. Premature infants are particularly vulnerable because they can't selectively limit or inhibit incoming stimuli and their physiologic impact.

The persistence of developmental problems may be associated with the noise and light stimulation of the NICU environment exceeding the preemie's coping mechanism.[6]

Other studies have also gauged the effects of equipment on noise levels. A study of noise levels in a 78-bed NICU revealed the following noisemakers: conversation, alarm volumes, objects placed on tops of incubators, unquieted crying babies, slammed portholes and drawers, ringing beeping buzzing phones, radios playing, water burbling in ventilators and tubes, hard unblanketed surfaces, the constant noise of general activity, loud alarms, people tapping or banging or writing on incubators and ventilators, and physicians and clinicians touring the ward on rounds.

In another study, weekly sound surveys were collected, using 5 s sampling intervals, for two modern NICUs. Median weekly equivalent sound pressure levels ranged from 61 to 63 dB. Sound levels exceeded 45 dB more than 70% of the time for all levels of care. Hourly levels below 50 dB were exceeded in more than 70% of recorded samples.[7]

Some noise comparisons, from the American Academy of pediatrics

heartbeat	10	dB(A)
whispering	20-30	
home ambient noise	40	
light traffic	50	
regular talking	60	
vacuum cleaner	70	
bubbling in vent tube	70	
heavy traffic	80	
tapping on incubator	80	
pneumatic drill	90	
slamming cabinet under incubator	90	
lawnmower	100	
closing plastic porthole	100	
boom box	120	
dropping the top of the mattress	120	
jet plane	140	

In another recent study researchers examined the baseline acoustic environment in several mid-Atlantic region NICUs. Ambient sound levels were taken at 5-minute intervals over a 2-hour period during both day and night shifts. Hourly mean sound levels in each NICU ranged from 53.9 dB to 60.6 dB, with no statistically significant difference between noise levels recorded on day shift versus night shift, and no statistically significant difference among sites. Key contributing factors to increased sound levels were stated as monitors or alarms, performing invasive procedures, presence of family, nurses or doctors giving report or rounds, and ringing phones. Noise levels were found to be above the American Academy of Pediatrics—recommended 45-dB level and often louder than 50-dBs.[8]

Solutions

According to the article in Neonatal Network, reducing noise levels in the NICU can improve the physiologic stability of sick neonates and therefore enlarge the potential for infant brain development. Recommendations include covering incubators with blankets, removing noisy equipment from the incubator environment, implementing a quiet hour, educating staff to raise awareness, and encouraging staff to limit conversation near infants.[6]

Researchers in India performed a prospective longitudinal study in a level III NICU, wherein a noise reduction protocol that included behavioral and environmental modification was implemented. The noise levels were measured sequentially every hour for 15 days before and after this intervention. The protocol reduced noise levels in all the rooms of the NICU to within 60 dB with high statistical significance. The extent of noise reduction in the ventilator room was reduced by 9.58 dB, in the stable room by 6.54 dB and in the isolation room by 2.26 dB. The intervention was most cost-effective in the ventilator room.[9]

Training of NICU staff is, of course, one way to mitigate noise levels, and does have some limited effect. In a Canadian study, a hospital evaluated the results of nurse training about minimizing sound levels in the NICU. Noise levels were recorded before and after the training, and throughout eight shifts. The average

pre-training levels were 53, 61 and 65 dB for the night, day and evening shifts, all of which exceeded the recommended 45 dB level. While the study showed that training reduced sound levels, the reductions were certainly undramatic. Ultimately, reducing noise levels is best accomplished by noise intervention through control of the equipment.[10] But training of staff must be complemented by active efforts to reduce noise, by purchasing quiet equipment, and using it in a way that minimizes aural disturbances.

Gemma Brown's research focused on ways to change practices to reduce noise levels within NICUs. Some approaches to reducing noise, she discovered, are "quiet hours," which resulted in significant noise reduction, with 84.5% of infants in light or deep sleep compared to 33.9% percent in a non-quite-hour control group. Covering the incubator with a blanket was another way to cut noise, by reducing the noise levels inside the incubator. In one study, noise levels in the covered incubators were significantly lower, an average of 4.8 dB. Interrupting HVAC airflow and stopping conversation decreased noise levels to 4.5 dB.[6]

The holistic approach to care that led neonatal health providers to consider noise and its effects also provides the solution to the problem they intuited and demonstrated. NICUs that initiate and maintain an all-encompassing approach to noise reduction will likely achieve the most success. NICU equipment manufacturers have now become aware of the importance of noise reduction, and have designed ventilators that produce significantly lower noise levels. The use of such equipment, combined with systematic, proactive guidelines and practices, can successfully mitigate noise-level damage to infants in the NICU.

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An Incidentally Detected Hepatic Subcapsular Hematoma in a Very Low Birth Weight Newborn

Hye Shin Ahn, Yun-Woo Chang, Dong Whan Lee, Kui Hyang Kwon, Seung Boo Yang

Abstract

Introduction: A hepatic subcapsular hematoma in a neonate shows a non-specific presentation such as the presence of an abdominal mass without symptoms of hemorrhage and is clinically less distinguished as compared to cases detected during an autopsy.

Case presentation: A neonate was delivered by vaginal delivery after 29 weeks and three days gestation with breech presentation. In a laboratory study, there were slightly increased levels of liver enzymes but the platelet count and hemoglobin level were normal. An abdomen ultrasonography and CT image demonstrated the cystic mass containing an internal thin septum with compression of the lateral margin of the right hepatic lobe and Morison's pouch. A CT image showed an irregular low-density lesion in the dome of liver that was suspected parenchymal laceration.

Conclusion: We have described the sonographic and CT findings of an incidentally detected subcapsular hematoma of the liver in a neonate who showed a breech presentation, very low birth weight and was premature.

Introduction

A subcapsular hematoma of the liver in a neonate may be uncommonly reported in clinical and imaging series as an asymptomatic or small size hematoma, although autopsy series have demonstrated an incidence rate of up to 15%.[1-8] This lesion should be suspected in infants with unexplained anemia or hypovolemia and in large infants and infants born by breech delivery.[1-8] We describe the sonographic and CT findings of a subcapsular hematoma of the liver in a neonate with nonspecific clinical features for a breech, very low birth and premature infant.

Case presentation

A premature Korean female was delivered by vaginal delivery after 29 weeks and three days gestation to a mother with vaginal bleeding and premature labor with a breech presentation. The female patient had a difficult delivery and the patient developed a left clavicular fracture and cyanosis due to respiratory distress syndrome. The birth weight was 1420g, and Apgar scores were 3 and 7 at one and five minutes, respectively. The infant was intubated shortly after birth with mechanical ventilation and respiratory distress syndrome had improved as seen on follow-up.

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In a laboratory study performed at one day of age, there were increased levels of liver enzymes with an aspartate aminotransferase (AST) level of 164 U/L and alanine aminotransferase (ALT) level of 25 U/L and a total bilirubin level of 2.2mg/dl, but the platelet count and hemoglobin level were normal. For the coagulation profile, the prothrombin time was prolonged at 15.6 seconds (normal range 9.9-13.1 seconds) and the active partial thromboplastin time was prolonged at 69.7seconds (normal range, 23.5-37.5 seconds).

An abdomen ultrasonography examination was performed at two days of age and demonstrated the presence of an approximate 1.2 x 4.2cm size cystic mass containing an internal thin septum with compression of the lateral margin of the right hepatic lobe. In addition, a cystic lesion in Morison's pouch was seen with the same features as that in the lateral area of the liver. (Figure 1 and 2) Abdomen CT imaging was performed for the differential diagnosis including a subcapsular hematoma, liver abscess and panperitonitis. A CT image showed an approximate 3.1 x 1.0cm size well defined, oval shape cystic mass in the lateral subcapsular area of the liver and the lesion compressed the adjacent liver parenchyma (Figure 3). An approximate 1.8 x 0.7cm size cystic lesion was also noted in the area between the liver and the right kidney. An irregular low-density lesion in the dome of liver that was seen and parenchymal laceration was suspected. The CT finding was suspicious for a subcapsular hematoma because of the liver parenchymal laceration (Figure 4). A follow up ultrasonography examination was performed at seven days of age, and the previous noted cystic lesions adjacent to the liver and Morison's pouch had improved (Figure 5).

In a follow-up laboratory study, levels of liver enzymes had decreased but the level of total bilirubin had gradually increased and was 13.0mg/dl at 27 days of age. Total bilirubin had decreased since 27 days of age. The platelet count decreased and was 8.2 mg/dl at 21 days of age. After transfusion of approximately 28 cc of blood, the platelet count gradually increased as seen in a follow-up study. The patient was discharged without abnormality.

Discussion

A hepatic subcapsular hematoma in a neonate usually presents as a gradually increasing abdominal mass without symptoms of hemorrhage. Although autopsy series have demonstrated an incidence rate of up to 15%, the lesion is clinically less distinguished.[1-8] There are three major causes of hepatic injury in neonates, including obstetrical causes such as difficult labor, early travail and a breech presentation, neonatal causes such as hepatomegaly, coagulopathy, resuscitation, prematurity or post-maturity and maternal causes such as eclampsia and an elderly mother.[1-8] As was similar for the present case, a hepatic

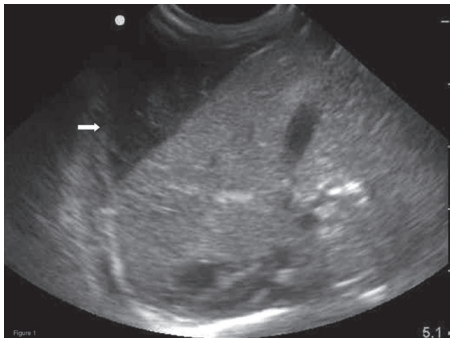

Figure 1: Imaging findings are shown for a subcapsular hematoma in a one-day old infant. An abdominal sonogram shows a cystic mass containing an internal thin septum with compression of the liver parenchyma in the right lobe of liver (arrow).

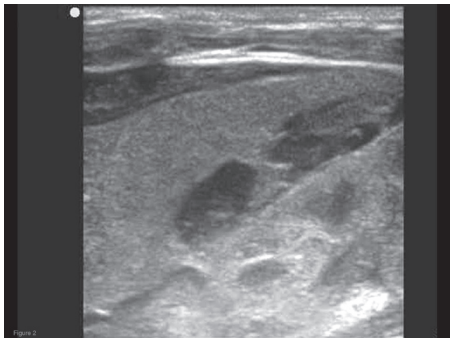

Figure 2: A cystic mass with an internal septum is noted in Morrison's pouch.

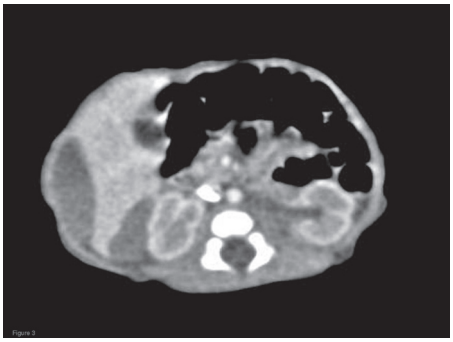

Figure 3: A contrast-enhanced abdominal CT scan shows a well-defined, oval shape, non-enhancing, slightly low-density cystic mass in the subcapsular area of the lateral portion of the liver and hepatorenal space.

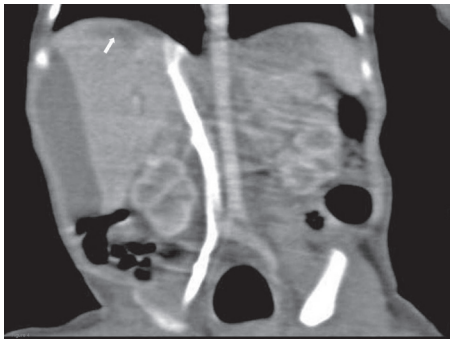

Figure 4: A multi-planar reformatted coronal CT scan shows a partial linear low-density lesion in the dome of the liver presumed to be parenchymal laceration (arrow). An non-enhancing cystic mass is seen in the lateral margin of the liver with hepatic compression.

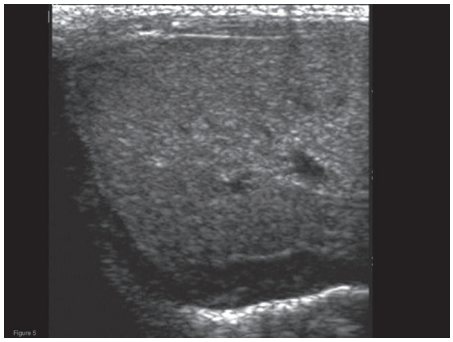

Figure 5: A follow-up sonogram obtained after seven days reveals a markedly improved cystic lesion in the lateral portion of the liver.

hematoma is common for premature infants and low birth weight infants with a breech presentation or thrombocytopenia as demonstrated in several cases. Many patients require management such as umbilical venous catheter insertion or mechanical ventilation and resuscitation that can cause a hepatic hematoma.[3] In a preterm infant, the abdominal configuration exposes more hepatic surface below the rib cage due to extramedullary hematopoiesis and liver laceration is induced by chest compression during delivery, which is due to stretching of attached multiple hepatic ligaments.[1,3]

An abdominal sonogram shows non-specific findings and an intrahepatic hematoma can suggest a different diagnosis such as a liver abscess or hepatic mass.[7,8] In our case, cystic masses that contained multiple thin septa of the perihepatic area and Morison's pouch were noted on a sonogram. The presence of the masses and panperitonitis is required for the differential diagnosis. The usefulness of CT or MRI is disputable, but these imaging modalities may assist in the differential diagnosis.[4,6-8] A follow-up sonogram is helpful to confirm the diagnosis of a subcapsular hematoma and to identify a mass that has decreased in size.[4,6,8] Early detection of a subcapsular hematoma is important in an infant delivered via normal vaginal delivery with no significant clinical symptoms due to the difficulty of recognition of liver laceration. If a large amount of peritoneal bleeding progresses the bleeding can be fatal.[4,6] Conservative treatment is initially performed because of a great extent of a subcapsular hematoma is naturally absorbed. We have described the sonographic and CT findings of an incidentally detected subcapsular hematoma of the liver in a neonate who showed a breech presentation, very low birth weight and was premature.

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Approaching the Diagnosis of Growth-Restricted Neonates

Popi Sifianou

Abstract

Background: The consequences of in utero growth restriction have been attracting scholarly attention for the past two decades. Nevertheless, the diagnosis of growth-restricted neonates is as yet an unresolved issue. Aim of this study is the evaluation of the performance of simple, common indicators of nutritional status, which are used in the identification of growth-restricted neonates.

Methods: In a cohort of 418 consecutively born term and near term neonates, four widely used anthropometric indices of body proportionality and subcutaneous fat accretion were applied, singly and in combination, as diagnostic markers for the detection of growth-restricted babies. The concordance of the indices was assessed in terms of positive and negative percent agreement and of Cohen's kappa.

Results: The agreement between the anthropometric indices was overall poor with a highest positive percent agreement of 62.5% and a lowest of 27.9% and the κ ranging between 0.19 and 0.58. Moreover, 6% to 32% of babies having abnormal values in just one index were apparently well-grown and the median birth weight centile of babies having abnormal values of either of two indices was found to be as high as the 46th centile for gestational age (95%CI 35.5 to 60.4 and 29.8 to 63.9, respectively). On the contrary, the combination of anthropometric indices appeared to have better distinguishing properties among apparently and not apparently well-grown babies. The median birth weight centile of babies having abnormal values in two (or more) indices was the 11th centile for gestational age (95%CI 6.3 to 16.3).

Conclusions: Clinical assessment and anthropometric indices in combination can define a reference standard with better performance compared to the same indices used in isolation. This approach offers an easy-to-use tool for bedside diagnosis of in utero growth restriction.

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Background

"The diagnosis of impaired fetal growth in newborn infants continues to depend largely on two major parameters: birth weight and gestational age." This is the introductory statement in a paper by Miller and Hassanein on the diagnosis of impaired growth in newborns, which aimed at documenting the insufficiency of using birth weight to uncover fetal growth disturbances. Almost forty years later, a neonatal test that produces a definitive diagnosis of in utero growth-restricted babies is not yet available. Consequently, small for gestational age babies are taken in as utero growth restricted (IUGR), despite increased awareness that the two terms are not synonymous.

From a theoretical perspective growth-restricted neonates could be detected through reduced prenatal growth. Nevertheless, in addition to the numerous potential errors involved in biometric measures there is no consistently superior parameter reflecting fetal growth accurately and the most commonly used fetal biometric parameters were found to correlate poorly with size at birth. Doppler velocitometry and components of the biophysical profile, in combination, are definitively superior regarding diagnostic accuracy, even though these approaches have not been standardized.

Pediatricians are called to identify IUGR babies promptly and accurately, so as treat appropriately even those who have had no medical care prenatally, ie all IUGR babies irrespective of the level of prenatal care. Therefore, an easy-to-use tool for bedside diagnosis of growth-restricted neonates is desirable.

Methods

Subjects: All consecutive singleton babies, delivered after 35 weeks of gestational age (GA) at General & Maternity Hospital "Elena Venizelou" during four randomly selected weekly periods, were prospectively studied.

Data collection: Babies were evaluated and measured between 12 and 24 hours of life, except for birth weight (BW) which was recorded at birth. The evaluation included assessment of nutritional status and of GA, using the Expanded New Ballard Score. The former was based on the Clinical Assessment of Nutritional Status (CANS) scoring method, which evaluates subcutaneous fat accretion at eight body locations and features of the hair. In the present study, this last criterion was replaced by one evaluating the skin, under the following formulation: Skin well hydrated, vernix caseosa possibly present especially in body

Table 1. Agreement of the anthropometric indices

	MAC to PI	MAC to CC	MAC to MAC/HC	PI to CC	PI to MAC/HC	CC to MAC/HC
p_{pos}	27.9%	40.0%	62.5%	29.3%	29.2%	32.6%
p_{neg}	91.0%	92.7%	95.1%	92.3%	91.6%	92.2%
κ	0.19	0.33	0.58	0.21	0.21	0.25
SE	0.09	0.08	0.07	0.09	0.09	0.09
95%CI	0.01 to 0.39	0.16 to 0.49	0.44 to 0.71	0.03 to 0.40	0.03 to 0.39	0.07 to 0.43

folds (4 points); rather dry skin, peeling over palm and soles, vernix caseosa absent even in babies of 37 to 38 weeks gestation (3 points); skin overall dry, desquamating on the extremities (2 points); skin peeling off in large flakes, parchmentlike skin (1 point). GA was calculated in completed weeks from the last menstrual period and compared with that derived from babies' clinical assessment. If in disagreement for over 2 weeks the clinical score was recorded.

Included in the measurements were: a) the birth length (BL), b) the largest occipitofrontal circumference (HC), c) the chest circumference (CC) at the level just below the nipples and d) the mid-arm circumference (MAC) at the midpoint between acromion and olecranon of the right arm placed next to the chest with the palm facing the thigh. Circumferences were measured to the nearest 0.1 cm with a plastic tape measure of 0.9 cm width. Birth length was measured by Rollameter (Harlow Printed Ltd, UK) to the nearest 0.1 cm. All measurements were taken in triplicate and the mean was recorded. At the end of the data collection ponderal index (PI), i.e. weight in g/(length in cm)3 X 100, and the ratio MAC/HC were calculated. Abnormal values of the anthropometric indices and of BW were defined as values ≤10th percentile for GA. Per definition a CANS score ≥27 describes apparently well-grown babies. Pregnancy and delivery history were obtained by reviewing the medical records and by interviewing the mother.

Data analysis: Statistical analysis was performed using MedCalc for Windows, version 10.4 (MedCalc Software, Mariakerke, Belgium). Anthropometric measurements were expressed as percentiles. Mann-Whitney test for independent samples was used to determine differences between anthropometric indices of individual groups of babies and chi-square test for categorical variables. $p<0.05$ was considered statistically significant. The agreement of diagnostic markers was estimated using the Cohen's kappa for chance-corrected agreement as well as the positive and negative percentage agreement. Positive agreement of two indices was calculated as the number of cases having abnormal values in both indices divided by the sum of cases with abnormal values in each index. Negative agreement was calculated in the same way taking into account the normal values of the indices.

Results: The study included 418 consecutively born, singleton neonates between 35 and 41 weeks GA (208 boys/ 210 girls). No statistically significant sex difference was detected in MAC (p=0.08), PI (p=0.07), CC (p=0.13) and MAC/HC (p=0.32). GA estimation was based on clinical evaluation in 15 cases: in 3 cases with unavailable last menstrual period data and in another12 due to the disagreement between clinical assessment and maternal dates; in 9 of the last 12 cases a history of irregular menses was present.

Agreement of the anthropometric indices: The agreement of the anthropometric indices was studied in terms of positive (p_{pos}) and of negative (p_{neg}) percent agreement, as well as of chance-corrected agreement, i.e. Cohen's kappa. As shown in Table 1 the agreement beyond chance between the anthropometric indices was fair, with κ values ranging between 0.19 and 0.33. The only exception was the agreement between MAC and MAC/HC, which appeared stronger probably owing to their common component. The κ was 0.58 and the p_{pos} 62.5%.

Given the low level of agreement, all individual cases with abnormal values in one anthropometric index were subsequently examined for co-occurrence of abnormal values in all three remaining indices. For instance, all cases having PI ≤10th centile were tested for values of MAC ≤10th centile and those cases with abnormal PI, but normal MAC values, were tested for abnormal CC values and so forth. The percentage of cases with abnormal values of PI and of at least one more index was 51% (22 cases out of a total of 43 cases with abnormal values of PI in the study population). Hence, almost half of the cases with abnormal PI values agreed with at least one more of the three remaining indices (and the other half with none). This percentage was 74% (37/50) for cases with MAC ≤10th centile, 62.5% (25/40) for cases with CC ≤10th and almost 74% (34/46) for cases with MAC/HC ≤10thcentile. These results are illustrated in Figure 1. Unfilled

Table 2. Comparison of babies having abnormal values of one or more indices

		CANS					BW centiles		
		n	Median	95% CI	p	Score ≥27 (no/total)	Median	95% CI	p
MAC ≤10th centile	**S**	13	22	21.9 to 25.0	.32	0/13	12.7	5.8 to 18.3	.44
	C	37	22	21.0 to 24.0		3/37	9.5	4.6 to 15.7	
PI ≤10th centile	**S**	21	27	24.0 to 27.2	<.0001	14/21	46.5	35.5 to 60.4	<.0001
	C	22	22	20.0 to 24.0		0/22	10.8	4.1 to 21.8	
CC ≤10th centile	**S**	15	26	21.0 to 27.0	.01	5/15	10.4	5.3 to 22.3	.03
	C	25	22	20.4 to 23.8		2/25	5.5	2.1 to 11.2	
MAC/HC ≤10th centile	**S**	12	25	23.6 to 27.0	.0002	3/12	45.2	29.8 to 63.9	<.0001
	C	34	22	21.0 to 24.0		2/34	12.3	5.5 to 21.1	

areas in the columns represent the proportion of cases with abnormal values of the indicated index but normal values of all three remaining indices.

Misclassification of babies as IUGR by using anthropometric indices singly: BW centiles and CANS scores of babies having abnormal values in a single index were compared with those of babies having abnormal values of this same index and at least one more. Mann-Whitney test for independent samples was used to assess the statistical significance of the differences. The results are collectively presented in Table 2. Cases with abnormal values in each of the four indices were divided into two sub-groups on the basis of the presence or absence of abnormal values of other indices. The sub-group S includes cases having abnormal values in a single index and the sub-group C those having abnormal values in a combination of indices. Babies with abnormal values of MAC were found to have comparable CANS scores irrespective of the presence or absence of abnormal values of the other three indices; median CANS scores of both the S and C sub-groups of babies having MAC ≤10th centile were 22 (p=0.32). However, CANS scores were significantly different between babies having abnormal values of only PI or CC or MAC/HC (S sub-groups) and babies having abnormal values of more than one of the indices (C sub-groups). For instance, median CANS score of cases having only PI ≤10th centile (S sub-group) was 27 versus 22 of the C sub-group (p<0.0001). Moreover, taking into account that a CANS score ≥27 describes, per definition, babies with apparently normal subcutaneous fat mass, it was evident that apparently well-grown babies had abnormal values in a single index, e.g., 14 out of 21 babies with abnormal values of PI but normal values of MAC, CC and MAC/HC. On the contrary, none of the cases with abnormal values of PI and of at least one more index (C sub-group) was apparently well-grown; median CANS score was 22 in the latter group versus 27 in the former. Consequently, if PI, CC or MAC/HC were used as single indicators of growth restriction, a relatively high proportion of babies designated as IUGR would be wellgrown babies; 32.6%, 17.5% and 10.9%, respectively.

A similar picture emerged when BW centiles were taken into consideration (Table 2). The median BW centile of babies having abnormal only PI or only MAC/HC values (S sub-groups) was the 46th centile, an inappropriately high median BW centile for supposedly in utero growth-restricted babies. BW centiles were significantly lower in the groups of babies who had more than one abnormal value in anthropometric index (C sub-groups) compared to the groups of babies who had only one abnormal value (S sub-groups). Again, in addition to CANS scores, no statistically significant differences in BW centiles were found in the two groups of babies with abnormal MAC values.

As a group, the median BW centile of babies having abnormal values in only one anthropometric index was 26.8 (95%CI 17.8 to 37.6) versus 11.4 (95%CI 6.3 to 16.3) in babies having abnormal values in at least two indices (p<0.0001). The corresponding median CANS scores were 25 (95%CI 24.0 to 26.5) and 22 (95%CI 21 to 24), respectively (p<0.0001).

Categorization of study babies on the basis of abnormal values of indices: Overall 47 babies (out of 418 studied) were found to have abnormal values in two or more of the four anthropometric indices. Of those, 24 babies were appropriate and 23 small for GA. In the total population, 328 babies were appropriate and 47 small for GA. Thus, the prevalence of babies having abnormal values in at least two indices was 7.4 % and 48.9 % among appropriate and small for GA, respectively.

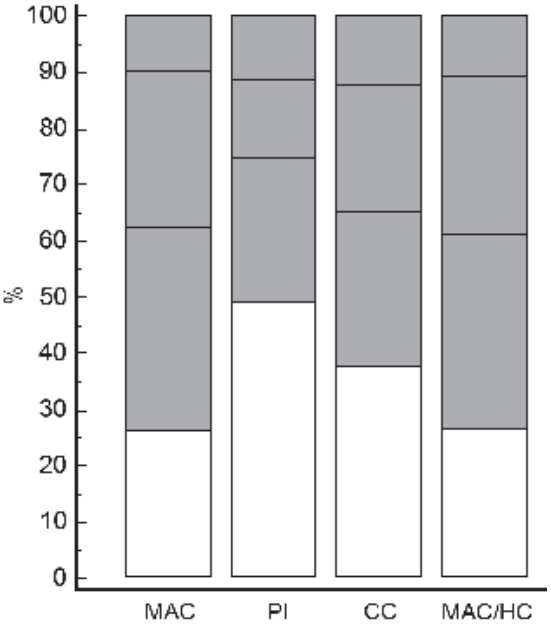

Figure 1. Proportion of babies with abnormal values in one or more anthropometric indices

Discussion

The high rate of morbidities in growth-restricted neonates has been well documented. Moreover, accumulated evidence over the last two decades converges on an increasing risk of metabolic syndrome among individuals who have experienced growth restriction during fetal life. For both these reasons the distinction between growth-restricted and non-restricted babies is of paramount importance.

Irrespective of cause, fetuses with inadequate nutrition will not deposit fat as long as their basic metabolic needs are not met. Conversely, a baby with abundant subcutaneous fat cannot have suffered from in utero malnutrition. On the basis of this principle, the evaluation of fat deposits is an appropriate means for the distinction between IUGR and non-IUGR neonates. To this end, anthropometry has been carried out for years. Indeed, numerous studies dealing with short or long term consequences of in utero growth restriction consider their subjects as growth-restricted if the ratios BW to BL (principally PI), MAC, the ratio MAC to HC and less frequently CC are lower than a given threshold value. Rarely is the distinction between IUGR and non- IUGR babies based on clinical signs at birth suggestive of fetal malnutrition, in an atypical or in a structured form, like CANS score. Both the anthropometric indices and the clinical evaluation of nutritional status have been proven more sensitive predictors of early neonatal morbidities, ascribed to in utero growth restriction, as compared to BW.

Despite their interchangeable use in the relevant studies, the above diagnostic markers of in utero growth restriction perform differently, as evidenced in the present study. Only 28% of babies with MAC ≤10th centile had also PI at or below this level. Since high accuracy entails high agreement, the relatively low level of agreement between the anthropometric indices could be ascribed to their low diagnostic accuracy in the identification of IUGR babies. This assumption is supported by the relatively

high proportion of babies, found in the present study, who had abnormal values of individual indices, despite their being apparently well-nourished, eg 32.6% of cases having abnormal PI values. The low diagnostic performance of PI is in agreement with other studies.

Whenever a reference standard is not available, the optimal method that has been suggested for the distinction between diseased and non-diseased individuals is the combination of several imperfect diagnostic tests; in the broad sense of the term "test." Depending on the availability of a nearly perfect test, on the diagnostic performance of individual tests, on their interdependence, etc several methods and rules for combining tests have been developed. Moreover, the combination of several diagnostic tests appears to be a reasonable approach for a highly complex and multi-factorial process, like intrauterine growth. In utero growth restriction is not a uniform condition with respect to its severity and duration, the underlying pathogenesis and the developmental stage of the fetus at the time of its occurrence. Therefore, a single anthropometric index or any other test cannot suffice to detect all babies with impaired in utero growth accurately. In the present study, the combination of anthropometric indices proved to have better performance in the diagnosis of not apparently well-grown babies over the isolated use of the same indices.

A diagnostic test should have the potential to be implemented in clinical practice. Moreover, IUGR babies should be identified immediately after birth, so as to receive the appropriate care promptly. Contrary to more sophisticated imaging techniques, which are expensive and impractical to use in clinical settings, anthropometry is not only a relatively simple, but also a reliable tool for bedside quantification of body composition and proportions. A noticeable limitation of all the anthropometric indices mentioned is their dependence on GA. Subsequently, any inaccurate estimation of GA will impact on the accuracy of the identification of IUGR neonates (which, however, also holds for BW). By contrast, this problem does not pertain to CANS score, which is unrelated to GA. This scoring method helps the clinician get insights into babies' nutritional status, by focusing on those body areas where subcutaneous fat should have been accumulated during in utero life, and eventually quantify his evaluation. Its major drawback is its subjective nature, like all other scoring methods used in the evaluation of neonates. The method could be used as a screening or confirmatory test.

All in all, the combined over the isolated use of anthropometric measurements appears to offer a better approach in the identification of growth-restricted babies. In every term or near term baby with clinical signs of wasting (eg, absence of chin fatfolds, skin easily grasped and lifted in fold, visible or prominent ribs, reduced gluteal fat) MAC and CC can be measured at bedside easily. In addition, PI and the ratio MAC/HC can be calculated using measures included in neonatal records. Babies with abnormal values in more than one anthropometric index can be managed as growthrestricted. Abnormal values in more than one index in apparently well-grown babies may necessitate a re-evaluation of GA. Undoubtedly, further research is needed, using a greater range of confirmatory information. Search and evaluation of alternative indices or other simple indicators of growth restriction might also contribute to a more accurate identification of IUGR babies.

Conclusions

Research evidence of many decades points to in utero growth restriction as a leading cause of early neonatal morbidity. It is highly likely that at least part of it (eg hypoglycemia, especially in appropriate for GA babies) escape our attention due to the lack of a precise diagnostic tool. To this end, the idea of a combined reference standard, as the one proposed above, can improve our capacity to identify and manage growth-restricted babies appropriately.

for neonatal RDS

Infasurf®

(calfactant)
Intratracheal Suspension

Why we're little pharma.

EDMUND EGAN, M.D.
ONY FOUNDER • SURFACTANT PIONEER

Sometimes, the smaller your organization, the more details matter. That's why ONY, Inc., our little company in Amherst, New York, produces only Infasurf ®(calfactant) – an area we pioneered over 20 years ago.

All our reps are neonatal intensive care professionals. And though we're not big pharma , we've been successful in making a difference for high-risk RDS newborns for over a decade.

Why is our product so different? Infasurf delivers the highest SP-B to phospholipid ratio on the market, resulting in:

- A PROLONGED EFFECT THAT CAN MEAN FEWER DOSES
- RAPID IMPROVEMENT IN VENTILATION
- APPROVAL FOR BOTH PREVENTION AND TREATMENT OF RDS

Mortality rates for all approved surfactants have been shown to be similar. But to us at ONY, the small differences in Infasurf can have a big impact on the tiny infants and their families that you help every day.

THE LITTLE THINGS MATTER MOST

Infasurf® for neonatal RDS
(calfactant) Intratracheal Suspension

Sterile Suspension for Intratracheal Use Only

Rx Only Rev. 06/09

DESCRIPTION

Infasurf® (calfactant) Intratracheal Suspension is a sterile, non-pyrogenic lung surfactant intended for intratracheal instillation only. It is an extract of natural surfactant from calf lungs which includes phospholipids, neutral lipids, and hydrophobic surfactant-associated proteins B and C (SP-B and SP-C). It contains no preservatives.

Infasurf is an off-white suspension of calfactant in 0.9% aqueous sodium chloride solution. It has a pH of 5.0 - 6.2 (target pH 5.7). Each milliliter of Infasurf contains 35 mg total phospholipids (including 26 mg phosphatidylcholine of which 16 mg is disaturated phosphatidylcholine) and 0.7 mg protein including 0.26 mg of SP-B.

CLINICAL PHARMACOLOGY

Endogenous lung surfactant is essential for effective ventilation because it modifies alveolar surface tension thereby stabilizing the alveoli. Lung surfactant deficiency is the cause of Respiratory Distress Syndrome (RDS) in premature infants. Infasurf restores surface activity to the lungs of these infants.

Activity: Infasurf adsorbs rapidly to the surface of the air/liquid interface and modifies surface tension similarly to natural lung surfactant. A minimum surface tension of ≤3 mN/m is produced in vitro by Infasurf as measured on a pulsating bubble surfactometer. *In vivo*, Infasurf restores the pressure volume mechanics and compliance of surfactant-deficient rat lungs. *In vivo*, Infasurf improves lung compliance, respiratory gas exchange, and survival in preterm lambs with profound surfactant deficiency.

Animal Metabolism: Infasurf is administered directly to the lung lumen surface, its site of action. No human studies of absorption, biotransformation, or excretion of Infasurf have been performed. The administration of Infasurf with radiolabeled phospholipids into the lungs of adult rabbits results in the persistence of 50% of radioactivity in the lung alveolar lining and25% of radioactivity in the lung tissue 24 hours later. Less than 5% of the radioactivity is found in other organs. In premature lambs with lethal surfactant deficiency, less than 20% of instilled Infasurf is present in the lung lining after 24 hours.

Clinical Studies: The efficacy of Infasurf was demonstrated in two multiple-dose controlled clinical trials involving approximately 2,000 infants treated with Infasurf (approximately 100 mg phospholipid/kg) or Exosurf Neonatal®. In addition, two controlled trials of Infasurf versus Survanta®, and four uncontrolled trials were conducted that involved approximately 15,900 patients treated with Infasurf.

Infasurf versus Exosurf Neonatal®

Treatment Trial

A total of 1,126 infants ≥72 hours of age with RDS who required endotracheal intubation and had an a/A PO_2 < 0.22 were enrolled into a multiple-dose, randomized, double-blind treatment trial comparing Infasurf (3 mL/kg) and Exosurf Neonatal® (5 mL/kg). Patients were given an initial dose and one repeat dose 12 hours later if intubation was still required. The dose was instilled in two aliquots through a side port adapter into the proximal end of the endotracheal tube. Each aliquot was given in small bursts over 20-30 inspiratory cycles. After each aliquot was instilled, the infant was positioned with either the right or the left side dependent. Results for efficacy parameters evaluated at 28 days or to discharge for all treated patients from this treatment trial are shown in

Table 1- Infasurf vs Exosurf Neonatal®: Treatment Trial

Efficacy Parameter	Infasurf (N=476) %	Exosurf Neonatal® (N=550) %	p-Value
Incidence of air leaks[1]	11	22	<0.001
Death due to RDS	4	4	0.95
Any death to 28 days	8	10	0.21
Any death before discharge	9	12	0.07
BPD[2]	5	6	0.41
Crossover to other surfactant[3]	4	4	1

[1] Pneumothorax and/or pulmonary interstitial emphysema.
[2] BPD is bronchopulmonary dysplasia, diagnosed by positive X-ray and oxygen dependence at 28 days.
[3] Protocol permitted use of comparator surfactant in patients who failed to respond to therapy with the initial randomized surfactant if the infant was <96 hours of age, had received a full course of the randomized surfactant, and had an a/A PO_2 ratio <0.10.

Prophylaxis Trial

A total of 833 infants <29 weeks gestation were enrolled into a multiple-dose, randomized, double-blind prophylaxis trial comparing Infasurf (3 mL/kg) and Exosurf Neonatal® (5 mL/kg). The initial dose was administered within 30 minutes of birth. Repeat doses were administered at 12 and 24 hours if the patient remained intubated. Each dose was administered divided in 2 equal aliquots, and given through a side port adapter into the proximal end of the endotracheal tube. Each aliquot was given in small bursts over 20-30 inspiratory cycles. After each aliquot was instilled, the infant was positioned with either the right or the left side dependent. Results for efficacy parameters evaluated to day 28 or to discharge for all treated patients from this prophylaxis trial are shown in Table 2.

Table 2- Infasurf vs Exosurf Neonatal®: Prophylaxis Trial

Efficacy Parameter	Infasurf (N=411) %	Exosurf Neonatal® (N=422) %	p-Value
Incidence of RDS	15	47	<0.001
Incidence of air leaks[1]	10	15	0.04
Death due to RDS	2	5	<0.01
Any death to 28 days	12	16	0.10
Any death before discharge	18	19	0.56
BPD[2]	16	17	0.60
Crossover to other surfactant[3]	0.2	3	<0.001

[1] Pneumothorax and/or pulmonary interstitial emphysema.
[2] BPD is bronchopulmonary dysplasia, diagnosed by positive X-ray and oxygen dependence at 28 days.
[3] Protocol permitted use of comparator surfactant in patients who failed to respond to therapy with the initial randomized surfactant if the infant was < 72 hours of age, had received a full course of the randomized surfactant, and had an a/A PO_2 ratio < 0.10.

Infasurf versus Survanta®

Treatment Trial

A total of 662 infants with RDS who required endotracheal intubation and had an a/A PO_2 <0.22 were enrolled into a multiple-dose, randomized, double-blind treatment trial comparing Infasurf (4 mL/kg of a formulation that contained 25 mg of phospholipids/mL rather than the 35 mg/mL in the marketed formulation) and Survanta® (4 mL/kg). Repeat doses were allowed ≥6 hours following the previous treatment (for up to three doses before 96 hours of age) if the patient required ≥30% oxygen. The surfactant was given through a 5 French feeding catheter inserted into the endotracheal tube. The total dose was instilled in four equal aliquots with the catheter removed between each of the instillations and mechanical ventilation resumed for 0.5 to 2 minutes. Each of the aliquots was administered with the patient in one of four different positions (prone, supine, right, and left lateral) to facilitate even distribution of the surfactant. Results for the major efficacy parameters evaluated at 28 days or to discharge (incidence of air leaks, death due to respiratory causes or to any cause, BPD, or treatment failure) for all treated patients from this treatment trial were not significantly different between Infasurf and Survanta®.

Prophylaxis Trial

A total of 417 infants ≥30 weeks gestation and <1251 grams birth weight were enrolled into a multiple-dose, randomized, double-blind trial comparing Infasurf (4 mL/kg of a formulation that contained 25 mg of phospholipids/mL rather than the 35 mg/mL in the marketed formulation) and Survanta® (4 mL/kg). The initial dose was administered within15 minutes of birth and repeat doses were allowed ≥6 hours following the previous treatment (for up to three doses before 96 hours of age) if the patient required ≥30% oxygen. The surfactant was given through a 5 French feeding catheter inserted into the endotracheal tube. The total dose was instilled in four equal aliquots with the catheter removed between each of the instillations and mechanical ventilation resumed for 0.5 to 2 minutes. Each of the aliquots was administered with the patient in one of four different positions (prone, supine, right, and left lateral). Results for efficacy endpoints evaluated at 28 days or to discharge for all treated patients from this prophylaxis trial showed an increase in mortality from any cause at 28 days ($p=0.03$) and in death due to respiratory causes ($p=0.005$) in Infasurf-treated infants. For evaluable patients (patients who met the protocol-defined entry criteria), mortality from any cause and mortality due to respiratory causes were also higher in the Infasurf group ($p = 0.07$ and 0.03, respectively). However, these observations have not been replicated in other adequate and well-controlled trials and their relevance to the intended population is unknown. All other efficacy outcomes (incidence of RDS, air leaks, BPD, and treatment failure) were not significantly different between Infasurf and Survanta® when analyzed for all treated patients and for evaluable patients.

Acute Clinical Effects: As with other surfactants, marked improvements in oxygenation and lung compliance may occur shortly after the administration of Infasurf. All controlled clinical trials with Infasurf demonstrated significant improvements in fraction of inspired oxygen (FiO2) and mean airway pressure (MAP) during the first 24 to 48 hours following initiation of Infasurf therapy.

INDICATIONS AND USAGE

Infasurf is indicated for the prevention of Respiratory Distress Syndrome (RDS) in premature infants at high risk for RDS and for the treatment ("rescue") of premature infants who develop RDS. Infasurf decreases the incidence of RDS, mortality due to RDS, and air leaks associated with RDS.

Prophylaxis

Prophylaxis therapy at birth with Infasurf is indicated for premature infants <29 weeks of gestational age at significant risk for RDS. Infasurf prophylaxis should be administered as soon as possible, preferably within 30 minutes after birth.

Treatment

Infasurf therapy is indicated for infants ≥ 72 hours of age with RDS confirmed by clinical and radiologic findings and requiring endotracheal intubation.

WARNINGS

Infasurf is intended for intratracheal use only.

THE ADMINISTRATION OF EXOGENOUS SURFACTANTS, INCLUDING INFASURF, OFTEN RAPIDLY IMPROVES OXYGENATION AND LUNG COMPLIANCE. Following administration of Infasurf, patients should be carefully monitored so that oxygen therapy and ventilatory support can be modified in response to changes in respiratory status.

Infasurf therapy is not a substitute for neonatal intensive care. Optimal care of premature infants at risk for RDS and new born infants with RDS who need endotracheal intubation requires an acute care unit organized, staffed, equipped, and experienced with intubation, ventilator management, and general care of these patients.

TRANSIENT EPISODES OF REFLUX OF INFASURF INTO THE ENDOTRACHEAL TUBE, CYANOSIS, BRADYCARDIA, OR AIRWAY OBSTRUCTION HAVE OCCURRED DURING THE DOSING PROCEDURES. These events require stopping Infasurf administration and taking appropriate measures to alleviate the condition. After the patient is stable, dosing can proceed with appropriate monitoring.

PRECAUTIONS

When repeat dosing was given at fixed 12-hour intervals in the Infasurf vs. Exosurf Neonatal® trials, transient episodes of cyanosis, bradycardia, reflux of surfactant into the endotracheal tube, and airway obstruction were observed more frequently among infants in the Infasurf-treated group.

An increased proportion of patients with both intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL) was observed in Infasurf-treated infants in the Infasurf-Exosurf Neonatal® controlled trials. These observations were not associated with increased mortality.

No data are available on the use of Infasurf in conjunction with experimental therapies of RDS, e.g., high-frequency ventilation.

Data from controlled trials on the efficacy of Infasurf are limited to doses of approximately 100 mg phospholipid/kg body weight and up to a total of 4 doses.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis studies and animal reproduction studies have not been performed with Infasurf. A single mutagenicity study (Ames assay) was negative.

ADVERSE REACTIONS

The most common adverse reactions associated with Infasurf dosing procedures in the controlled trials were cyanosis (65%), airway obstruction (39%), bradycardia (34%), reflux of surfactant into the endotracheal tube (21%), requirement for manual ventilation (10%), and reintubation (7%). These events were generally transient and not associated with serious complications or death. The incidence of common complications of prematurity and RDS in the four controlled Infasurf trials are presented in Table3.Prophylaxis and treatment study results for each surfactant are combined.

Table 3 - Common Complications of Prematurity and RDS in Controlled Trials

Complication	Infasurf (N=1081) %	Exosurf Neonatal® (N=978) %	Infasurf (N=351) %	Survanta® (N=306) %
Apnea	44	44	36	36
Patent ductus arteriosus	47	48	45	46
Intracranial hemorrhage	29	31	26	26
Severe intracranial hemorrhage[1] (III and IV)[2]	12	10	6	7
	7	7	5	5
Sepsis	20	22	28	27
Pulmonary air leaks	12	22	10	10
Pulmonary interstitial emphysema	7	17	10	10
Pulmonary hemorrhage	5	7	5	6
Necrotizing enterocolitis	5	7	17	18

[1] Grade III and IV by the method of Papile.
[2] Patients with both intraventricular hemorrhage and periventricular leukomalacia.

Follow-up Evaluations

Two-year follow-up data of neurodevelopmental outcomes in 115 infants enrolled in 5 centers that participated in the Infasurf vs. Exosurf Neonatal® controlled trials demonstrated significant developmental delays in equal percentages of Infasurf and Exosurf Neonatal® patients.

OVERDOSAGE

There have been no reports of overdosage with Infasurf. While there are no known adverse effects of excess lung surfactant, overdosage would result in overloading the lungs with an isotonic solution. Ventilation should be supported until clearance of the liquid is accomplished.

DOSAGE AND ADMINISTRATION

FOR INTRATRACHEAL ADMINISTRATION ONLY

Infasurf should be administered under the supervision of clinicians experienced in the acute care of newborn infants with respiratory failure who require intubation.

Rapid and substantial increases in blood oxygenation and improved lung compliance often follow Infasurf instillation. Close clinical monitoring and surveillance following administration may be needed to adjust oxygen therapy and ventilator pressures appropriately.

Dosage

Each dose of Infasurf is 3 mL/kg body weight at birth. Infasurf has been administered every 12 hours for a total of up to 3 doses.

Directions for Use

Infasurf is a suspension which settles during storage. Gentle swirling or agitation of the vial is often necessary for redispersion. DO NOT SHAKE. Visible flecks in the suspension and foaming at the surface are normal for Infasurf. Infasurf should be stored at refrigerated temperature 2° to 8°C (36° to 46°F). THE 3mL VIAL MUST BE STORED UPRIGHT. Date and time need to be recorded on the carton when Infasurf is removed from the refrigerator. Warming of Infasurf before administration is not necessary.

Unopened, unused vials of Infasurf that have warmed to room temperature can be returned to refrigerated storage within 24 hours for future use. Infasurf should not be removed from the refrigerator for more than 24 hours. Infasurf should not be returned to the refrigerator more than once. Repeated warming to room temperature should be avoided. Each single-use vial should be entered only once and the vial with any unused material should be discarded after the initial entry.

INFASURF DOES NOT REQUIRE RECONSTITUTION. DO NOT DILUTE OR SONICATE.

Dosing Procedures

General

Infasurf should only be administered intratracheally through an endotracheal tube. The dose of Infasurf is 3 mL/kg birth weight. The dose is drawn into a syringe from the single-use vial using a 20-gauge or larger needle with care taken to avoid excessive foaming. Administration is made by instillation of the Infasurf suspension into the endotracheal tube.

Administration for Treatment of RDS

Initial Dose

Infasurf should be administered intratracheally through a side-port adapter into the endotracheal tube. Two attendants, one to instill the Infasurf, the other to monitor the patient and assist in positioning, facilitate the dosing. The dose (3 mL/kg) should be administered in two aliquots of 1.5 mL/kg each. After each aliquot is instilled, the infant should be positioned with either the right or the left side dependent. Administration is made while ventilation is continued over 20-30 breaths for each aliquot, with small bursts timed only during the inspiratory cycles. A pause followed by evaluation of the respirator; status and repositioning should separate the two aliquots.

Repeat Doses

Repeat doses of 3 mL/kg of birth weight, up to a total of 3 doses 12 hours apart, have been given in the Infasurf controlled clinical trials if the patient was still intubated.

In the Infasurf vs. Survanta® trials, Infasurf was administered through a 5 French feeding catheter inserted into the endotracheal tube. The total dose was instilled in four equal aliquots with the catheter removed between each of the instillations and mechanical ventilation resumed for 0.5 to 2 minutes. Each of the aliquots was administered with the patient in one of four different positions (prone, supine, right, and left lateral) to facilitate even distribution of the surfactant. Repeat doses were administered as early as 6 hours after the previous dose for a total of up to 4 doses if the infant was still intubated and required at least 30% inspired oxygen to maintain a PaO_2 ≤ 80 torr.

Administration for Prophylaxis of RDS at Birth

The amount of a prophylaxis dose of Infasurf should be based on the infant's birth weight. Administration of Infasurf should be given as soon as possible after birth. Usually the immediate care and stabilization of the premature infant born with hypoxemia and/or bradycardia should precede Infasurf prophylaxis.

The dosing procedures are described under Administration for Treatment of RDS.

Dosing Precautions

During administration of Infasurf liquid suspension into the airway, infants often experience bradycardia, reflux of Infasurf into the endotracheal tube, airway obstruction, cyanosis, dislodgment of the endotracheal tube, or hypoventilation. If any of these events occur, the administration should be interrupted and the infant's condition should be stabilized using appropriate interventions before the administration of Infasurf is resumed. Endotracheal suctioning or reintubation is sometimes needed when there are signs of airway obstruction during the administration of the surfactant.

HOW SUPPLIED

Infasurf (calfactant) Intratracheal Suspension is supplied sterile in single-use, rubber-stoppered glass vials containing 3 mL (NDC 61958-456-03) and 6 mL (NDC 61958-456-06) off-white suspension.

Store Infasurf (calfactant) Intratracheal Suspension at refrigerated temperature 2° to 8°C (36° to 46°F) and protect from light. **THE 3mL VIAL MUST BE STORED UPRIGHT.** Vials are for single use only. After opening, discard unused drug.

Rx only

Manufactured by:
ONY, Inc.
Amherst, NY 14228

Rev. 06/09

Co-bedding as a Comfort Measure for Twins Undergoing Painful Procedures

Marsha L. Campbell-Yeo, C. Celeste Johnston, K.S. Joseph, Nancy L. Feeley, Christine T, Chambers, Keith J. Barrington

Abstract

Background: Co-bedding, a developmental care strategy, is the practice of caring for diaper clad twins in one incubator (versus separating and caring for each infant in separate incubators), thus creating the opportunity for skin-to-skin contact and touch between the twins. In studies of mothers and their infants, maternal skin-to-skin contact has been shown to decrease procedural pain response according to both behavioral and physiological indicators in very preterm neonates. It is uncertain if this comfort is derived solely from maternal presence or from stabilization of regulatory processes from direct skin contact. The intent of this study is to compare the comfort effect of co-bedding (between twin infants who are co-bedding and those who are not) on infant pain response and physiologic stability during a tissue breaking procedure (heelstick).

Methods/Design: Medically stable preterm twin infants admitted to the Neonatal Intensive Care Unit will be randomly assigned to a co-bedding group or a standard care group. Pain response will be measured by physiological and videotaped facial reaction using the Premature Infant Pain Profile scale (PIPP). Recovery from the tissue breaking procedure will be determined by the length of time for heart rate and oxygen saturation to return to baseline. Sixty four sets of twins (n=128) will be recruited into the study. Analysis and inference will be based on the intention-to-treat principle.

Discussion: If twin contact while co-bedding is determined to have a comforting effect for painful procedures, then changes in current neonatal care practices to include co-bedding may be an inexpensive, non invasive method to help maintain physiologic stability and decrease the long term psychological impact of procedural pain in this high risk population. Knowledge obtained from this study will also add to existing theoretical models with respect to the exact mechanism of comfort through touch.

Background

An increasing number of multiple pregnancies and increasing obstetric intervention at preterm gestation has led to a rising number of preterm twin infants being admitted into Neonatal Intensive Care Units (NICU). These preterm infants undergo repeated and often untreated procedural pain that can contribute to immediate stress and may have a long term impact on the normal maturation of regulatory systems. The practice of co-bedding twins simulates various aspects of the intrauterine environment. Co-bedding allows twins to remain in close proximity and have skin-to-skin contact with each other, thus creating opportunity for familiar recognition of auditory and olfactory stimuli and for a continuation of the twin relationship that began in utero.

Given the potential benefits of co-bedding, theoretical and conceptual underpinnings, and compelling evidence related to the effects of environmental context, it is important to examine the possibility that twins placed in close proximity could provide comfort and protection against the numerous stressful procedural assaults experienced during hospitalization. The intent of this study is to compare the comfort effect of co-bedding (contrasting twin infants who are co-bedding versus those who are not) on pain response during a tissue breaking procedure (heelstick). Pain response will be measured in all infants and will be determined by physiological and behavioral reaction.

Summary of Literature Review: a. Recent increase in twin births and preterm births among twins: During the past two decades, significant advances in medical technology have contributed to the increased survival of critically ill, preterm, and very low birth weight infants.[1] As mortality rates have declined, the focus has shifted to decreasing morbidity and adverse neurodevelopmental outcomes for these high-risk infants.[2] An additional change in the surviving population within NICU's is that the numbers of twins admitted has escalated as the occurrence of multiple births is continuing to rise in North

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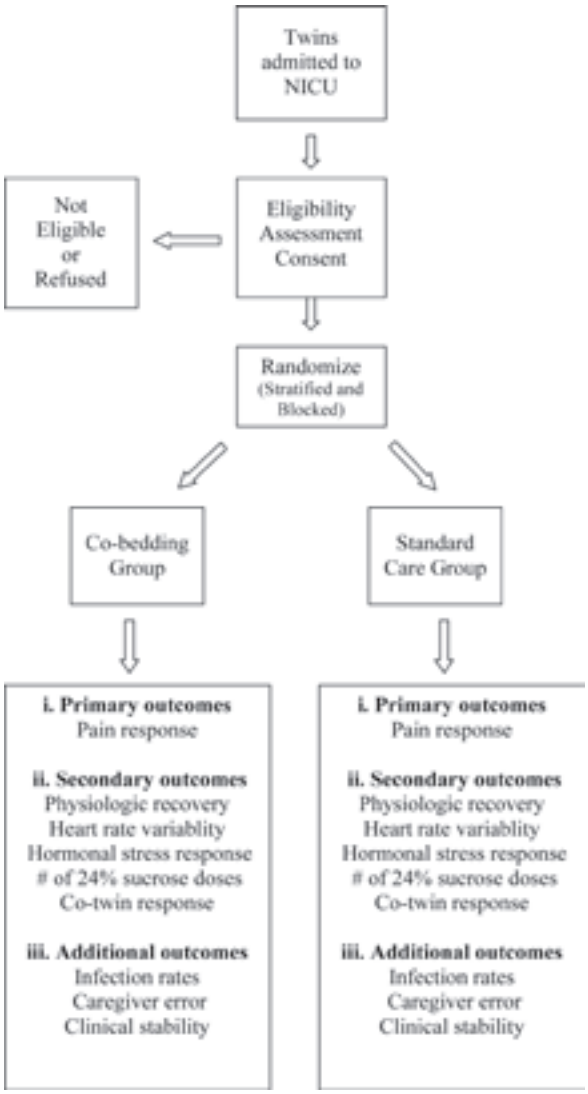

Figure 1. Allocation of participants to study groups.

America.[3] In Canada, multiple births increased from 2.1 per 100 total births in 1991 to 2.7 per 100 total births in 2000,[4] and to 3.0 per 100 total births in 2004.[5] Advanced maternal age and increased fertility treatments have been reported as the main reasons for this increase.[3,6-8] These factors have been primarily associated with a rise in dizygotic twins. Although race has some effect on the on the incidence of dizygotic twinning (10-40 per 1000 live births among people of African descent compared to 7-10 per 1000 among people of European descent), higher maternal age and assisted reproductive technologies are strongly associated with multiple gestation.[9] Occurrence of monozygotic twinning has been less affected with a stable incidence of 4 per 1000 total births worldwide.

Preterm birth is the leading cause for hospitalization during the neonatal period and is responsible for more than 75% of all cases of perinatal morbidity and mortality.[10] The incidence of preterm birth among multiples has risen substantially over the past several decades in North America. In the United States, preterm birth rates among twins increased by 19.6%, from 40.9% in 1981 to 55% in 1997[11] and to 60.5% in 2005.[12] In Canada, the rate of preterm birth among twin live births increased by 14.5%, from 42.5% between 1985 and 1987 to 49.6% between 1994 and 1996,[13] to 53.0% in 2000[4] and 57% in 2004.[14] Furthermore, twin pregnancies that followed assisted reproduction were more likely to result in lower mean gestational age (33.1 versus 34.2 weeks) and mean birth weight (2,029 versus 2,177 g for the first twin and 1,897 versus 2,136 g for the second twin) than those occurring spontaneously, with longer associated NICU stays.[15] In a similar study in 2002, examining the effect of multiple births on perinatal indicators over two decades in Canada, the British Isles, France and the Unites States, twins contributed to a disproportionate share of preterm deliveries and low birth weight newborns.[16] Maternal and neonatal complications associated with twin pregnancies also contribute to the increased likelihood of NICU admission and prolonged hospitalization. Excess maternal risks in twin pregnancies include gestational hypertension, placental abruption, and placenta previa, all which are positively correlated with adverse neonatal sequellae.[17] In a 2005 Canadian review of 3,242 infants born at or before 32 weeks of gestational age and admitted to 24 Canadian NICUs, twins had approximately similar mortality when gestational age and severity of illness were accounted for (adjusted odds ratio 1.3, 95% confidence interval 1.0-1.6).[18] Weight discordance, chorionicity, and gestational age at birth were more closely associated with adverse outcomes than plurality of pregnancy.[19] However, the higher likelihood of these factors in twin versus singleton birth created the additional morbidity risk associated with multiple births.[20]

b. Ubiguitous pain exposure in the neonatal intensive care unit: Given the higher likelihood of preterm birth and associated morbidity leading to the need for NICU admission, twin infants often face increased medical challenges and can be neurodevelopmentally less prepared to cope with multiple stimuli after birth when compared to healthy full-term infants.[21] Data from several countries have consistently shown that neonates undergo multiple painful and stressful procedures during hospitalization in the NICU. Scandinavian[22] and British[23] studies report an average of 10-15 procedures daily with younger neonates (<28 weeks) undergoing as many 700 painful procedures during their hospital stay.[24] Recently, Carbajal[25] conducted a 2-week prospective chart review of 431 infants in 13 European NICUs. These infants endured 60,969 painful procedures and a mean of 16 exposures (range 0 to 62) of painful or stressful procedures per day. Pain management for infants undergoing procedural pain associated with most frequent procedures such as tracheal suctioning, heelstick, tape removal, venepuncture and intravenous line insertions, although improved in recent years, was suboptimal. Almost 40% of infants undergoing heelstick for blood collections, the most commonly performed tissue breaking procedure in the NICU setting, did not receive any form of non-pharmacologic or pharmacologic intervention and 41% of infants underwent tracheal intubation without the benefit of any pain relieving strategies.[25] In a similar 1-week prospective chart review of pain practices in 14 tertiary level NICU's in Canada, Johnston and colleagues[26] reported that 582 infants underwent a total of 30,416 procedures. Thirty-five different procedures were identified with 3553 (11.7%) being classified as tissue breaking (i.e. skin-breaking or endotracheal intubation or an ophthalmologic examination). On average infants had 26 exposures (0-469) per week, just less that 4 per day. Although these findings support a slight reduction in previously reported average number of daily painful procedures that infants in the NICU endure, pain relieving strategies were still not routinely used. Forty-six percent (tissue) and 57% (non-tissue) damaging procedures performed were not accompanied by any form of pain relieving treatment.

Table 1: Key variables, measures proposed, data sources, and time of administration

Variables	Measures	Method/Sources	Time of administration
Pain response	Premature Infant Pain Profile (PIPP)	Videotape of facial responses	Baseline, warming heelstick and recovery
Physiologic recovery	Heart rate, Oxygen saturation	Somté software	Baseline, warming heelstick and recovery
Heart rate variability	Cardiac monitoring	Somté software	Baseline, warming heelstick and recovery
Hormonal stress response	Cortisol	Sorbette oral swab	Prior to heelstick (basal) and 20 minutes after (stress) the heel stick
Frequency of 24% sucrose administration	Count	Chart medication record, confirmed with videotape recording	2 minute prior and during intervention
Co-twin Response	All measures identical to the twin undergoing heelstick, except sucrose count	Identical measures, except sucrose count	Baseline, warming heelstick and recovery
Safety surveillance	Caregiver error Infection rate	Institutional adverse event and infection control surveillance	Quarterly
Clinical Stability	Supplemental oxygen Incidence of apnea Bradycardia	Chart review	Baseline, warming heelstick and recovery

Animal studies have linked pain to adverse developmental changes in the brain[24,27] and in the spinal dorsal horn.[28,29] In human infants, immediate responses to untreated pain such as physiological elevations in heart rate, blood pressure, and oxygen requirements, can lead to fluctuations in intracranial pressure, possibly leading to intraventricular hemorrhage (IVH) and periventricular leukomalacia.[30,31] Increased stress hormone release triggered by pain impedes normal regulation of growth and tissue repair[32] and has adverse effects on cognition, memory, and behaviour systems.[33] Stress associated with pain can lead to prolonged structural and functional alteration in pain pathways that lasts into adult life, permanently altering normal or common responses to pain.[34,35] Given the extreme plasticity of the preterm brain and immature regulatory processes, it is not surprising that exposure to repeated skin breaking procedural pain may disrupt the normal development of physiological, hormonal, behavioural and hypothalamic-pituitary-adrenal (HPA) axis that may contribute to these long term effects. Recently, Grunau and colleagues have reported a blunting of hypothalamic-pituitary-adrenal (HPA) axis response in infants who had undergone numerous painful procedures in the NICU.[29,36] Preterm infants in contrast to infants born at term[37,38] appear to experience a down-regulation of behavioural responses and a decrease in sympathetic recovery contributing to higher physiological instability.

Despite a surge in the literature illustrating various methods to accurately assess and manage pain and the provision of consensus practice guidelines[39] minimal improvement in the treatment of pain associated with routine NICU procedures has ensued. The reasons for this lack of practice change are unclear. Issues related to research utilization (i.e. education, unit context and institutional facilitation) and lack of consensus regarding optimal pain management strategies for routine procedural pain are the most likely cause. In addition, evidence that morphine (a commonly used neonatal analgesic) which is known to attenuate postoperative and severe pain, is less effective for pain associated with mechanical ventilation and heelstick[40] as well as possible adverse outcomes associated with its prolonged use[41] has led to further inquiry regarding the role of non-pharmacologic measures and environmental context in the minimization of acute pain.

c. Environmental context and comfort for alleviation of pain: Infants have been shown to have cortical perception[42,43] and memory of pain, both exhibited by peripheral hypersensitization[37] and behavioural response.[29,44,45] Recently, two studies using near infrared spectroscopy (NIRS) to measure pain experience in preterm infants, revealed that infants as young as 28 weeks of gestation exhibit cortical response during heelstick.[42,43] Functional MRI imaging of adults has demonstrated that pain perception and inhibitory mediation appears to involve multiple areas of the brain, referred to as the "pain matrix,"[46] and that perception and response can be mediated by visual cues and relational factors.[47] Although not yet proven with neonatal neuroimaging, the assumption that neonates may also perceive and respond to pain and distress in a similar interlinked manner is highly plausible. It is known that pain in newborns can be soothed with alterations in environmental context and provision of non-pharmacological interventions involving orogustatory, vestibulokinesthetic, and/or olfactory and tactile systems. Sweet tasting solutions, breastfeeding and nonnutritive sucking regulated through endogenous opiate and serotonin systems have been shown to diminish pain response associated with procedural pain.[48-51] Containment, felt to enhance regulation of infant state via swaddling and facilitated tucking have also been shown to be beneficial.[49] Although the benefits of music and vestibular action may be less promising in isolation (ie, without the mother), these results have helped us better understand the importance of maternal presence and relationship with respect to pain response.[52,53]

Both term and preterm infants have olfactory memory. They not only show preference for their own mother's amniotic fluid and breastmilk, but this recognition has been shown to diminish crying during maternal separation and pain response

during heelstick.[54-57] Interestingly, olfactory recognition of a familiarized smell can elicit a similar comforting response[58,59] indicating both memory and ability to learn, remember and have emotional connections even in young, very preterm infants. Kangaroo mother care (KMC) or skin-to-skin care (SSC) provides a multisensorial context encompassing tactile, olfactory, and relational systems. It has been shown to diminish pain response and improve physiological stability in both term and preterm infants.[60-66] Whether the mother is an essential aspect of this comfort during skin-to-skin contact has yet to be proven.

The discovery and practice of new and innovative approaches to minimize the effects of infant pain should be a primary focus of neonatal health care researchers.[67] Numerous possible non-pharmacologic measures or alternative environmental contexts within the NICU have yet to be fully explored as primary or adjunctive methods to relieve pain and diminish potential long lasting effects of pain on the development of regulatory pathways. The increased incidence of multiple gestation births and admission of these fragile babies to neonatal units also raises questions regarding the differences in care of twins and higher order multiples versus singletons. Despite the ever increasing numbers of at-risk twin infants, specific interventions targeted at this population have not been studied.

d. Co-bedding as a potential comfort measure: At birth, preterm twins are typically separated as individual health needs are met. This leads to an interruption in their shared uterine environment and disrupts the expected developmental trajectory of a twin pregnancy. Co-bedding of twins is an example of a developmental care initiative. Its purpose is to minimize neurodevelopmental sequellae associated with admission to a NICU.[21,68,69] The practice of co-bedding is based on the premise that extrauterine adaptation of preterm twins is enhanced by continued physical contact with the other twin rather than sudden deprivation of such stimuli.[69,70] Maintaining this presence may assist twins to cope with pain associated with routine procedural pain by stabilizing self regulatory pathways.

In summary, twins, the majority of whom are born preterm, are exposed to painful procedures as part of their essential medical care. The adverse effects are both immediate and potentially long-term, affecting future sensation and behaviour.[27,34,71] Given that the practice of co-bedding simulates numerous aspects of environmental context—proximity, tactile, olfactory, auditory, memory and relationship—that have been shown to provide comfort to newborns, it is reasonable to propose that the contact or presence of a twin who has shared the same uterine space since conception would have a similar comforting effect.

Purpose: The purpose of this study is to determine the efficacy of twin comfort during a tissue breaking procedure (heelstick) in the NICU.

Hypotheses: The pain response of a twin undergoing a heelstick will be significantly altered when co-bedding.

Methods/Design: a. Study Objectives: The intent of this study is to evaluate the effect of co-bedding among at-risk twins on pain response during a painful procedure. Secondary objectives include the effect of twin co-bedding on changes in physiologic stability and recovery following the painful procedure, heart rate variability, salivary cortisol, frequency of dosages of 24% sucrose given during painful procedures and the response of the twin not receiving the tissue breaking procedure; b. Study design: We propose to carry out a randomized controlled trial comparing the comforting effect of co-bedding on twins undergoing a tissue breaking procedure in the NICU; c. Study population:

The source population consists of all twin pairs admitted to a tertiary level NICU at the IWK Health Centre, Halifax, Nova Scotia and St. Justine Hospital, Montreal, Quebec, who are considered medically stable and who require at least one medically indicated heelstick for blood procurement; d. Inclusion criteria: All medically stable twin infants admitted to the NICU of the IWK Health Centre and St Justine Hospital will be eligible for the study. Twins will be deemed to be medically stable if they are: a. Free from infection, and b. Breathing room air or receiving oxygen via nasal prongs. Twins may be receiving feeds via gavage tubes, IV therapy via peripheral or central line, and may be experiencing periods of apnea. Additionally, parents of the twins must understand written and spoken English or French; e. Selection criteria for study subjects: The parent (s) of twin pairs who meet the inclusion criteria will be approached by the study investigator/nurse and informed of the study. Signed written informed consent will be obtained before recruitment into the study; f. Exclusion criteria: Twin infants to be excluded are those who at the time of study entry: i. Weigh less than 1000 grams; ii. Are receiving mechanical ventilator support; iii. Have chest tubes or umbilical catheter in situ; iv. Have major congenital anomalies or chromosomal aberrations; v. Only one of the twin pair requires overhead phototherapy; [for allocation of participants to trail groups, see Figure 1]; h. Randomization: Eligible infants whose parent(s) have provided consent will be randomized by a computerized website accessed by the principal investigator or research nurse. Allocation concealment will be ensured using randomly permuted blocks of two, four or six. Infants less than or equal to 31 6/7 weeks will be randomized separately from those twins greater than or equal to 32 weeks. Infants from different study sites will also be randomized separately to ensure identical proportions within the co-bedding and standard care groups.

Due to the unblinded nature of the intervention, it is important to strictly adhere to rigorous methods to eliminate potential bias. The use of an off-site computerized website for group allocation will decrease the risk of allocation bias. The individuals coding pain response will be blinded to the twins treatment status (whether co-bedding or receiving standard care). The video camera will be set up to focus only on the infant's face and will be controlled by the investigator or research nurse. Coding of pain scores will be calculated using the Premature Infant Pain Profile (PIPP).[72] The PIPP is considered a reliable and valid tool to measure procedural pain in both preterm and term neonates.[73-75] Both composite PIPP scores and combined behavioral (facial) indicators will be reported in each group. Coding will be carried out at McGill University at Dr. Johnston's lab by 2 coders (coder A and coder B). Each coder will only code data on infants who are co-bedding (A) or code data on infants who are receiving standard care (B). Coders will not enter the unit, communicate with each other or compare data sets (ie PIPP scores will be estimated without knowledge of group assignment). The use of different coders (who have no previous knowledge of patient enrolment and randomization to code separately for infant facial responses, etc and who will remain blinded to each other's assessments), is expected to minimize observer bias. Research coders A and B will be trained separately by the principal investigator and a member of Dr

Johnston's research lab team. Training will be standarized and coding performances assessed so that an interclass coeffecient (ICC) of 0.85 is reached between the coders' standarized scores. Following the initial training, coders will be retested quarterly using standarized videotapes to ensure inter-rater reliability. If the ICC drops below 0.75, re-training and re-coding will take place. This reliability check conducted with standarized tools will minimize the likelihood of observer bias. Every three months, coders A & B will also re-code two randomly selected videotapes from the first weeks of coding to ensure intra-rater reliability. ICC's of 0.75 will be considered the cutoff point of acceptability. Following study completion, previously assigned group coders will be asked to code a random selection of approximately 20% (n=6) of the tapes from the alternate group. Inter-rater scores will be correlated to ensure that if differences are found between the groups, these differences are related to the intervention of co-bedding and not to systematic error between the two coders scoring techniques. In addition, every attempt will be made to assign the same nurse to care for a set of twin pairs regardless of which group they have been assigned. Adherence to this aspect of the study protocol will be recorded daily until the study heelstick has been completed.

Intervention and proposed duration of treatment: a. Co-bedding care: Following randomization to the co-bedding group, twin infants will be placed together in a Giraffe Incubator or crib lying side-by-side. Twins will be diaper clad and nested together in boundaries consistent with neonatal care practices. Larger infants may be partially clothed if in an open crib but still able to freely touch one another and remain nested together. Twins will be positioned close to each other (lying face-to-face, back-to-back, or in spooning positions), permitting contact between them. All infants will have cardio-respiratory monitoring while co-bedding. One side of the incubator/crib will be for twin 'a' and one side will be for twin 'b' and infants and their equipment will be colour coded. Incubator temperatures will be determined using clinical reasoning, anticipated neutral thermal environmental needs (based on infant weight, gestational and post natal age) and incubator settings prior to initiation of co-bedding. If servo temperature regulation is required, most likely in the case of younger twin pairs or discordance in infant weights, the servo probe will be placed on the larger infant. Infant temperatures will be closely monitored and recorded throughout the co-bedding condition to maintain normal axilla readings between 36.8 and 37.2 degrees Centigrade.

All infants will be co-bedded for no less than 24 hours prior to heelstick to allow for stabilization following transfer. The heelstick being studied will occur no greater than 10 days following initiation of co-bedding. Duration of co-bedding will be recorded and controlled for in the analysis if necessary. Limiting the length of co-bedding duration decreases the degree of variance possible for this variable yet still allows adequate time for a heelstick to be ordered as part of usual care.

The medically indicated heelstick will be performed by a designated group of experienced nurses and lab technicians who have performed heelstick procedures in previous studies in the NICU in a standardized manner according to the institutional and unit policy. The nurse assigned to care for the twin will assist with the heelstick procedure. Their role will be to provide non-pharmacologic measures as per the NICU pain guidelines as they would do normally. None of the members of the research team or nurses conducting heelstick will prompt the bedside nurse to alter their care in any way. All non-pharmacologic strategies for pain relief implemented by the nurse including number of 24% sucrose doses given will be recorded and confirmed with video recorded data.

Infants assigned to the co-bedding group, may continue co-bedding, should their parents choose, up to 48 hours prior to discharge at which time monitors will be disconnected and the infants separated; b. Standard care:

For infants who are randomized to receive standard care, the twin pair will remain in separate incubators as per current NICU policy. The twins will be nested in boundaries consistent with neonatal care practices. The heelstick may occur at any time following randomization but within 10 days to maintain consistency between groups. Twins will undergo a medically indicated heelstick in the incubator or crib in an identical fashion as outlined above.

Data will be collected simultaneously on both the infant undergoing the heelstick and his/her twin. Data collection using monitoring (Somté and Massimo oxygen saturation systems) and video-tape recording will take approximately 20 minutes per participant—a baseline period (1-2 minutes prior to heelstick), warming (2-3 minutes), heelstick (2-5 minutes), and recovery phase (approximately 1-10 minutes). If both infants require a medically indicated heelstick on the same day, they will occur no less than 30 minutes apart.

All chart data will be collected following randomization and data collection will continue until completion of the heelstick. Prior painful procedures will include all procedures from birth until completion of heelstick.

Proposed outcome measures: a. Primary outcome: The pain response to heelstick determined by physiological and behavioral reactions to a painful event (Premature Infant Pain Profile (PIPP) scores) will be compared between co-bedding and standard care groups; b. Secondary outcomes: The physiological recovery in response to heelstick determined by the length of time for heart rate and oxygen saturation to return to normal (baseline), heart rate variability, hormonal stress response, frequency of 24% sucrose administration, and the response of the twin not receiving the painful procedure when his/her twin undergoes a heelstick procedure will be compared between co-bedding and standard care groups; c. Other outcomes: Clinical stability (incidence of apnea or bradycardia, and need for supplemental oxygen prior, during and following (ie recovery period) heelstick, the number of painful procedures experienced by the neonate prior to the heelstick procedure, infection rates, and caregiver error will be compared between the groups. The measurement of the main variables of the study relies on three strategies: video recording of facial actions, monitoring of cardio-respiratory measures and oxygen saturations, collection of salivary cortisol and chart review.

Sample Size: Previous studies examining the effect of maternal contact or the effect of sucrose on pain response during heelstick have revealed a greater than 2 point difference in PIPP scores.[48,53,61,66] In those studies the intervention (i.e. maternal skin-to skin contact or sucrose administration) were compared to a usual care group that received no form of pain relieving intervention. As practice guidelines now indicate, it is anticipated that all twins regardless of group assignment

will receive 24% sucrose prior to undergoing heelstick. Since it is known that sucrose has a large effect on pain response, the intervention of co-bedding will be considered an additional comfort measure. A one-point additional decease in PIPP scores would therefore be considered clinically significant.

We based our PIPP score assumptions on previous studies which reported PIPP scores of 10.7 (2.3) vs 12.9 (2.5) from a study on kangaroo skin-to skin care versus incubator care in preterm infants 32-36 weeks of gestational age[61] and PIPP scores 8.9 (CI 7.9-9.9) vs 10.7 (CI 9.6-11.8) in preterm infant 28-31 6/7 weeks of gestational age. Based on these reported 0.5 and 0.6 standard deviation pain scores[66] and the reported values in the above studies, we used a conservative standard deviation estimate of 2.0 as our proposed study population will encompass both groups of infants. Sample size was calculated using a 2-sided alpha error of 0.05 and a power of 80%. We designed the study to detect a difference of 1 point or greater change (SD 2.0) in the PIPP scores. One hundred and twenty-eight infants would be required to identify this variation in the PIPP scores if such a difference is in fact caused by co-bedding. With this sample size, we will also have over 95% power to detect a greater than 15 second mean difference in physiological recovery (heart rate and oxygen saturation) between groups. In a recent study of skin-to-skin care,[66] the time to return to baseline heart rate following the application of the plaster signifying the end of the procedure was significantly different, 123 seconds (CI 103-142) for the Kangaroo Mother Care condition and 193 seconds for Incubator condition (CI 158-227, p<.00001). Since all infants will receive 24% sucrose, we do not expect that the differences seen in time to recovery will be this large. Therefore, by using the larger sample, and conservatively accounting for the use of regression techniques, our study will recruit 128 participants (64 sets of twins, 32 assigned to the co-bedding group and 32 to the standard group).

Recruitment rate: The IWK Health Centre NICU admits on average 70 sets of twins per year. Ste. Justine Hospital has a similar admission rate, averaging 80 sets per year. Recruitment rates for similar trials previously conducted in these units have ranged from 55-80%. Given a conservative recruitment rate of 60%, and expected later start date at Ste. Justine Hospital (within 6 months of initial enrolment at the IWK Health Centre), anticipated length of time for recruitment for the study is 12-15 months.

We have conducted a previous pilot study[76] and are conducting a larger clinical trial examining twin regulation during co-bedding over an extended period of time and have not encountered issues related to compliance. Given the short duration of data collection (during one heelstick procedure), we do not anticipate problems with compliance. Nevertheless, we will monitor compliance to group allocation through daily observation and direct staff communication.

Analysis and inference will be based on the intention-to-treat principle. Efforts will be made to ensure that follow up is complete for all subjects and that there are no missing values for any of the subjects for any variable. Blinding of independent coders will be retained until after the analysis is completed. Baseline characteristics of study subjects will be contrasted to ascertain that randomization has in fact produced comparable groups with respect to all variables that effect pain response and physiologic stability. The primary outcome of interest will be the pain response of the infant experiencing a tissue breaking procedure while co-bedding with his/her twin when compared to a twin infant experiencing a tissue breaking procedure receiving standard care (alone in incubator or crib). This analysis will compare the means in the two groups before and after treatment and contrast the mean difference between groups using 95% confidence intervals and a p value. The stratified nature of the randomization will be accounted for in the analysis. Also, since twin pairs will be randomized together (i.e. to co-bedding or standard care), the analysis will be corrected for potential non independence of outcomes between twin pairs This will involve appropriate variance adjustment which will be carried out using Generalized Estimating Equations (GEE) procedures using SAS software (Proc Genmod, SAS 8.2, SAS Institute Inc. Cary, NC).[77] If differences are noted in baseline characteristics, inferences will be made based on observed and (linear regression) adjusted differences between groups. Analysis for secondary outcomes will be done in an identical fashion as pain response and recovery by comparing the mean changes in the two groups before and after treatment and contrasting the mean differences between groups using 95 percent confidence intervals and a p value.

Trial Management: The principal investigator will assume the role of study coordinator as part of the requirements of her PhD studies. She will be responsible for the day-to-day management of the trial at the IWK Health Centre. An experienced research nurse will assume the role of coordinator and responsibilities at the IWK during any absences by the principal investigator. A research nurse, having weekly contact with the principal investigator, will coordinate and oversee data collection at the St Justine site.

Expected Contributions: A number of clinical and theoretical contributions are expected from this study. First, it is anticipated that the results from this study will contribute to evidence-based research in the field of pain in preterm neonate health, specifically as it relates to co-bedding and developmentally sensitive care practices. If twin contact while co-bedding is determined to have a positive effect then changes in current neonatal care practices to include co-bedding for twins may be an inexpensive, non-invasive method to minimize preterm twin infant pain during painful procedures. Additionally, the role of a twin in the care of his co-twin may be clarified with this study. As it was stressed in the review of literature, very little is known about the short or long term contribution that a twin can make through their continued presence with their co-twin during hospitalization. Utilizing the practice of co-bedding as an intervention to reduce pain in their preterm newborn can add to our understanding of the potential strength of the relationship between twins. Additionally, given the increased incidence of multiple gestation births and admission of these high risk infants to neonatal units, if co-bedding is found to be beneficial it may raise further questions regarding the need for possible differences in care of twins and higher order multiples versus singletons in the NICU setting.

Theoretically, this area of research is important because there is an increasing realization that alleviation of pain among infants is critical for healthy growth and long-term development. This research will clarify the role of co-bedding and provide at-risk infants with comfort that will facilitate their optimal growth and development. Data will provide valuable information to help better understand the mechanisms contributing to increased comfort within a multisensorial context. Lastly, the results of this

study will provide valuable insight into the relationship between twins—whether they are able to provide comfort to each other. Data from the response of the co-twin as an exploratory question will also address this relationship.

Potential risks to the safety of participants involved in the study: All twins will have continuous cardio-respiratory monitoring and ongoing surveillance for any adverse effects. If a co-bedded infant shows clinical signs of sepsis, twins will be separated until sepsis has cleared. If the incidence of co-infection among co-bedded twins increases significantly above the unit norm, the trial will be discontinued.

Confidentiality of all data collected will be maintained. All information gathered would be coded before analysis and data will be stored in a secure, locked location accessible only to the principal investigator and research nurse. The list of code numbers and names will be stored separately from the coded data. When the study results are published or presented at a health care conference, the information shared will not contain any personal identifiers. The salivary cortisol samples, coded with a number will be kept frozen in a locked freezer located at the IWK Health Centre and St. Justine NICU until it is couriered in batches for analysis at the McGill University laboratory. Cortisol samples will not be used for any other purpose. All videotapes will be encrypted. Master copies of research data will be kept secure in a locked location until five years past the age of majority of the infants.

Co-bedding is considered to be a safe practice for twins. Nevertheless, a careful watch will be kept on all study participates with regard to any possible adverse effects of co-bedding. Infants will be monitored as per the NICU Care Unit standard of care and their clinical condition will be evaluated daily as part of medical rounds and by the study team. Heelstick procedures are an aspect of usual care for infants in the NICU and will not be conducted solely for the purpose of this study. Study participation will not interfere with routine care practices. Routine strategies for pain relief including sucrose administration and non-pharmacologic measures will be provided as per standard IWK Health Centre NICU care.

Co-bedding twins is not considered to be a standard of care in the NICU. This study provides no direct benefit for the parents or infants enrolled. Compensation will not be offered. There will be no study restrictions regarding the continued practice of co-bedding until 48 hours prior discharge for those infants allocated to the co-bedding group

The initial preparation time for this study will be two weeks. During that time, information will be given to the staff of the NICU regarding study protocol. A second site (Ste. Justine) will commence recruitment within 6 months of initiation in the first site (IWK Health Centre). Subject accrual and data collection will extend over 12-15 months. It will take an additional 4 months to analyze the data and prepare a manuscript. The study results will be widely disseminated through conference proceedings and peer reviewed publication. The total duration of the study is expected to be 20-24 months.

Discussion

All staff and parents will be informed that we are co-bedding twins while in the NICU for the purposes of research only. We do not intend for this research to indicate support of co-bedding after discharge. Since there is currently little research completed to support the benefits or risks of co-bedding, this will remain a parental decision. We will recommend that parents follow the back-to-sleep program and refrain from smoking regardless of which ever sleep arrangements they choose.

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Perfusion Index Variations in Clinically and Hemodynamically Stable Preterm Newborns in the First Week of Life

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Abstract

Background: The perfusion index, derived from the pulse oximeter signal, seems to be an accurate predictor for high illness severity in newborns. The aim of this study was to determine the perfusion index values of clinically and hemodynamically stable preterm newborns in the first week of life.

Methods: Perfusion index recordings were performed on the first, third and seventh day of life on 30 preterm newborns. Their state of health was assessed according to clinical and behavior evaluation and to the Score for Neonatal Acute Physiology.

Results: The median(interquartile range) perfusion index values were 0.9 (0.6) on the first, 1.2 (1.0) on the third, and 1.3 (0.9) on the seventh day, with a significant increase between the first and the third day.

Conclusions: Perfusion index proved to be an easily applicable, non-invasive method for monitoring early postnatal changes in peripheral perfusion. Its trend during the first week of life suggests that its clinical application should take age into account. Further studies are needed to obtain reference perfusion index values from a larger sample of preterm newborns, to identify specific gestational age-related cut-off values for illness and to test the role of perfusion index in monitoring critically ill neonates.

Background

Newborns admitted to neonatal intensive care units (NICU), and in particular preterm newborns are at high risk for morbidity and mortality during the first week of life because of respiratory distress and bronchopulmonary dysplasia, apnea and bradycardia, necrotizing enterocolitis, intraventricular hemorrhage and periventricular leukomalacia, feeding difficulties, hypoglycemia, hyperbilirubinemia and neonatal sepsis.[1] Most of these neonatal morbidities, and in particular severe neonatal sepsis, which accounts for11%-27% of NICU admissions,[2-4] are often associated with high mortality rates. Early diagnosis of these neonatal complications represents one of the greatest challenges to neonatologists.

In the latest years, the pulse oximeter has become a vital NICU instrument.[5] The perfusion index (PI), derived from the pulse oximeter signal, has been reported to reflect real-time changes in peripheral blood flow[6,7] and to identify inadequate peripheral perfusion in critically ill newborns. In particular, low PI values have been demonstrated to be an accurate predictor for high illness severity in newborns.[8] The pulse oximeter is an easily applicable, non-invasive diagnostic tool for early screening of perinatal inflammatory diseases such as subclinical chorioamnionitis.[9-11] Reference PI values in newborns have been recently published.[12] However, only few literature data on PI values in preterm neonates are available. Our aim was to evaluate PI values in a sample of clinically and hemodynamically stable preterm newborns in the first week of life as a prelude to the clinical application of this index.

Methods

Patients: Thirty preterm newborns among those admitted to our Neonatal Care Unit (Regina Margherita Children's Hospital, Turin, Italy) were recruited consecutively for this observational study, between November 2007 and April 2008. The inclusion criteria were clinically and hemodynamically stable conditions, gestational age between 28 and 36 weeks; Apgar score at 1 minute 6 to 10; no need for mechanical ventilation or other invasive procedures at birth. The patients were considered stable according to the following criteria: normal skin color, respiratory pattern and cry; normal posture, muscle tone and movements. No need for fraction of inspired oxygen 0.24, normal heart rate (100-180 beats/min), normal respiratory rate (40-70 breaths/min), absence of prolonged apnea episodes (>20 sec).

Newborns with risk factors for neonatal sepsis (prolonged or premature rupture of membranes, stained amniotic fluid, presence of maternal infections and/or fever immediately before delivery, chorioamnionitis, very preterm birth, perinatal asphyxia and presence of a central venous catheter) and newborns with congenital malformations (congenital heart diseases, congenital diaphragmatic hernias, neural tube defects) were excluded from the study. The Institutional Ethics Committee approved the study protocol. The parents were asked to provide background data with particular attention to pregnancy and delivery, and gave their written informed consent.

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Study design: Clinical examinations, PI measurements and blood analyses were performed in the first week of life in compliance with the following protocol. During the first 24 hours after admission, clinical and laboratory evaluations were carried out to assess the state of health, and the Score for Neonatal Acute Physiology (SNAP) was calculated.[13]

On the first, third and seventh day of life, PI values were recorded by an operator, as well as oxygen saturation (SpO_2), pulse rate (PR) and respiratory rate (RR). PI measurement was assessed for 5 min/day in the morning, before feeding, while asleep or quietly awake and far from IV treatment. Because ambient light could affect oximeter operation, the probes were wrapped in opaque material. Body temperature and arterial blood pressure (BP) were also measured. Clinical examination was performed to evaluate vigilance, reactivity, crying pattern, skin color, muscle tone and reflexes, bregmatic fontanelle. The study protocol also stated that, in case of any clinical sign and/or symptom suggesting cardiac pathologies, patients should undergo a cardiological examination and echocardiography, and that they should be excluded from the study if necessary. The presence of vomit and diarrhea was also evaluated according to Nurse reports. On the first and seventh day of life, a blood sample was collected after PI recording to evaluate gas analysis, hemachrome, creatinine, blood urea, glucose, indirect and direct bilirubin, electrolytes and C-reactive protein.

Techniques: PI measurement was assessed with VitaGuard VG3100 monitoring system (Getemed Medizin- und Informationstechnik AG, Teltow, Germany) based on Masimo signal extraction technology (SET) (Masimo Corp, Irvine, CA) with the SpO_2 sensor placed randomly on either foot and three cardiac electrodes on the chest.

In pulse oximeter, a constant amount of light is absorbed by skin, other tissues, and non-pulsatile blood, whereas a variable amount of light is absorbed by pulsating arterial inflow. PI is a scalar value derived from the magnitude of the pulsations displayed on the plethysmographic waveform. It is calculated as the ratio of the pulsatile component to the non-pulsatile component of the infrared signal returning from the monitoringsite, and it reflects the ratio of the pulsatile to the non-pulsatile component of the bloodstream.10 For Masimo Radical SET the PI upper and lower limits reported by the manufacturer are 0.02–20.00%. The recorded pulse oximeter signals were stored in a personal computer and analyzed through the VitaWin 3 software (Getemed Medizin- und Informationstechnik AG, Teltow, Germany). Only the parts of the waveform where the recorded signal resulted to be artefact-free, and where oximeter-derived heart rate corresponded to cardiac electrode-derived heart rate, were considered valid for statistical analysis. The median PI for each measurement was obtained from the average of PI values recorded at 6-second intervals. Systolic and diastolic BP were measured indirectly using an oscillometric device (Passport 2, Datascope Corp, Mahwah, NJ).

Statistical analysis: The primary outcome of this study was to identify the PI values in a sample of clinically and hemodynamically stable preterm newborns during the first week of life. The sample size was estimated on the basis of the PI values obtained from a previous pilot study on 10 patients satisfying the inclusion criteria for the present study (unpublished data) in order to obtain a statistical power of 0.8, a 95% confidence interval for PI with a precision of 0.3 and an estimated standard deviation of 0.8. Normality was assessed by the Kolmogorov-Smirnov test and by exploratory data analysis. Data were expressed as mean and standard deviation (SD) or medians and inter-quartile range (IR) as appropriate. Differences between paired samples were evaluated by the Friedman test and by a post hoc multiple comparison analysis using the Least Significant Difference (LSD) method.[14,15] Ninety-five percent confidence intervals for median PI values were calculated with a bootstrap procedure with 10,000 replications. All statistical calculations were performed using commercially available software: Resampling Procedures Version 1.3 (Department of Psychology, University of Vermont, Burlington) for the bootstrap of the medians and SPSS for Windows, Version 15, (copyright SPSS Inc, Chicago, IL).All statistical tests were two-tailed and P values <0.05 were considered significant.

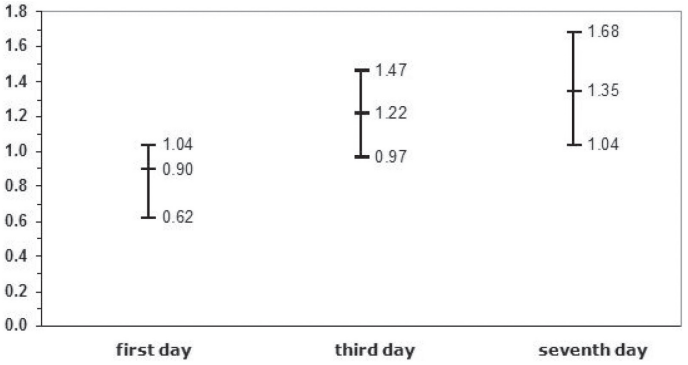

Figure 1. Median and 95% confidence intervals for median PI values on the first, third and seventh day of life

Results

All the thirty preterm newborns enrolled (14M, 16F) completed the trial. Table 1 gives an overview of their general characteristics. All patients had a normal SNAP score (score values <10) within the first 24 h after admission; they were thus classified as low severity illness newborns. Their clinical conditions, body temperature, blood pressure, blood and gas analyses and behaviour were normal in the first day of life and remained stable during all the study period. All patients had a progressive reduction in oxygen requirement. None of the patients showed evidence of cardiac pathologies and/or required blood transfusions or pharmacological treatments with cardiorespiratory or peripheral perfusion effects (ie xantine, diuretics, steroids, etc).

The median PI, PR, SpO_2 and BP values were evaluated on day 1, 3 and 7; ninetyfive percent confidence intervals for Median PI were illustrated in figure 1. The PI showed a growth trend with significant weight gain on day 3 and day 7 versus day 1, whereas no significant differences were observed between the third and the seventh day. A similar trend was found comparing the median PR values. There were no significant differences for

Table 1. Baseline characteristics of the study population

Study population characteristics	mean (SD)
Gestational age (weeks)	32.5 (2.1)
Weight (g)	1700 (401)
Length (cm)	41.1 (3.3)
Head circumference (cm)	29.9 (1.6)
Apgar score at 1 minute	8 (1)
Apgar score at 5 minutes	9 (1)

Table 2. Median values (inter-quartile range) of PI, PR, RR, SpO2 and BP

Variables	first day	third day	seventh day	p value*
PI	0.9 (0.6)	1.2 (1.0)	1.3 (0.9)	<0.001
PR (beats/min.)	126.5 (14.6)	137.4 (20.7)	137.4 (16.7)	0.001
RR (breaths/min.)	42.0 (11.6)	40.1 (6.9)	40.5 (8.8)	0.889
SpO2 (%)	99.7 (1.0)	100.0 (0.6)	99.6 (1.4)	0.078
systolic BP (mmHg)	53.5 (10.0)	55.0 (7.0)	56.5 (14.0)	0.722
diastolic BP (mmHg)	36.0 (11.0)	37.0 (7.0)	38.0 (8.0)	0.845

* Friedman test.

RR, SpO_2 (%) and BP (systolic/diastolic) values during the study period (table 2).

Discussion

This is the first observational longitudinal study to evaluate PI values during the first week of life in a sample of clinically and hemodynamically stable preterm newborns, with low risk of morbidity. Our results showed age-related differences in peripheral PI recordings with a significant increase in the median PI value between the first and the third day of life, whereas there was no significant difference between the third and the seventh day. The peripheral PI trend observed may reflect the physiological variability of the peripheral microvascular blood flow immediately after preterm birth and it could be related to the intrinsic hemodynamic adaptation which occurs in the first days of life. According to this hypothesis, a recent study of systemic blood flow in preterm newborns has pointed out the existence of a perfusion cycle in which low blood flow and high vascular resistance in the first 24 hours are followed by normal-high flow and low resistance, presumably due to vasodilatation.[16]

Recently Granelli et al. have published reference values for peripheral PI in a very large sample of healthy newborns between 1 and 120 h of age.[12] Peripheral PI values reported in their study were higher if compared to our data, suggesting that values lower than 0.70 could indicate illness. Our data suggest that physiological PI values in preterm newborns could be lower than in term newborns, thus the cut-off values for PI indicating morbidity should be reconsidered in preterms. Most patients, in fact, (70% on the first measurement, 83% on the second and 90% on the third) presented PI values higher than 0.70, but for some subjects (8, 4 and 2 respectively) PI values were lower than 0.70.

The two studies used different monitoring conditions, which might have affected the results. It is well known that the reliability, accuracy and clinical utility of pulse oximeter remain problematic under certain conditions, such as ambient light exposure, skin pigmentation, dyshemoglobinemia, low peripheral perfusion states and motion artefact.[5] Moreover, during the preliminary phases of our study, we observed that PI recordings were also influenced by the circadian rhythm, time from feeding, contemporary IVtreatments, jaundice and sleep/wake state. Pathological conditions such as neonatal sepsis, hypovolaemia and left-to-right shunting congenital heart diseases frequently occur in preterm neonates in the transitional period and can modify microvascular blood flow and cardiovascular adaptation in early neonatal life.[17-19] In order to exclude the presence of these conditions, which could affect peripheral PI, the state of health of our patients was monitored at the enrolment and during the study period through clinical examination, measurement of respiratory and cardiovascular parameters and blood analysis. Moreover, preterm newborns whose gestational age was lower than 28 weeks were not recruited in the present study; this is because very preterm newborns tend to be particularly unstable and often undergo invasive procedures (ie mechanical ventilation, CVC, surfactant, PN, etc) which might affect peripheral perfusion.

Conclusions

Our results suggest that PI is an easily applicable, non-invasive method for monitoring early postnatal changes in peripheral perfusion in preterm infants. The PI trend observed suggests that its clinical application should take subject age and recording conditions into account. Further research on a larger sample of preterm newborns is needed to obtain reference PI values under standardized monitoring conditions, to identify specific gestational age-related cut-off values for illness and to test the role of PI monitoring critically ill neonates.

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Significant Weight Loss in Breastfed Term Infants Readmitted for Hyperbilirubinemia

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Abstract

Background: Weight loss of greater than 7% from birth weight indicates possible feeding problems. Inadequate oral intake causes weight loss and increases the bilirubin enterohepatic circulation. The objective of this study was to describe the association between total serum bilirubin (TSB) levels and weight loss in healthy term infants readmitted for hyperbilirubinemia after birth hospitalization.

Methods: We reviewed medical records of breastfed term infants who received phototherapy according to TSB levels readmitted to Caja Petrolera de Salud Clinic in La Paz, Bolivia during January 2005 through October 2008.

Results: Seventy-nine infants were studied (64.6% were males). The hyperbilirubinemia readmission rate was 5% among breastfed infants. Term infants were readmitted at a median age of 4 days. Mean TSB level was 18.6 ±3 mg/dL. Thirty (38%) had significant weight loss. A weak correlation between TSB levels and percent of weight loss was identified ($r=0.20$; $p<0.05$). The frequency of severe hyperbilirubinemia (>20 mg/dL) was notably higher among infants with significant weight loss (46.7% vs. 18.4%; $p<0.05$). The risk of having severe hyperbilirubinemia was approximately 4 times greater for infants with significant weight loss (OR: 3.9; 95% CI: 1.4-10.8; $p<0.05$).

Conclusions: Significant weight loss could be a useful parameter to identify breastfed term infants at risk of severe hyperbilirubinemia either during birth hospitalization or outpatient follow-up visits in settings where routine pre-discharge TSB levels have not been implemented yet.

Background

In the current worldwide context of short postpartum hospital stays, it is important to assess factors associated with potentially preventable causes of newborn readmissions.[1-6] Hyperbilirubinemia and feeding difficulties with or without dehydration are the most frequent indications for readmission in the first 2 weeks of life[6,7] and strongly related each other due to inadequate oral intake, particularly in term infants.[8-11] Exclusively breastfed healthy term infants in whom breastfeeding has not been well established by the time of discharge are at greater risk of poor caloric intake, dehydration associated with decreased volume and frequency, and the secondary delayed gastrointestinal motility determines an increase in the enterohepatic circulation of bilirubin.[8,12,13] Weight loss in the infant of greater than 7% from birth weight indicates possible breastfeeding problems.[14] Several studies have previously reported significant weight loss in patients with extreme hyperbilirubinemia;[15,16] however, only few have analyzed separately this association in breastfed otherwise healthy term infants. The objective of this study was to determine the overall readmission rate due to hyperbilirubinemia and to describe the association between total serum bilirubin (TSB) levels and weight loss during the first two weeks of life in breastfed term infants who were discharged home after birth hospitalization and considered to be well infants.

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Methods

This retrospective study included breastfed otherwise healthy term infants readmitted for hyperbilirubinemia during their first two weeks of life after birth hospitalization at Caja Petrolera de Salud Clinic, a tertiary care facility in La Paz, Bolivia from January 2005 through October 2008. In our nursery, neonates are routinely discharged around 48 hours after vaginal delivery, and those of mothers who had undergone cesarean section at 72-96 hours. Breastfeeding is encouraged. Before discharge, all newborns are evaluated for clinical jaundice through skin color observation. Outpatient follow-up visits are scheduled based on physician's criteria in the absence of systematic follow-up protocols in the unit. Pre-discharge bilirubin screening has not been implemented yet.

A readmission was defined as admission of an infant for hyperbilirubinemia after a first hospital discharge diagnosis of healthy term infant. Readmission rate was calculated by using the number of readmissions as the numerator, divided by the total number of healthy term infants born during the period of study. To avoid potential confounding causes of hyperbilirubinemia readmission, we excluded infants with hemolytic disease, infection, major congenital anomalies, respiratory distress, and feeding intolerance. Cephalohematoma and mild bruising were also exclusion criteria.

On readmission, all patients had criteria for phototherapy according to total serum bilirubin (TSB) levels.[12] TSB was measured by colorimetric methods using centrifuged venous blood samples. Only breastfed term (39-41 weeks) infants with a birth weight >2500 g were included in this study. No tests for 6GPD deficiency were performed in these patients. Birth weight was obtained using an electronic baby weighing scale with a precision of 5 g (Seca 728 Ultimate Digital Baby Scale, Seca Corporation, Hamburg, Germany). The same instrument

Table 1: Characteristics of exclusively breastfed term infants readmitted for hyperbilirubinemia (n = 79)

	Severe hyperbilirubinemia (≥ 20 mg/dL) n = 23	Significant hyperbilirubinemia (< 20 mg/dL) n = 56	p
Perinatal history			
Birth weight (g) Mean ± SD	3060 ± 482	3197 ± 505	0.69
Gender male/female (%)	69.6/30.4	62.5/37.5	0.55
Maternal age (yr) Mean ± SD	29.4 ± 5.6	30.3 ± 6.1	0.50
Birth from vaginal delivery (%)	39.1	37.5	0.89
On admission			
Age (d) Mean ± SD	6.3 ± 3.6	4.0 ± 2.1	< 0.05
Weight (g) Mean ± SD	2920 ± 367	2880 ± 475	0.69
Infant's weight loss from birth (g) Mean ± SD	277 ± 221	179 ± 149	< 0.05
Percent of weight loss from birth Mean ± SD	8.8 ± 4.8	5.9 ± 4.7	< 0.05
Length of hospital stay (d)	3.0 ± 1.6	2.4 ± 1.1	0.13
Significant weight loss (%)	60.9	28.6	< 0.05

was used to determine the weight on readmission. Significant weight loss was defined as weight loss from birth weight greater than 7%. A bilirubin level ≥20 mg/dL (342 µmol/L) was chosen to define severe hyperbilirubinemia since an infant with this degree of jaundice is thought to be at major risk for neurologic damage.[9,17-19]

The chart review was performed with approval of Caja Petrolera de Salud Research & Ethics Committee. Statistical comparisons were done using t-tests for continuous variables and â tests for categorical variables. Pearson correlation was calculated to compare TSB levels and percent of weight loss from birth. The risk was estimated by odds ratio (OR) and confidence intervals (CI) using contingency tables All statistical tests were two-tailed and P-values <0.05 were considered statistically significant. The data were analyzed using SPSS 17.0 for Windows.

Results

From a population of 2,140 live term births, 137 (6.4%) term infants were readmitted for hyperbilirubinemia during their first two weeks of life. About 90% of these neonates were exclusively breastfed infants. Fourteen infants were excluded (6 patients had simultaneously diagnosis of infection, 4 had minor congenital anomalies, 3 had hemolytic disease, and one had a cephalohematoma). One hundred eight infants met the criteria of being exclusively breastfed otherwise healthy term infants. Of these infants, only 79 infants had sufficient data on medical records for analysis. Table 1 summarizes clinical and demographic characteristics of these infants according to the severity of hyperbilirubinemia on admission.

Breastfed term infants were readmitted for hyperbilirubinemia at a median age of 4.7 days. Approximately two-thirds of these infants were males (64.6%). Mean TSB level on admission was 18.6 ±3.0 mg/dL (range: 15.1-31.3 mg/dL). Thirty (38%) infants readmitted for hyperbilirubinemia had significant weight loss. Two thirds of these patients (60%) had weight loss >10%. Mean TSB levels in infants with hyperbilirubinemia alone was significantly lower than mean TSB levels in infants with hyperbilirubinemia and significant weight loss (18.0 vs. 19.5 mg/dl; p<0.05). Figure 1 shows a weak positive correlation between TSB levels and percent of weight loss (r=0.20; p<0.05). The frequency of severe hyperbilirubinemia was higher among infants with significant weight loss (46.7% vs. 18.4%; p<0.05). The risk of having severe hyperbilirubinemia was approximately 4 times greater for infants with significant weight loss compared with infants who had acceptable weight loss (OR: 3.9; 95% CI: 1.4-10.8; p<0.05). The risk was greater for infants who had weight loss >10% (OR: 4.2; 95% CI: 1.4-12.7; p<0.05). The length of hospital stay (median: 2 days) did not differ between groups (3.0 vs. 2.4 days; p=0.13). The route of delivery did not influence significantly on differences between TSB levels (p=0.65), age at admission (p=0.93), and percent of weight loss at admission (p=0.66). Infants with severe hyperbilirubinemia were readmitted at a mean of 6.3 days and those with hyperbilirubinemia alone at 4 days (p<0.05). Extreme hyperbilirubinemia (>25 mg/dL) was identified in three patients (3.8%).

Discussion

In this study, significant weight loss was notably associated with hyperbilirubinemia readmission in exclusively breastfed otherwise healthy term infants. The overall readmission rate was 64 per 1000 term infants, and approximately 50 per 1000 exclusively breastfed term infants. Hyperbilirubinemia readmission rates in term infants usually vary from 2 to 21.7 per 1000.[2-6,10,20,21] Exclusive breastfeeding is not only a major risk factor for hyperbilirubinemia but also for dehydration, particularly if nursing is not going well and weight loss is excessive.[12,22-26] Weight loss >5% was observed in about 25% of breastfed infants during their first 24 hours of life.[27] Approximately one-third of breastfed term infants readmitted for hyperbilirubinemia (mean TSB level of 22.8 mg/dL) showed to

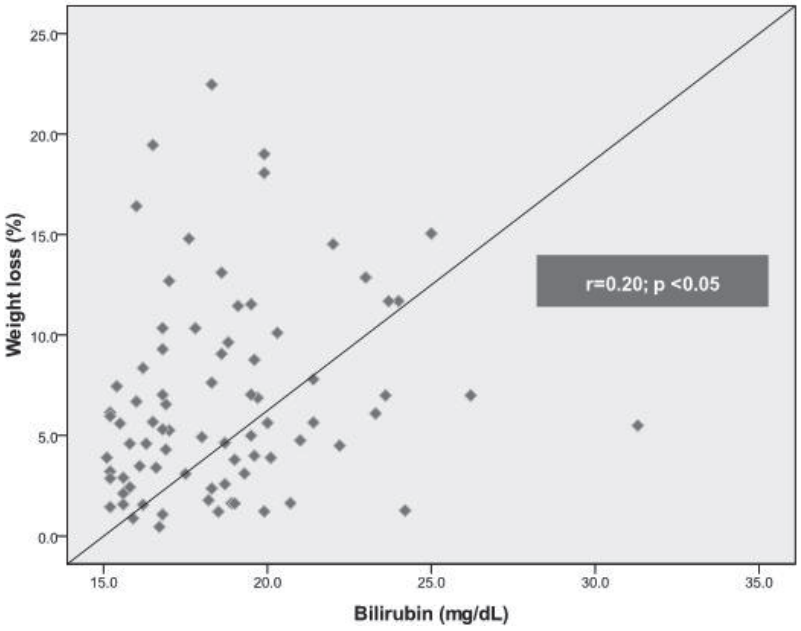

Figure 1. Linear correlation between TSB levels and percent of weight loss in exclusively breastfed term infants readmitted for hyperbilirubinemia

have weight loss from birth >12%.[6] In addition, breastfed infants with significant hyperbilirubinemia (>12.9 mg/dL) showed greater weight loss from birth than bottle-fed infants (6.9% vs. 4.2%).[11] Also, significant hyperbilirubinemia was associated with a greater weight loss after 72 hours of life (8.0% vs. 6.4%).[8] Fasting and poor caloric intakes seem to have a greater effect on the regulation of serum bilirubin than breastfeeding per se.[8,11] We found a significant difference in percent of weight loss between infants with severe and significant hyperbilirubinemia (8.8% vs. 5.9%, respectively). Our study also showed that approximately 60% of infants readmitted for severe hyperbilirubinemia had significant weight loss.

A mean age at admission of 4.7 days found in our study is comparable to previous reports.[1,4-6,10,23,28] Breastfed infants experience their maximum weight loss by day 3.[12] In a previous study, the majority of newborns readmitted for feeding problems were 4 to 7 days old, and many had concurrent dehydration and jaundice (34.3%).[26] Since infants with severe hyperbilirubinemia were readmitted approximately 2 days later than infants with hyperbilirubinemia alone, we could assume that a significant proportion of these infants would have been detected early in follow-up visits based on weight loss from birth according to the weak positive correlation found in this study. This analysis is consistent with the findings of a recent study which demonstrated that if weight loss >10% leads to interventions to improve nutrition and hydration, no association with extreme hyperbilirubinemia is found.[13]

Interestingly, the percentage of infants delivered by cesarean section (CS) was unexpectedly higher in this report. Some common indications for CS such as gestational diabetes, pregnancy-induced hypertension, and premature rupture of membranes are risk factors for readmissions in term infants.[1,10] In addition, length of stay after CS is a significant predictor of readmission for breastfeeding difficulties, mainly because lactogenesis was shown to occur later for women after cesarean delivery either for physiologic reasons or because of a delay in the initial feeding after surgery.[1] In contrast, several studies have showed that CS is a protective factor for neonatal hyperbilirubinemia. CS would reduce the risk of admission for increased maternal rest, teaching, and enhanced lactation during the third hospital day.[6] Furthermore, longer inpatient hospital stays have been associated with breastfeeding success after cesarean delivery.[29] Also, it has been suggested that infants born by emergency cesarean section are stressed before birth and, therefore, induce conjugating enzymes before delivery. Finally, less placental transfusion in infants born by cesarean section has also been proposed as a protective factor.[8] In our study, although the history of a cesarean delivery was frequent among term infants readmitted for hyperbilirubinemia, this variable does not seem to affect the severity of weight loss, age of presentation, or TSB levels on admission.

Initially, length of hospital stay (LOS) <48 hours showed to be a risk factor for hospital readmission due to hyperbilirubinemia;[3,4] however, inadequate nursing seemed to have the greatest impact on hospital readmission since jaundiced infants showed greater weight loss than non-jaundice infants (6.8 vs. 4.0%).[4] Accordingly, recent regression analysis revealed no increased odds of readmission with LOS <2 days. Infants delivered vaginally with 1 night of hospital stay and adequate prenatal and postnatal care outside the hospital had no increased risk of readmission.[2] In addition, no significant increased risk of readmission for hyperbilirubinemia was found among infants who were born vaginally and discharged <24 h after birth.[10] Similarly, no association between dehydration and neonatal or maternal LOS was reported.[22] Finally, early discharge following an uncomplicated postpartum hospital stay appeared to have no independent effect on the risk of readmission in infants with feeding-related problems.[26] Based on these reports, the best intervention would be to help mothers to nurse their infants more effectively from the moment of birth.[1] Outpatient follow-up strategies occurring between 24 and 48 hours after discharge would also prevent dehydration and hyperbilirubinemia.[22] Therefore, discontinuing early hospital discharge practices may not be the best means to decrease the risk of hospital readmission for hyperbilirubinemia.[3] The specific age at time of discharge after their birth hospitalization was not determined in this study, but we agree that improving our follow-up programs will have a greater impact on reducing the risk of severe hyperbilirubinemia rather than modifying the current global tendency of shorter newborn hospital stays.

A major limitation of this analysis is the lack of information regarding infant feeding. The second major limitation of this report is the absence of data related to the timing and extent of newborn follow-up in the outpatient setting. As mentioned above, the timing of follow-up may reduce readmissions if jaundice and/or feeding problems are caught early enough. One additional limitation is our inability to compare these results with a normal newborn population. Another important consideration is that the use of neonatal readmission as a primary outcome has advantages and disadvantages, which have been extensively reviewed and discussed.[1] Finally, our study was conducted in a high-altitude city (3600 m above sea level). At similar altitude, incidence of neonatal hyperbilirubinemia, defined as TSB levels >12 mg/dl, showed to be approximately four times the incidence reported in the literature for sea level.[30]

Despite the limitations of this study, we found that significant weight loss increase approximately 4 times the risk to develop severe non-hemolytic hyperbilirubinemia in breastfed term infants and it seems to be worst when the cut point to define significant weight loss is higher (infants with a weight loss of 10% have odds 4.2 times higher). Both hyperbilirubinemia and feeding problems persist worldwide despite well-intentioned guidelines for care showing that practice related to newborn care and follow-up seem to be resistant to change, particularly in less-developed countries. Our findings also highlight the need for better data about the content of outpatient follow-up visits.

Conclusion

Significant weight loss reflects feeding problems and seems to be an important factor associated with severe hyperbilirubinemia in breastfed term infants. If these findings are confirmed by large prospective studies in order to determine not only association but also a cause-effect relationship, weight loss from birth could become a useful clinical parameter to identify breastfed term infants at risk of severe hyperbilirubinemia either during birth hospitalization or follow-up visits, particularly in settings where routine pre-discharge TSB levels have not been implemented yet.

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A Prospective Study of the Effect of Delivery Type On Neonatal Weight Gain Pattern In Exclusively Breastfed Neonates

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Abstract

Background: In this exploratory study, the contribution of delivery type to the weight gain pattern for full-term infants with exclusive breastfeeding in the first month of infancy was determined. In addition, breastfeeding success among cesarean section (c-section) delivery mothers based on their neonate's weight gain at the end of the first month of infancy was evaluated.

Methods: A cohort of 92 neonates born in Shiraz, from July 10 to August 10, 2007 was followed longitudinally. The data were collected during the first month postpartum at three occasions: 3 to 7 days postpartum, 10-21 days postpartum and 24-31 days postpartum.

Results: Among 92 mothers in this study, 35 (38%) were delivered by c-section. Generalized estimating equation (GEE) showed that delivery type ($p<0.01$), receipt of advice about breastfeeding ($p=0.03$) and neonate's age ($p<0.01$) significantly affected weight gain. GEE estimated the values of the parameters under study and the testing contribution of each factor to weight gain, leading to the conclusion that gender, parities and maternal education did not contribute to weight gain. The neonate's weight gain pattern for C-section deliveries lies below that of normal vaginal deliveries until 25 days postpartum, when weight gain for C-section deliveries became higher than that for normal vaginal deliveries.

Conclusions: Type of delivery contributes strongly to the weight gain pattern in the first month of infancy. In spite of greater weight loss among C-section birth neonates in the first days of life, at the end of the first month neonates showed a similar weight gain. Consequently, mothers with c-section delivery can successfully exclusively breastfed.

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Background

It is normal for newborns to lose weight during the first days of life. Although much of this weight loss is thought to be due to changes in the volume and distribution of water in the body, some studies show that early skin-to-skin contact, initiating breastfeeding as soon as possible, and feeding practices also influence the degree of weight loss. Dehydration and/or failure to thrive during the first days postpartum may occur as a result of lactation failure and lack of awareness about feeding problems. Recent reports recommend monitoring infants' weight through the neonatal period.

Extensive research on the biology of human milk and health outcomes associated with normal methods of infant feeding have established that breastfeeding is more beneficial than formula feeding, although breastfed infants initially lose more weight and take longer to regain their birth weight than formula fed infants. One of the factors affecting breastfeeding initiation and duration is birth by cesarean section.

In recent years c-section has been performed upon request for births that would otherwise have been vaginal. In Iran, the c-section rate is about 50%-65%, however in some private hospitals the rate reaches 90%.

A study in Mexico shows that c-section is a risk factor for not initiating breastfeeding and for breastfeeding for less than one month, but it is unrelated to the duration of breastfeeding among women who breastfeed their babies for one month or more. Similar studies performed in Puerto Rico and Athens show that C-section delivery was negatively related to breastfeeding initiation. Breastfeeding in post-cesarean women has a protective effect on infant health, as demonstrated by the decrease in illness-related hospitalizations in the first year of life.

International agencies emphasize the need for exclusive breastfeeding during the first months of life. A new international growth standard chart has been prepared based on children who are fed according to World Health Organization recommendations, which entail exclusive breastfeeding for the first six months of life. An increase in weight indicates a child's well-being. The rate of growth is relatively high during an infant's first months of life and is susceptible to decelerating forces that may compromise a child's ultimate level of growth. Research evidence showed both biological and experiential conditions influence growth. Biologic conditions that may influence these components include gender and gestational maturity at birth,

that is, premature or full-term. Mother's care-giving and infant feeding behavior also influence infant growth.

The neonate growth pattern does not have a uniform rate of increase during the first month postpartum. Weight loss, rather than weight gain, may occur in the first week postpartum.

To the best of our knowledge, there are no studies exploring the relationship between the type of delivery (cesarean-section (CS) or normal vaginal (NV)) and the pattern of neonatal weight gain during the first month. Therefore, the purpose of this study is to explore the impact of type of delivery on the pattern of weight gain for exclusively breastfed neonates through the first month postpartum. A second purpose is to compare infant weight at first month postpartum in exclusively breastfed infants who were born by vaginal birth or cesarean-section.

Methods

A sample of mothers of singleton full-term infants weighing ≥2500g who were exclusively breastfeeding and presented at Shiraz healthcare centers within three to seven days postpartum were recruited to participate in the study. All the mothers initiated breastfeeding within two hours after birth. The participants were recruited from 10 July to 10 August 2007 and were followed up for one month. Initially, 104 mother-infant pairs were recruited. However, if the mothers reported they were no longer exclusively providing breast milk to their neonate at follow-up visits they were excluded from further participation in the study. In addition, if the neonate was hospitalized during the study, the mother-infant pair was excluded. Based on these criteria, 10 mother-infant pairs from the CS group and 6 from the NV group]were excluded because of formula use and 2 mother-infant pairs (one from the CS group and another from the NV group) were excluded due to infant hospitalization during the study. Thus, at the end of the study, 12 pairs were excluded, leaving 92 mothers and their exclusively breastfed neonates remaining.

Two data collection tools were developed by the researchers; The first questionnaire, completed at the time of recruitment to the study, included maternal and neonatal demographic and background data. Mothers were also asked if they received professional advice about breastfeeding at healthcare centers or maternity hospitals. The questionnaires were completed during the first month at three occasions: 3 to 7 days postpartum, 10-21 days postpartum and 24-31 days postpartum, when mothers presented in healthcare centers. One nurse at each of the seven healthcare centers was responsible for completing the neonatal assessment and questionnaires. The nurses were trained in the measurement of anthropometric indices by a healthcare center physician. Inter-rater reliability among the nurses was checked by the inspectors of the Deputy for Health at Shiraz University of Medical Sciences.

The weights were measured to the nearest 10 grams on sophisticated balance scales calibrated at each healthcare center. The nurses were instructed to weigh the neonates naked. If this was not possible, the type of clothing was recorded. Later, using these data, the neonate's weight was adjusted for baby clothes. Age at each measurement was recorded exactly based on the difference between the date of measurement and date of birth in days.

The sample size for each group required a meaningful difference in the neonatal weight gain. Assuming 20% withdrawal, n ≥37 for each group were required. Therefore we continued data collection until we had 40 CS delivery mothers; in this period 64 NV delivery mothers were recruited.

Generalized Estimating Equation (GEE) modeling was used to determine factors related to neonatal weight gain.

Ethical considerations

Ethical approval was obtained from the Ethic in Research Committee at the Deputy of Research of Tehran University of Medical Sciences. There were no anticipated physical, social or legal risks associated with participation. Informed consent was implied if participants completed the first questionnaire. It is standard practice in Iranian healthcare centers to ask participants to complete questionnaires at health checks without written consent.

Results

At the end of this study we had 92 mother/infant pairs. Among them, 57 (62%) mothers had NV delivery and 35 (38%) had CS delivery. Among the mothers with CS delivery, 20 (57%) were primiparous and among the mothers with NV delivery, 32 (56%) were primiparous. All forty multiparous mothers had previous breastfeeding experience. None of the mothers were cigarette smokers. There was no significant difference in maternal education, mother's age, parity, neonate's gender, birth weight and birth length between CS and NV deliveries. Chi-Square testing showed that family income was a very strongly related factor with the method of delivery. Eighty percent of mothers who lived in excellent income families had CS delivery. This percentage was, respectively, 44%, 31% and 0% for good, fair and poor income families. Also, the rate of CS was significantly different between private and public hospitals. Most CS delivery mothers (77%) received advice about breastfeeding at the first occasion, but among NV delivery mothers this rate was 47%. The proportion of mothers who received advice about breastfeeding increased during the study, with significantly higher proportions among the CS delivery mothers at all occasions.

As seen in all previous studies, the boys' weight is greater than that of the girls in all occasions and for both types of delivery.

In addition to the type of delivery, some factors such as gender, mother's education, received advice about breastfeeding (mother's knowledge about breastfeeding) and parity (mother's experience) were included in the model. Except for the type of delivery, receiving advice about breastfeeding, age and interaction between age and type of delivery, the other factors do not contribute significantly to weight gain at different times during the first month of infancy. Therefore, they were excluded from the model.

Weight gain values for the first 5 days of NV deliveries and the first 7 days of CS deliveries of postpartum are negative, which means weight loss for both groups in this period. Neonates with CS deliveries lost more weight and took longer to regain their birth weight than NV deliveries. Also, the weight gain pattern for CS deliveries is lower than that of NV deliveries until 25 days postpartum. At this time the pattern starts to rise and continues until 31 days postpartum.

The mean weight of boys with CS delivery at birth is below the 25 WHO growth standards percentile, but at the end of the first

month, this reached a higher level than standards percentile. Also, the mean weight of boys with NV delivery at birth is a little higher than the 25 WHO growth standards percentile, but at the end of the first month, this reached about 50 percentile. The mean weight of girls with CS delivery at birth is higher than the 25 WHO growth standards percentile, but at the end of first month, this approached 50 percentile. Also, the mean weight of girls with NV delivery at birth is less than the 25 WHO growth standards percentile, but at the end of the first month this reached higher than 25 percentile.

Discussion

The most important finding of this study was the strongly significant association between type of delivery and neonatal weight gain. Neonates born by vaginal birth gained 14 gram weight per day more than those born by cesarean section. In Iranian hospitals, most of the c-sections are performed with general anesthesia, so very early skin-to-skin contact and breastfeeding occur immediately post-cesarean. That negatively affects milk supply and breastfeeding practices, and as a result neonates' weight gain during the early postpartum period. However, due to the significant negative interaction between the infant's age and type of delivery, this difference has decreased over time. This means that the effect of CS delivery has been reduced as well. Therefore, the CS weight gain curve reaches the NV weight gain curve in 25 days postpartum. After 25 days, the weight gain for CS deliveries is significantly greater than that in NV deliveries. We found that infant gender, maternal education and parity did not contribute significantly to weight gain during the first month of infancy.

Receiving advice about breastfeeding is another significant factor for neonatal weight gain. Neonates whose mothers received advice about breastfeeding gained 7.7-gram weight more than those who did not. This factor does not interact with age, but does have a constant effect during the first month of infancy. Higher rates of receiving advice about breastfeeding among CS delivery mothers may have helped them in successful breastfeeding practices and improve their neonate's weight gain at the end of the first month following CS. No previous growth charts, including World Health Organization Growth Standards Charts, have focused on the first month of infancy. A monotonous increase in weight is shown, but most of the breastfed neonates lose weight in the first days postpartum. Neonatal weight decreased in the first days of life and increased after 5-7 days. Therefore, we obtained a weight chart for the first month of infancy by age and delivery type separately for boys and girls. These figures show that, disregarding the type of delivery, weight of the neonates that exclusively breastfed at the end of the first month was higher than their standard percentiles at birth.

For some mothers, the reason for the neonate's weight loss in the first days postpartum is their insufficient milk. This causes them to use formula feeding and may lead to early breastfeeding cessation. The result of this study shows that the weight gain pattern improves after the first week and mothers can be hopeful that their neonates will gain more than 40 grams of weight per day.

The model used to investigate the related factors in this research is more robust than those examined in earlier studies. The advantage of these models compared with other methods in this area is that the size of each covariate effect using regression model parameters is introduced.

Conclusion

Gender, mother's education and parity did not contribute to weight loss in the first days postpartum; however delivery type and receiving advice about breastfeeding contribute strongly to the weight gain pattern in the first month of infancy. Neonates with CS delivery in the first days postpartum lose more weight than those with NV delivery; however at the end of the first month there is no difference between the weights of breastfed infants born by CS or NV delivery. Consequently, if mothers with CS delivery continued exclusively breastfeeding they could have successful breastfeeding and these results lead to calling for early skin-to-skin contact and support of professionals and family post-cesarean delivery.

Delivery of a Baby With Severe Combined Immunodeficiency at 31 Weeks Gestation Following an Extreme Preterm Prelabor Spontaneous Rupture of the Membranes

Sally J. Watkinson, Christopher C.T. Lee, Christopher V. Steer

Introduction

If left untreated, severe combined immunodeficiency can lead to an acute susceptibility to infection. The intrauterine environment is sterile until the amniotic membranes rupture. The vaginal flora then ascends into the genital tract, thus increasing the risk of chorioamnionitis. An extremely premature and prolonged membrane rupture is associated with a dismal prognosis for an immunocompetent preterm fetus. There are no case reports to date that detail the outcome of an immunocompromised preterm baby following prolonged rupture of membranes.

We present the case of a 32-year-old Indian woman who delivered a 31-week gestational baby who had a severe combined immunodeficiency following premature prelabour prolonged rupture of the membranes at the 14th week of gestation.

Extreme preterm prelabour spontaneous rupture of membranes in an underlying condition of severe combined immunodeficiency does not necessarily lead to an unfavorable outcome.

Introduction

Severe combined immunodeficiency (SCID) is a combined cellular and humoral immunodeficiency resulting from a lack of functional T and B lymphocytes. In some cases, SCID is also combined with a deficiency of natural killer cells. This condition is extremely rare, affecting approximately only 1 in 100,000 live births. SCID is usually diagnosed after the third month of gestation, during the onset of one or more serious infections such as recurrent or persistent infections despite conventional treatment, infections with opportunistic organisms such as Pneumocystis, and a failure to thrive. SCID is usually X-linked and can be diagnosed through genetic testing.

Babies in general are more susceptible to infections as compared to adults. This susceptibility is even more pronounced in preterm babies and those who have been potentially exposed to maternal flora following a breach in the amniotic membrane due to a prolonged prelabor spontaneous rupture of the membranes (SROM). Pathogens gaining entry into the baby's system through the mucosa of the respiratory and gastrointestinal tracts are poorly localized. The preterm baby can thus easily become systemically unwell.

The sterile environment of the intrauterine amniotic sac limits the need for learned immune responses to specific antigens prior to birth. Upon birth, a normal baby has some immunoglobulins (Ig), with IgG as predominant because it is small enough to cross the placenta and be transferred from the mother. The level of IgG at birth is similar to that of the mother and provides passive immunity to mainly viral infections in the first few months of life.

Meanwhile, IgM and IgA do not cross the placental barrier but are produced by the normal fetus in utero from approximately 28 weeks of gestation. Levels of IgM at term are 20% of those present in adults, unless intrauterine infection develops and the fetus mounts an immune response to further elevate IgM levels. IgM provides a degree of protection to the neonate from enteric infections. While IgA levels are very low at birth, its production increases rapidly following delivery to reach adult values within two months. IgA protects against infection of the respiratory tract, the gastrointestinal tract and the eyes. The levels of both IgM and IgG at birth are lower in preterm than in term neonates.[1]

There is no effect to the immune function of a female carrier of X-linked SCID. Thus, the fetus of such a woman generally has normal IgG levels in utero and at birth.

The prognosis for a normal pregnancy where the membranes rupture at 14 weeks is dismal due primarily to the risk of miscarriage secondary to infection. Even with appropriate treatment, approximately 50% of pregnancies are delivered each subsequent week following preterm SROM. Therefore, when the membranes rupture before 20 weeks of gestation the probability of reaching viability is <5%.[2]

A second reason for dismal prognosis is the risk of neonatal death secondary to pulmonary hypoplasia when pregnancy becomes viable. The chance of pulmonary hypoplasia is lessened if the fluid re-accumulates before 24 weeks of gestation. One study using a multivariate analysis suggested that the likelihood for neonate survival increases by 2.7 (95% CI 1.45 to 4.65) for every 5-mm increase in the depth of amniotic fluid during the follow-up from rupture up to the 24th week of gestation.[3] Despite dismal prognosis, however, expectant management for preterm SROM at 14 weeks may be appropriate if the mother is well-informed of the risks for the neonate.

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The conclusions of the ORACLE trials[4,5] indicated that a course of oral erythromycin is the antibiotic of choice in the treatment of expectantly managed preterm SROM. This is because erythromycin is associated with a reduction in neonatal infection, slight prolongation of pregnancy with no increase in the likelihood of developing necrotising enterocolitis. Based on evidence from a study of preterm SROM conducted by the Maternal-Fetal Medicine Units of the National Institute of Child Health and Human Development, 7 days of antibiotics should be prescribed because longer courses have not been shown to be more effective and may actually promote antibiotic resistance.[6]

Maternal protein C deficiency is associated with an increased risk of poor pregnancy outcome including miscarriage, stillbirth and preterm delivery.

Case Presentation

A 32-year-old Indian woman presented to our gynecology clinic with secondary subfertility. Routine screening found her to be positive for protein C deficiency. In 1999, the woman had previously delivered a son by elective cesarean section following a diagnosis of transverse lie at 39 weeks of gestation. The baby was subsequently diagnosed with SCID and died at 8 months due to this condition. A specialist genetic centre indicated that this was an X-linked condition and the woman is a carrier of the mutation c.283G>A (W90X) in exon 2 of her IL2RâC gene.

She was advised of a 50%-risk of any subsequent male offspring being affected by SCID and was thus offered preimplantation genetic diagnosis. However she subsequently conceived the index pregnancy spontaneously. She was commenced on aspirin, low molecular weight heparin (LMWH) and progesterone pessaries as soon as the pregnancy was confirmed by ultrasound at 6 weeks. Results of her nuchal translucency screening and first trimester anomaly scan were normal.

The woman presented with leakage of liquor at 14^{+5} weeks gestation. Spontaneous rupture of the membranes was confirmed clinically and through an ultrasonography. She was commenced on antibiotic prophylaxis with oral erythromycin and her medication of progesterone pessaries was discontinued. Serial specialist ultrasonography at 16, 18, 20 and 22 weeks confirmed a normally grown male fetus with no obvious structural defects. The placenta was posterior and low, and the severe oligohydramnios was persistent. In view of the oligohydramnios due to extreme preterm SROM, an invasive genetic testing was not felt to be appropriate. The risk of this male fetus being affected with SCID therefore remained at 50%. Because of the extremely poor prognosis for the baby, the couple was offered a termination of pregnancy but they declined. The pregnancy continued, septic markers remained negative, and she remained on continuous oral erythromycin, aspirin and LMWH.

At 24^{+4} weeks gestation, the woman self-referred with a history of unprovoked vaginal bleeding. She was given dexamethasone and was transferred to a center with Level 1 neonatal facilities. She stayed at the center until her transfer back to her local hospital at 28^{+5}. Erythromycin was discontinued at 25^{+6} weeks gestation, maternal clinical and laboratory signs of infection remained absent, and ultrasound scan at 28 weeks showed normal growth of the fetus and an amniotic fluid index of 8.4 cm. Upon readmission, she was recommenced on erythromycin and discharged from the hospital. She was advised instead to visit the antenatal day unit twice a week for regular assessments.

The woman remained stable until she presented again at 31^{+4} weeks with lower abdominal pain and recurrent slight vaginal bleeding. It was found that her cervix was dilating and that the baby's presentation was breech. An emergency cesarean section was thus performed under spinal anesthetic. She made a good postoperative recovery and was discharged after 5 days.

The baby boy was born with Apgar scores of 6^{1} and 10^{5} minutes and weighed 1830 g (50th percentile). He required some initial resuscitation but was transferred to our special care baby unit with spontaneous respiratory effort in facial oxygen. His white cell count and C-reactive protein level were within the normal range (6.3 and <5, respectively) while his blood cultures were negative at birth. The baby was treated with oral nystatin, intravenous benzyl penicillin and gentamicin. Isolation and barrier nursing was also advised.

X-linked SCID (consistent with the mother's carrier type) was confirmed by genetics testing during the neonatal period. He received intravenous therapy of 1 g immunoglobulin on Day 3 and was transferred to a specialist pediatric centre on Day 6. The baby underwent an unconditioned CD34-selected mismatched family donor bone marrow transplant (from his father) on Day 46. He continued to receive monthly 2 g intravenous immunoglobulin and regular outpatient specialist paediatric immunology reviews. As of this writing, the baby is thriving and still breastfeeding at 1 year of life. He is also showing a good response to his treatment.

Discussion

Fetuses affected by SCID have significantly lower levels of IgM and IgA at birth compared to gestationally age-matched immunocompetent babies. It is thus likely that SCID affected babies will be unable to mount any IgA and IgG immune response in utero in response to ascending infection as a result of SROM. As immunocompetent premature babies produce such a poor response in utero, the question is whether SCID affected babies in a condition of preterm SROM have a higher risk of in utero infection than those who do not have SCID.

Conclusion

This baby was born in good condition and is currently thriving and living a normal life. This unusual case of adverse prognostic factors, including an underlying genetic condition, prelabor preterm SROM and maternal protein C deficiency, demonstrates that the outcome for babies with this condition is not necessarily hopeless.

This baby was born without evidence of in utero infection despite the expected poor prognosis of having premature prelabor SROM from 14+ weeks. Had an infection occurred, the prognosis would have been certainly poor. However, this would not be as a result of the SCID condition, and the baby would have had normal levels of IgG at birth because of transplacental transfer from his mother. Because normal babies have a poor IgA and IgM immune response in utero at 31 weeks, it is very unlikely that the inability to mount any IgA or IgM response because of the SCID condition had any effect on the outcome in this case. It is therefore reasonable to conclude that the in utero management of fetuses with known or suspected primary congenital immunodeficiency including SCID should not be managed any differently than preterm prelabour SROM in normal pregnancies.

The counseling of parents regarding the possible prognosis following a diagnosis of SROM at extreme prematurity should not be altered if the baby is known or suspected to be affected with SCID. With regard to the antenatal use of antibiotics in babies with SCID, the standard dose and duration of treatment of erythromycin 250 mg 4 times daily for 7 days should be prescribed. Measures to discourage ascending infection such as the avoidance of vaginal examinations and sexual intercourse should be advised regardless of an underlying diagnosis of SCID.

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Neonatal Epididymo-Orchitis Caused by Pseudomonas Aeruginosa

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Abstract

Epididymitis and epididymo-orchitis are an uncommon causes of acute testicular pain in neonatal boys, epididymo-orchitis is infection or inflammation of epididymis and testis it's may be associated with urinary tract infections or reflux of urine predisposed by an underlying vasal anomaly. Pediatricians should examine the testicles meticulously after a baby is born.

We report a 7 day-old boy with urinary malformations (ureteral duplication, ureterocel and right hydro-ureteronephrosis) who presented with acute scrotum. The ultrasonography exploration of the testis showed findings consistent with epididymo-orchitis, confirmed by the needle scrotal aspiration of the pus. Further radiological investigations of urinary tract showed the multiples malformations. Epididymo-orchitis should be suspected initially with abnormal physical signs and laboratory findings. Prompt prescription of antibiotics is mandatory, and appropriate therapeutic measures (antibiotics) should be undertaken to prevent recurrences and sequelae.

Introduction

Neonatal testicular torsion and epididymo-orchitis are confusing and very difficult for medical doctors to diagnose. Scrotal swelling in newborn is not rare and more diagnosis must be distinguished, like: hydrocele, testicular torsion, orchitis, orchi-epididymitis, inguinal hernia, scrotal hematoma and tumors. The emergency cause is testicular torsion that requires surgical intervention but epididymo-orchitis is treated medically.

Case Presentation

A newborn Moroccan male was admitted in the intensive care unit at 2 hours with neonatal asphyxia signs. The laboratory exams for infections were normal. He was intubated with good evolution. At 7 days the patient presented the signs of infection: tachycardic and body temperature of 38.5°C. The clinical examination revealed a firm, dolorous, and erythematous right hemiscrotum (Figure 1). The laboratory exams revealed a WBC count of $28/10^9ml^{-1}$, C reactive protein of 71 mg/l, the blood culture was positive (presence of Pseudomonas aeruginosa). Cultures of the cerebrospinal fluid and Urine were negative. The color Doppler echography of testicular revealed increased vascular flow and heterogeneous aspects of the testis and epididymis with scrotal infusion. The needle punction aspirated the pus and the culture finds pseudomonas aeruginosa.

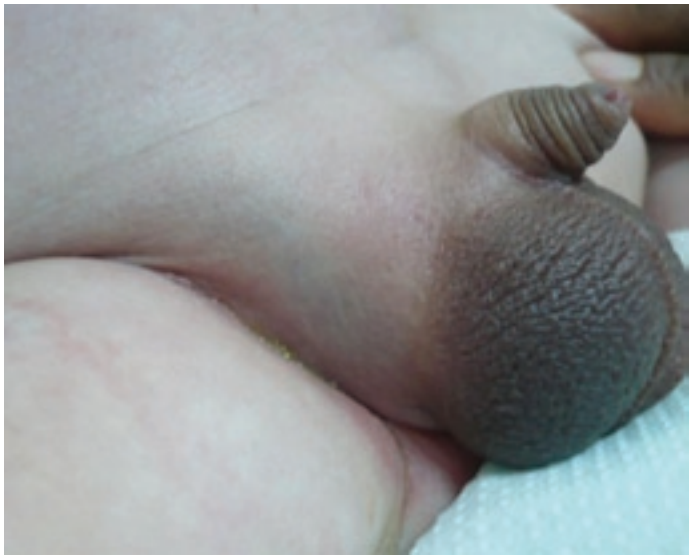

Figure 1. Swelling and erythematous right hemiscrotum.

The abdominal ultrasonography revealed a left hydro-ureteronephrosis with ureteral duplication and ureterocel. This malformative association was confirmed by abdominal magnetic resonance imaging (MRI) with Gadolium contrast (Figure 2). Antibiotics were started with the imepinime 30 mg/kg/j for 10 days and Amikacine 15 mg/kg/j for 3 days. The evolution was good and ultrasonographic control of the testis was normal.

Discussion

Epididymo-orchitis (EO) is a rare affliction in the neonatal period. It should be distinguished from testicular torsion to avoid unnecessary surgical exploration. Testicular torsion requires surgical intervention, but EO is managed medically.[1] The physical examination revealed a swollen testis, pain and fever, but these signs are not specific for EO.[1,2] The Color Doppler ultrasonography of the scrotum is capable of confirming the diagnosis and eliminated the testicular torsion. In EO, Doppler ultrasonography objective the increased vascular flow and the inhomogeneous echogenicity of the epididymis and the testis.[3]

Retrograde passage of sterile or infected urine along the patent vas deferens is the most frequent cause of EO. Bloodstream infection is also reported.[2,4] EO is usually occurred in patient

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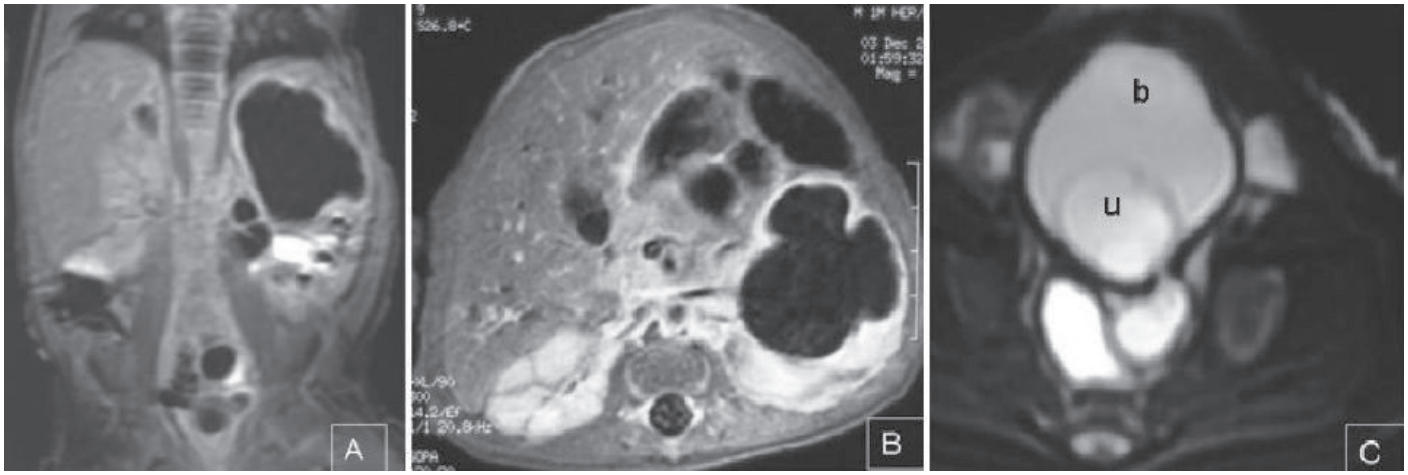

Figure 2. Uro-Magnetic Resonance Imaging showed a left ureteral duplication (A), hydro-ureternephrosis (A, B) and ureterocel (C), (b: bladder, u: ureterocel).

with predisposing anatomical abnormality. All patients with EO should have an ultrasound examination of the abdominal and pelvic in order to determinate the anatomical abnormality of the urinary tract, such as an ectopic uretere, ureteral duplication or others malformations.[2]

During the neonatal period, pseudomonas aeruginosa is responsible for nosocomial infection and it's difficult to treat. The acute epididymo-orchitis caused by pseudomonas aeruginosa is unusual and the clinical manifestations are similar to those caused by other microorganisms. Escherichia coli is an important gram-negative bacteria causing diverse neonatal infections and is also the common bacteria causing epididymo-orchitis from an ascending route. In our case it is the pseudomonas which was accused because we were dealing with a nosocomiale infection. The choice of the imepineme is motivated by the bacterial ecology of service constituted by pseudomonas resistant to C3G, sensitive to the imipinème. This was confirmed in the antibiogram.

Epididymo-orchitis is a rare affection in the neonatal period. After eliminate the torsion of the testicle, when EO is suspected, laboratory exams must done (urine exam, blood culture, and culture of the pus, and prompt antibiotics prescribed to avoid serious sequelae.

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Vein of Galen Arteriovenous Malformation With PAPVR and Use of Serial B-type Natriuretic Peptide Levels

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Abstract

Background: Arteriovenous malformation of the vein of Galen with partial anomalous pulmonary venous return can lead to a critically challenging condition associated with a high morbidity and mortality.

Case report: We report a case of a full term infant born with a vein of Gallen arteriovenous malformation complicated by partial anomalous pulmonary venous return and congestive heart failure where B-type natriuretic peptide was used as a vital tool in clinical assessment and treatment management.

Conclusions: Rapid diagnosis and treatment in infants with complex conditions such as this are imperative to expedite appropriate treatments, preventing long term negative outcome.

Introduction

Vein of Galen arteriovenous malformations (VGAM) account for less than 1% of the arteriovenous malformations which are estimated to be seen in only 2.5 out of 100,000 live births.[1] VGAM consists of a saccular dilatation of the vein of Galen pooling blood shunted directly from abnormally enlarged cerebral arteries and often causing congestive heart failure (CHF), hypoxic respiratory failure, and/or persistent pulmonary hypertension of the newborn (PPHN).

Neonates born with VGAM who have complex cardiac disorders as well can present with pulmonary hypertension and/or CHF with additional management challenges. Even when echocardiography is easily available, a non-invasive screening test such as B-type natriuretic peptide (BNP) assay can be helpful in assessing and managing CHF in patients presenting with complex cardiopulmonary conditions.

BNP is secreted by myocytes primarily from the cardiac ventricles and directly correlates with left ventricular end diastolic pressure and wall stress. Monitoring of BNP in infants has proven to be a helpful non-invasive diagnostic and management screening tool.[2,3] While BNP assays have commonly been used to assess CHF in adult patients, it has only recently been used in neonates to differentiate cardiopulmonary diseases and to monitor the clinical course of such diseases with serial testing.[3] Infants with cardiovascular problems have significantly higher BNP levels (>550 pg/mL, range 578-1,435) compared to infants with non-cardiac problems that present with respiratory difficulties (mean 240 pg/ml, range 118-388).[4] Healthy newborns tend to achieve a steady BNP level by 60 hours of life, with plasma concentrations highest on day of life (DOL) 0 (range approximately 56.7 ±49.6 pg/ml) and continuously decreasing, reaching adult levels at 3 months of age.[5] Past the neonatal period BNP levels should be less than 100 and before four months of age average around 21 pg/ml.[6]

Cases of VGAM causing high output heart failure complicated by PPHN are rare and complex. A current literature review produced a few case reports on the pathological basis of PPHN leading to fatalities,[7,8] rapid diagnostic imaging with ultrasound,[9,10] and minimally invasive surgical techniques.[11] Tan et al. reported serial BNP levels following endovascular embolization for a neonate with uncomplicated VGAM and heart failure.[12] However, this report presents the first case study following serial BNP assays for management of care in a neonate with VGAM with high output cardiac failure complicated by partial anomalous pulmonary venous return (PAPVR) with sinus venosus defect and pulmonary hypertension.

Case Presentation

This full-term female infant was born via spontaneous vaginal delivery to a 32-year-old gravida 4, para 1 Caucasian mother at 40 and 5/7 weeks gestational age. Mother's medical history was unremarkable and pregnancy, labor, and delivery were uncomplicated. Birth weight was 3330 grams. Apgar scores were 8 at 1 and 5 minutes of age, respectively. After delivery, oxygen saturation was 93% and a 2/6 systolic murmur was noted. During a workup for infection and respiratory distress, oxygen saturation dropped to the 80s. Chest radiography showed cardiomegaly. Cranial ultrasound demonstrated a large vein of Galen arteriovenous malformation with MRI with contrast confirming the diagnosis. Dopamine was initiated for treatment of hypotension. Secondary to high flow AVM, this patient was monitored closely for increased risk for heart failure with serial BNP levels starting on DOL 4 when it was found to be 2450 pg/mL. Echocardiogram on DOL 6 showed high-output heart failure and the combination of a large sinus venosus ASD, with partial anomalous pulmonary venous return (PAPVR; right upper pulmonary vein to superior vena cava) and patent ductus arteriosus with pulmonary hypertension resulting in

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right to left shunting. On DOL 9, a cerebral angiogram and Vein of Galen aneurysm embolization were performed, reducing the flow to 50%. BNP level obtained on DOL 10 was over 5000 pg/mL. Post-procedure, patient was placed back on high frequency oscillator, inhaled nitric oxide (iNO) was started at 20 parts per million, and continued for 6 days. A second embolization treatment that significantly reduced the flow was performed on DOL 16. By DOL 21, BNP levels dropped to 426 pg/mL with pulmonary hypertension still evident on echocardiogram. At 3 months of age, cardiac catheterization showed significant blood return to the superior vena cava, likely a result of the VGAM, and pulmonary hypertension. Sildenafil was started and BNP levels dropped below 100 pg/ml, as the patient's condition improved. The patient was discharged home on oxygen, diuretics and albuterol. She was readmitted 1 week later for shortness of breath and tachypnea. BNP level was 218 pg/mL. She went into CHF quickly and required a third coil embolization at 5.5 months of age after BNP levels reached 2020 pg/mL.

By six months of age, the patient required placement of a ventriculo-peritoneal shunt for hydrocephalus. She had one other brief hospitalization for an upper respiratory infection but remained stable and has not been hospitalized since. In no apparent respiratory or cardiovascular distress on DOL 295, her BNP level was 49 pg/mL. Figure 1 displays serial changes in BNP levels throughout her NICU and early pediatric hospital course.

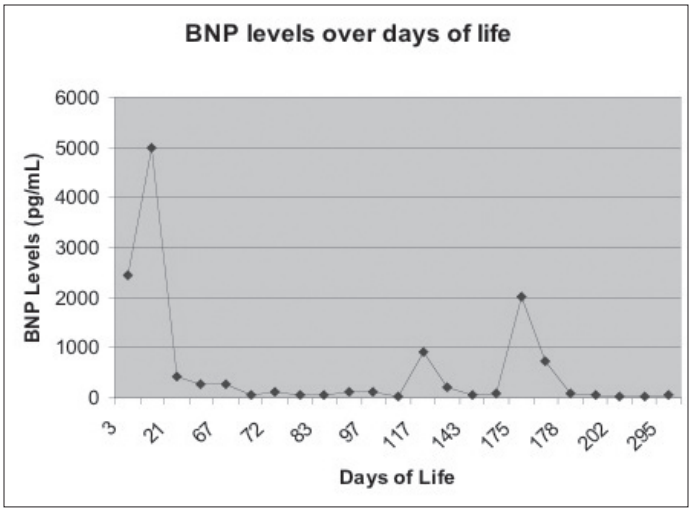

Figure 1. Serial changes in BNP levels throughout patient's NICU and early pediatric hospital course.

Developmental evaluation at 46 weeks of age identified global functional developmental delays. However, at 22 months of age, her functional development was within normal. At the time of her last brain scan, no obvious shunting through the VGAM was detected.

Discussion

During the neonatal period, symptomatic infants with VGAM present with severe cardiorespiratory alterations at or shortly after birth, with the majority of cases (94%) having high-output cardiac failure.[13,14] Severe PPHN may be a complicating factor. Since newborns classically develop CHF as a result of a tremendous left to right shunting through the low resistance vascular bed of the VGAM, symptomatic infants often appear cyanotic due to right ventricular volume and pressure overload.[10]

Echocardiography holds an essential role in estimating ventricular function and shunting across the PDA and atrial septum, right ventricles and pulmonary artery pressures, and identifying associated cardiac conditions in infants with VGAM.[13] In addition, echocardiography may reveal reversal of aortic flow during diastole, also known as a steal phenomenon that decreases peripheral perfusion.[10] Cardiac failure and pulmonary hypertension are the most dramatic and challenging concerns for medical stabilization of the symptomatic neonate. NO, the most effective therapy for treating pulmonary hypertension, has limited success in infants with VGAMs and PPHN.[10] While optimal strategies are yet to be clearly defined, diuretic and inotrope therapy may be successful in helping deferral of endovascular treatment for these patients. However, management of those diagnosed with coexisting pulmonary hypertension is demanding and warrants serial BNP tests to monitor the clinical course.

The endovascular treatment of a VGAM often requires several successive procedures. Staged embolization sessions initially aimed at controlling cardiac failure help avoiding the occurrence of parenchymal bleedings or massive venous thrombosis potentially endangering the normal venous drainage. Monitoring beyond the neonatal period includes checking for increased head circumference, hydrocephalus, seizures, and developmental delays. The etiology of often associated psychomotor disabilities derives from the cerebral steal phenomenon.[10]

Advances in endovascular techniques and perinatal management have led to more favorable long term outcomes.[10,15] A 30 month follow-up study reported that 55% of their patients were functionally normal.[15] While the past mortality rate for this population was close to 100%,[16] more recent studies report 9-15% mortality and little to no neuromorbidity in 61-66% of survivors.[17,18]

Rapid diagnosis and treatment in infants with complex conditions such as this are imperative to expedite appropriate treatments, preventing long term negative outcome. We speculate that including serial BNP levels in the arnament of assessment tools may aid the neonatal management and promote better outcomes in these complex patients.

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Stillbirths and Hospital Early Neonatal Deaths at Queen Elizabeth Central Hospital, Blantyre-Malawi

Aklilu M. Metaferia, Adamson S. Muula

Abstract

Much of the data on still births and early neonatal deaths from resource-limited settings are obtained via maternal recall from national or community level surveys. While this approach results in useful information to be obtained, often such data suffer from significant recall bias and misclassification. In order to determine the prevalence of stillbirths (SB), early hospital neonatal death (EHND) and associated factors in Blantyre, Malawi, a prospective study of pregnant and post-natal women was conducted at the Queen Elizabeth Central Hospital (QECH), Malawi.

A prospective observational study was conducted between February 1, 2004 and October 30, 2005. Consecutive women attending the hospital for delivery were recruited. Data were collected on the health status of the fetus on admission to labor ward and immediately after delivery, whether alive or dead. Gestational age (GA) and birth weight (BW) and sex of the newborn were also noted. Similar data were also collected on the live births that died in the delivery room or nursery. Data were analyzed using SPSS (Statistical Package for the Social Sciences) statistical package.

A total of 10,700 deliveries were conducted during the 12 months study period and of these deliveries, 845 (7.9%) were SB and EHND. Stillbirths comprised 3.4% of all deliveries; 20.2% of the ante-partum deaths occurred before the mother was admitted to the labor ward while a slightly higher proportion (22.7%) of fetal loss occurred during the process of labor and delivery.

Fifty-sex percent of the perinatal deaths (PD) were EHND. The mean gestational age for the perinatal deaths was 34.7 weeks and mean birth weight was 2,155 g (standard deviation=938 g). The majority, 468 (57.8%) of the perinatal deaths were males and 350 (43.2%) were females. Many of the perinatal deaths (57.9%) were deliveries between gestational ages of 20 and 37 weeks. Most (62.7%) of the mothers with a perinatal death had experienced a previous similar incident.

About 3.4% of all pregnant mothers past 20 weeks of gestation ended up in delivering a stillbirth; another 4.4% of the live births died before discharge from hospital, thus, 7.9% of pregnancy loss after 20 weeks (or 500 g estimated weight) of gestation. This is a higher loss when compared to international and regional data. We recommend attention be given to these unfavorable outcomes and preventive measures or intervention for preventable causes be considered seriously. These measures could include the provision of emergency obstetric care, improving access to deliveries by health professionals and resourcing of health facilities such that neonatal viability is promoted.

Background

The rates of stillbirths (SB) and early neonatal deaths (ENND) may be considered as indicators of the quality of ante-partum, intra-partum and neonatal care. Garne has however argued that perinatal deaths are not a good indicator of medical care. Data on the frequency and distribution of adverse birth outcomes are important for planning and execution of maternal and child health care intervention services in developing countries; information on local patterns of SB and ENND will be helpful in improving perinatal care at the local level.

The estimated incidences of SB and ENND vary worldwide based on socio-economic, demographic and clinical profiles. An earlier report from Malawi reported a perinatal death rate of 68.3 per 1000 births; 56% were SB and the remaining 44%, early neonatal deaths. In Kenya, among studied perinatal deaths, antepartum deaths comprised 23%, intrapartum deaths (fresh stillbirth) 38%, and neonatal deaths within 24 hours following birth at 39%. Investigators from Nigeria reported a perinatal mortality rate of 77.03 per 1000 total births; of these 73.5% were SB and the remaining 26.5%, early neonatal deaths.

In low income countries a significant proportion of SB occurs in the intrapartum period and these deaths are commonly attributed to avoidable factors related to inadequate maternity

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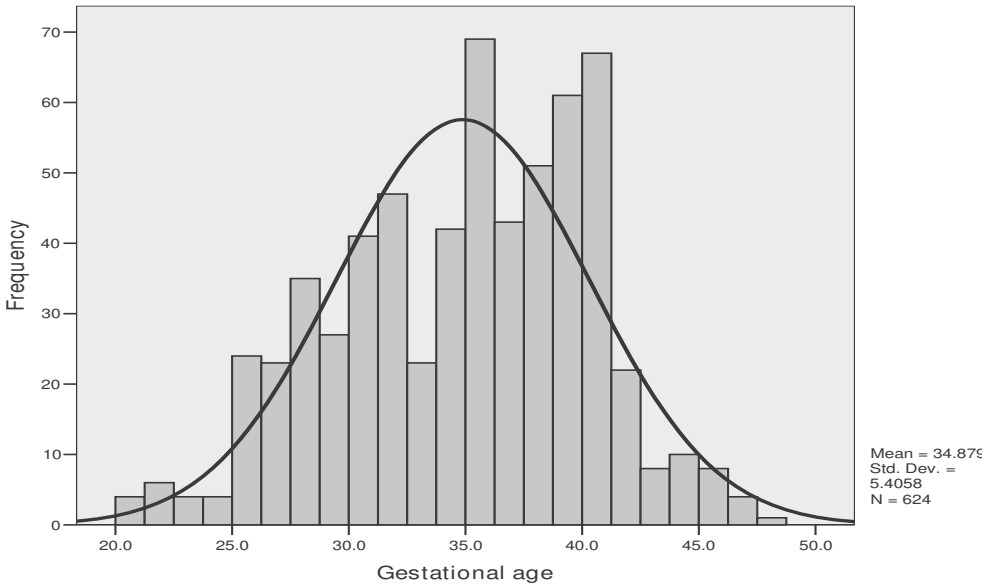

Figure 1. Distribution of gestational ages in weeks among perinatal deaths at QECH 2004-5.

care. In contrast, in developed nations these deaths are largely pre-partal with no apparent cause. Deprived societies in developed nations however, may suffer similar impediments to maternity care and adverse outcomes as are observed in resource-limited nations.

We undertook this prospective observational study to estimate the incidence of SB and END as well as assess how these relate to gestational age, birth weight and sex of the newborn at a referral health facility in Blantyre, Malawi, the Queen Elizabeth Central Hospital (QECH).

Methods

This was a prospective observational study conducted at the Gogo Chatinkha Maternity Unit and the Pediatrics and Child Health Departments at the QECH in Malawi between February 1, 2004 and October 30, 2005. The QECH is a public health facility serving as the referral facility for the southern region of Malawi (population estimated at 5 million), as well as a district hospital for Blantyre (population estimated at 650,000). The Department of Obstetrics and Gynecology at the hospital has often had between 3 and 6 specialist physicians, two to three registrars and 3 to 5 intern medical doctors. There are between two and four nurse midwives for each shift. There are about six pediatricians at the hospital.

The objectives of the study were to estimate the incidence of SB and ENND and assess the gestational age, birth weight and sex distribution of the perinatal deaths observed. During the 12 months study period a total of 10,700 deliveries were conducted at the study center.

Table 1: Perinatal death by Antepartum, Intrapartum and Neonatal periods in Blantyre, Malawi, 2004-5.

Period of death of fetus or neonate	Frequency (%)
Antepartum	171 (20.4
Intrapartum	192 (23.0)
Neonatal	473 (56.6)
Total	836 (100.0)

Consecutive women presenting for labor and delivery care were enrolled. Data were collected on SB and in hospital ENNDs using a standardized and pre-tested data capture sheet. Maternal and fetal variables of interest including GA, BW, sex of fetus or baby, vital status (dead or alive) were collected by a trained research midwife. Information on live births, but who might have died at home after discharge from the hospital, was unknown. No effort was made to follow-up women in the community who did not present for a postnatal visit.

Results

Maternal age ranged between 15 and 45 years with a mean of 23 years (SD=5 years). The majority (89.8%) of the mothers were married and 82% were housewives. Just over half (52%) reported having attended elementary school and 31% had reached secondary school. About one in ten (9%) of mothers did not attend any school and 1.4% had attended higher education. Some 38% of the perinatal deaths had occurred to first pregnancies. The majority, 80% of mothers attended at least two antenatal visits. 15.5% did not.

During the 21 months study period there were 10,700 deliveries of whom 845 (7.9%) resulted in perinatal deaths; 4% (N=363) of all the deliveries were SBs. Of all the perinatal deaths however, these were distributed as 363 (43%) stillbirths and 56% (n=473) neonatal deaths. A total of 171 (47.1%) of the SBs death occurred before admission to labor ward while 52.9% (192) occurred during labor and delivery process. Most of the women (62.7%) with a perinatal death had at least one previous episode of perinatal death. A total of 85.6% (n=723) of the deaths were singleton, 13.3% (n=112) were either or both of twins and the remaining five deaths were triplet deliveries.

ABO blood group and Rhesus factor (Rh) status were determined in only 42 mothers. In 138 (16.4%) mothers (16.4%), VDRL (venereal diseases reference laboratory) for syphilis was done of whom 14 (10.6%) were sero-reactive.

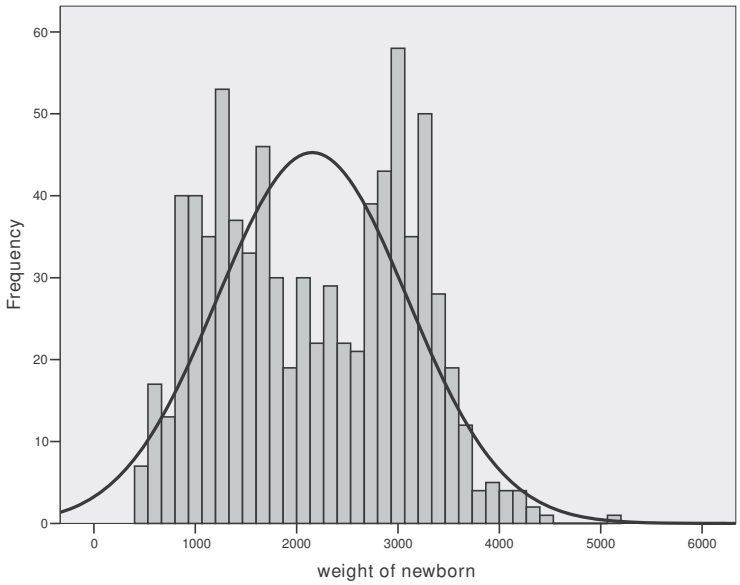

Figure 2. Birth weight (in grammes) distribution of perinatal deaths.

Gestational ages (GA) could be calculated on 72.5% (n=613) of the perinatal deaths based on reported last day of menstrual period and could not be estimated in 27.5% (n=232) of cases. Mean GA for perinatal deaths was 34.7 wks (SD=5.2 wks). The shortest duration of pregnancy recorded was 20 completed weeks; the longest 45.3 weeks. Most (58.9%) of the perinatal deaths were preterm deliveries. Table 1 shows the distribution of the perinatal deaths by gestational age categorized as preterm, term and post term deliveries.

Mean birth weight of the perinatal deaths was 2,155 grams. 56.6% (n=452) of perinatal deaths weighed between 500 and 2,499 g, ie low birth weight; 41.7% (N=333), between 200 g and 3,999 g. The lowest BW recorded was 500 g and the heaviest newborn weighed 5,150 g.

A total of 468 (55.4%) of perinatal deaths were males, while females accounted for 41.4% (350). The male to female ratio at birth for the perinatal deaths was 1.3:1. A total of 723 (85.6%) of the deaths were singleton, 112 (13.3%) were either or both of twins and the remaining five deaths were triplet deliveries.

Discussion & Conclusion

Still births and early neonatal deaths are an important and a fairly common outcome among pregnant and postnatal women at the QECH. We found a SB rate of 34/1,000 births. The perinatal deaths rate that we found may not be representative of hospitals in Malawi. This is because the QECH is a third level health facility which receives high risk referrals. Pregnant women who present to QECH come from the surrounding neighborhoods of the district of Blantyre, health centers and some patients come from the surrounding districts. These are women who are identified either as high risk or already have intrapartal complications that required advanced obstetric care.

The availability of laboratory services to maternity care women can be assessed by examining the proportion of women who accessed VDRL and Rhesus factor assessment among those who experienced a perinatal outcome. The RH factor and VDRL tests should be routinely done, but not always offered to pregnant women in Malawi due to non-availability of laboratory reagents and human resources. Only 5% and 16.4% women had Rh factor and VDRL tests done. This notwithstanding the fact that national maternity guidelines required all pregnant women to have a VDRL test done. Although we did not assess the contribution of syphilis to perinatal death, it is likely to be a leading factor in Malawi. Among the cases who had syphilis assessed with VDRL, prevalence was 10.6%. However, the fact that not all women received laboratory investigations for syphilis, rhesus factors and other tests means that the prevalence estimates for positive test results must be interpreted with caution.

Our study is likely to have underestimated the actual prevalence of prenatal mortality among the cohort that was observed. This is because we did not follow the women into the community. Some of the women may have experienced neonatal deaths after being discharged from hospital. A complete picture could have been obtained if an aggressive follow-up schedule were implemented.

Our findings however are of public health significance, because unlike estimates obtained within intervention studies, we studied the prevalence and the associated features within routine care. These findings are therefore of importance in the design, implementation and evaluation of maternity care improvements at the QECH teaching hospital. However, using routine care in a resource-limited setting as the tool to assess the prevalence and associated factors of perinatal deaths also meant that many other investigations that could explain the deaths were missed. Lack of human resources, laboratory and pharmaceutical supplies and poor adherence to clinical guidelines are likely to be contributors to the high perinatal mortality in Malawi.

We found the prevalence of perinatal deaths among women attending maternity care at a large teaching hospital in Blantyre, Malawi as 9.8%. Many of the deaths were associated with low birth weight and prematurity. This study showed a high rate of pregnancy wastage during pregnancy, labor and delivery process and after birth. We recommend further studies in this setting to assess the effect of intervention aimed to reduced pregnancy wastage in Malawi.

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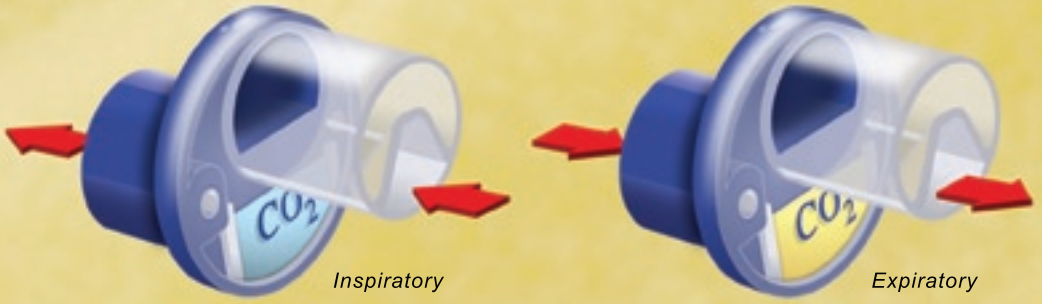

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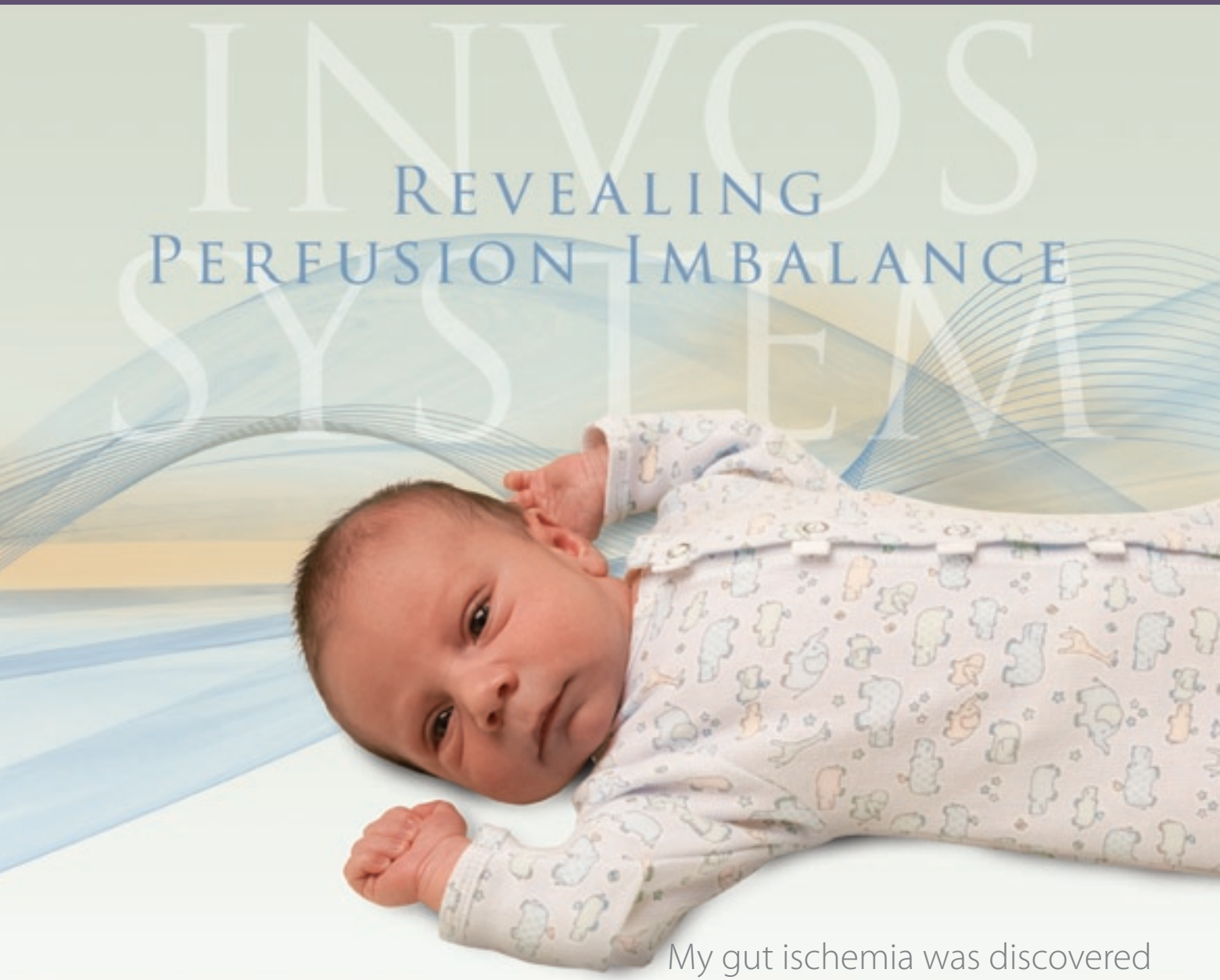

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