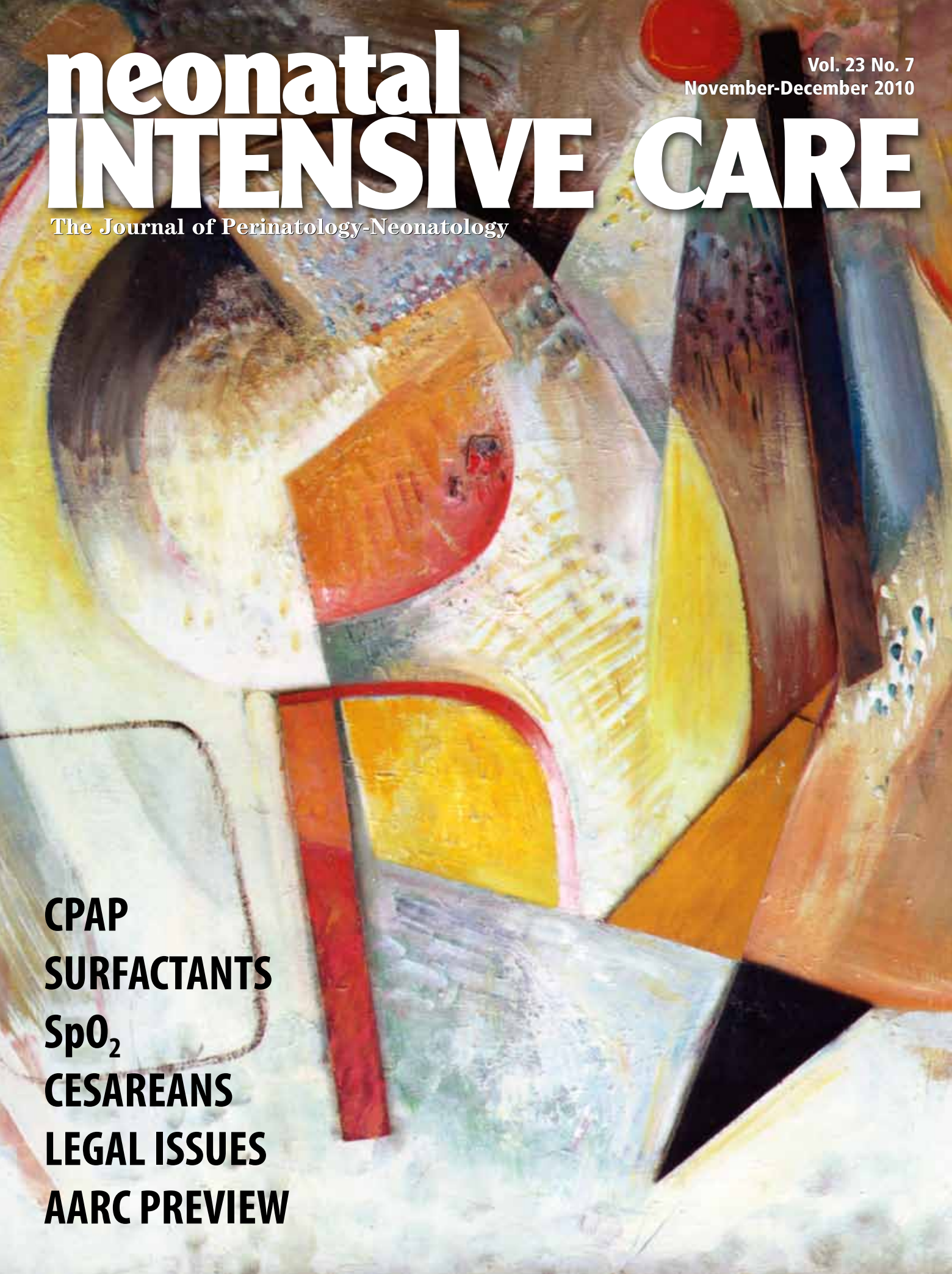
Vol. 23 No. 7
November-December 2010

neonatal INTENSIVE CARE

The Journal of Perinatology-Neonatology



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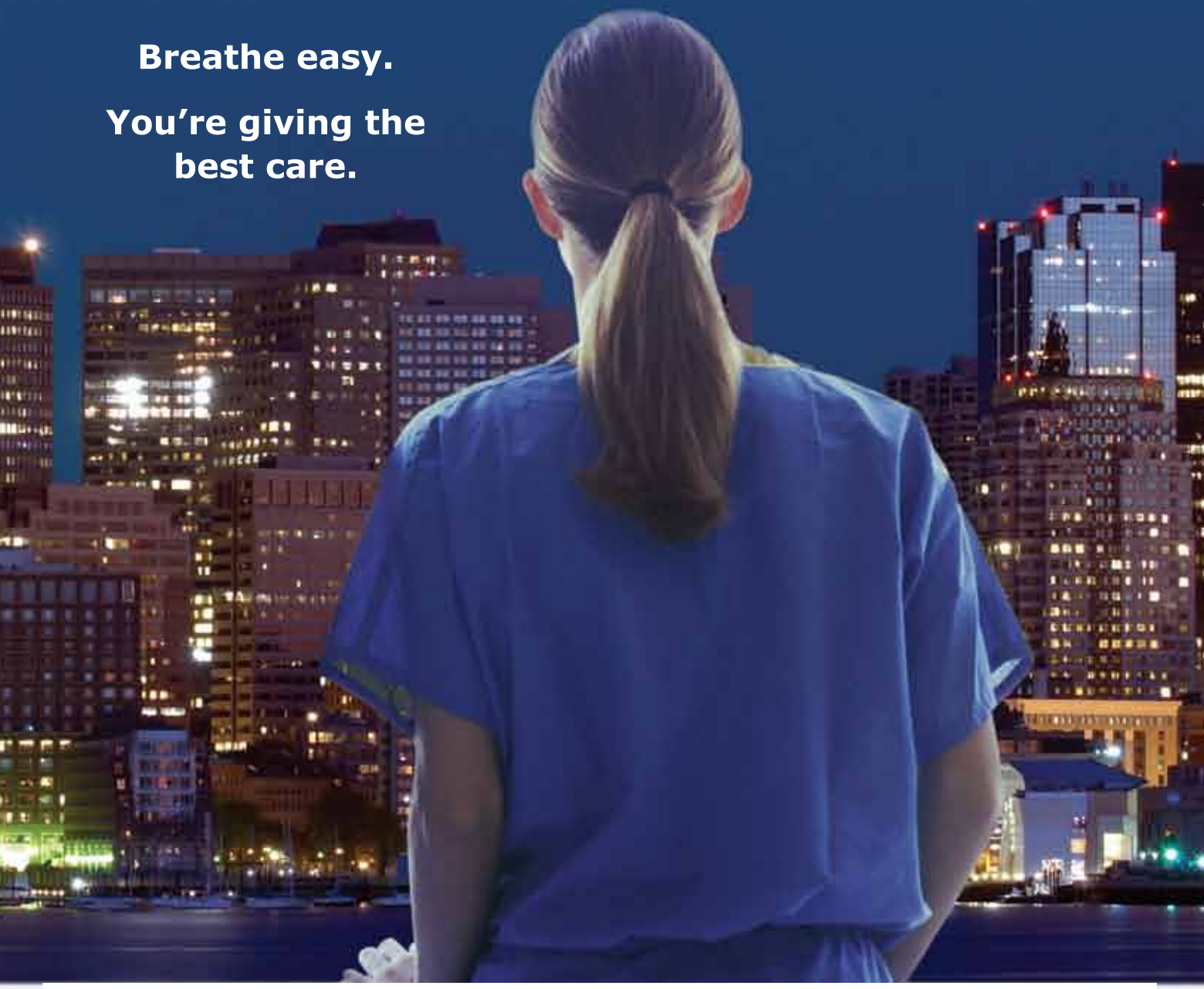

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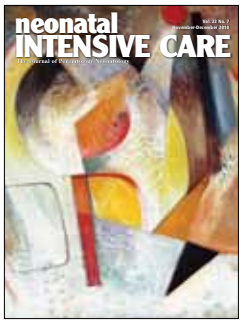

neonatal
INTENSIVE CARE

Vol. 23 No. 7
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ARTICLES

Editorial

Though at first I thought the subject of genetic screening was only of ancillary interest to neonatologists, I thought, again, about future technologies and how they affect the care of preemies and sick infants. The following is an excerpt from novelist Richard Powers, on a subject sure to affect all of us, if not now, soon enough.*

Powers writes: "And then what happened": from the earliest fable, this question has united hearers and tellers, doctors and patients. And from the earliest diagnostic chart, our need to know what happens next has slammed up against that classic source of dramatic tension: knowing what's coming does not shield us from living it. As patients [and as parents and caregivers to patients] growing ill and recovering, rallying and fading, are all experienced as narrative excursions inside wider story frames. So it hardly diminishes the empirical nature of medical diagnostics to say that medical *practice* is a narrative art. From taking the history to signing off on the postmortem, doctors read, and then help arrange, relevant clinical data into a series of causes and effects that forms a linear, time-driven story. Diagnosis and treatment are sometimes a detective novel, sometimes a domestic drama, sometimes a good old psychological character sketch. Every decent plot consists of exposition, complication, crisis, and denouement. But to our eternal dismay, we are each born in the middle of things, and die in the middle of things. To create a more satisfying story, we do everything in our power to read into the history around us a plot more harmonically turned to our own. By imagining how things beyond us will end, we give shape to the endless middle that we otherwise inhabit. Life is the act of revising, rewriting our lives. The art of medicine, too, must be a rewriter's art. Its chief goal is to open up the patient's story, to give new plot to possibility and new possibilities to the plot. But a story about medicine sometimes risks imagining that its job is the elimination of all constraint. In good narrative, though, constraint is the mother of possibility. When anything can happen, nothing tends to. At its best, predictive testing seeks to identify those plot complications and constraints that can be resolved in order to free up the patient's story and move it forward. But this isn't always what patients [or the parents of patients] seek. Something in us wants to read the determined future even as we race to write our alternatives. Today's genetic tests revive, in a high-tech setting, the ancient obsession with divination. Something in us seeks out ironclad prophecy, a reading of our preinscribed, inescapable fate – if only as the first step in trying to escape it. The arguments for and against genetic tests are themselves part of an unfolding story. We live at a dangerous moment, one when the gap between our ability to make a genetic prediction and our ability to alter it is widening precariously. When the results of a given genetic test are valid, they may still tell you nothing more definitive than a probability. When they're definitive... they may leave you with no way of changing those parts of your plot that may then obsess you. They may blind you to your own continued ability to generate and understand meaning. The only fully healthy patient may be the one who hasn't been fully worked up yet. Then again, tests may save or extend a story. Everything depends on how well we engage, not with some invariable database, but with the constantly private narrative at stake. This is the key: genetic tests are not about escaping the story; they are about figuring how best to be in it. The story-writing component of medicine, as such, remains the art of anticipating and identifying constraint, and getting that constraint to be the start of personal responsibilities, not its end. The patient often comes looking for palmistry. But the physician just as often has no more to offer than an informed weather prediction. Even when the physician can give a more definitive prophecy, the oracle tends to remain majestically sphinxlike until its words are lived through. The former director of the NIH has said, with regard to routine clinical use of the BRCA1 and 2 mutation test, "don't order a test if you lack the facts to know how to interpret the results." Tests may read the future, but they cannot write it. Plot does not determine meaning; readers do. There is always the danger of conflating prediction with explanation. The story, however, lies not in what happens, but in what characters *do* with what happens. **The above is from an essay by Richard Powers, A Brief Take on Genetic Screening, in the book Read Hard, published by McSweeney's, and also appeared in McSweeney's magazine The Believer. It has been edited and portions have been slightly altered or paraphrased for our readers.*

Les Plesko
Editor

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News

☐ November-December 2010

BRAINIACS
The Globe and Mail's Anne McIlroy recently reported on the latest imaging technology used to look at compromised baby brains. She reports on a day-old patient whose ultrasound showed that fragile blood vessels in his brain had ruptured. When the infant stabilized, he was cocooned in a special incubator designed to slip into a magnetic resonance imager. The neurologists at BC Children's Hospital used it to better see into the baby's brain than with other approaches and determine how newborn brain injury effects VLBW infants. In California, researchers are exploring whether erythropoietin can coax newborn brain cells that have been affected by a stroke, and concocting a cocktail of solutions to quickly repair injuries. Anne McIlroy described the picture MRI paints: "The cortex initially looks like a rounded coastline. Eleven weeks later, the coastline is marked by dozens of deep inlets and coves." Doctors want to find the tools that will protect these growing brains. Doctors are also studying how injuries incurred during the time of birth evolve and point out that preemies suffer damage to the brain's white matter, which it uses for auto-communication, unlike term babies, whose grey matter is more likely to be affected. A recent study at the University of British Columbia revealed that one in three preemies have white matter injuries. In the specific case noted above, the baby was born at 32 weeks, by cesarean, since the fetus had stopped growing in the womb. He weighed 3 lbs 9 ounces, had difficulty breathing, and had a collapsed lung. The initial MRI scan revealed that his ventricles had engorged from seepage from his ruptured vessels. A later scan revealed that the cavities had begun to shrink, so no shunt would be needed for drainage. Reported by Anne McIlory in The Globe and Mail, via the internet.

VAGINAL ACCESS
The American College of Nurse-Midwives called for concerted efforts to expand access to vaginal birth after a cesarean. Access to VBACs has plummeted, while the c-section rate has climbed to more than 33% of all births, more than double the WHO recommendations. A recent NIH statement requested that ACOG and the American Society of Anesthesiologists reassess their 2008 joint statement requiring immediately available surgical and anesthesia personnel for TOLAC. ACOG's requirement has led rural and community hospitals to cease offering trial of labor and VBAC completely. ACOG's 2010 guidelines still recommend TOLAC, and as such, the nurse midwives' statement says expanded access to VBAC isn't likely. According to ACNM's president, all women, including those who have had a prior cesarean birth, have the right to access to information, counseling and birthing options: "The benefits to mother and baby of trial of a labor and vaginal birth are often overlooked, as are the risks involved with repeat cesarean surgery. Women have the right to be fully informed of all of their options for childbirth, and the risks and benefits of those options." (See also, "Flip Flop" on page 10.)

CHOICE
The Lancet said UK moms shouldn't be able to opt for home births if it puts their babies at risk, though by British law they're allowed to do so. The journal said that home births were riskier than hospital delivery: in a US study of 500,000 births, the death rate for home births, two-tenths of a percent, was twice as high as in hospitals. In the UK, 3% of all births take place at home, thrice as much as in the US. By comparison, in the Netherlands, a third of births are at home. The National Childbirth Trust, responding to The Lancet, said, *pshaw*, because the NHS had better training in home-birth resuscitations. The Lancet countered that women don't have a right to put their babies at risk. The NCT said, in a manner of speaking, yes they did.

OPEN ACCESS
The Open Respiratory Medicine Journal is an open access online journal, which publishes research articles, reviews and letters in all areas of experimental and clinical research in respiratory medicine. The peer reviewed journal aims to provide the most complete and reliable source of information on current developments in the field. The emphasis will be on publishing quality papers rapidly and freely available to researchers worldwide. To access the site, type its name in Google.

CONSEQUENCES
The open-access website BioMed Central reported on an up upcoming trial, "Long-term health-related and economic consequences of short-term outcomes in evaluation of perinatal interventions," by Margreet Teune, et al, in BMC Pregnancy and Childbirth. In their abstract, the authors state: "Many perinatal interventions are performed to improve long-term neonatal outcome. To evaluate the long-term effect of a perinatal intervention follow-up of the child after discharge from the hospital is necessary because serious sequelae from perinatal complications frequently manifest themselves only after several years. However, long-term follow-up is time-consuming, is not in the awareness of obstetricians, is expensive and falls outside the funding period of most obstetric studies. Consequently, short-term outcomes are often reported instead of the primary long-term end-point. With this project, we will assess the current state of affairs concerning follow-up after obstetric RCTs and we will develop multivariable prediction models for different long-term health outcomes. Furthermore, we would like to encourage other researchers participating in follow-up studies after large obstetric trials (>350 women) to inform us about their studies so that we can include their follow-up study in our systematic review. We would invite these researchers also to join our effort and to collaborate with us on the external validation of our prediction models. The systematic review will provide insight in the extent and methods used for follow-up assessments after obstetric RCTs in the past." See BioMed Central and type the full title of the study for more info.

TWO NOT TWIN
A Utah woman was pregnant with two babies, but they weren't twins. The mom has didelphys, the rare condition that means she has two uteruses. The mom, 34, had given birth twice previously

to healthy kids. This time, she'd conceived in both uteruses, and the babies were at different stages, about a week apart. The chance of this occurrence is one in 5 million. The mom is a labor and delivery nurse. Upon discovering the situation, she'd said, "I'm a little nervous, just because I know what can happen, but I'm excited."

FLIP FLOP

ACOG has recently issued new guidelines on repeat cesareans, according to a report by Denise Grady in the New York Times, in light of medical caregivers and insurance companies refusing the option of normal birth after having a c-section. That decision had been based on fears of risk and lawsuits, but actual moms didn't like the idea, saying the medical profession was monopolizing control of childbirth. The new ACOG guidelines are intended to help women find caregivers who'll "allow" vaginal birth after VBAC. Some groups have responded that the guidelines don't go far enough to change behavior by doctors and insurance companies. These new guidelines reverse ACOG's earlier ones, which, Grady noted, "were exactly what led many hospitals to ban VBAC in the first place." ACOG, while insisting that its former guidelines didn't intent to limit vaginal birth, admitted that they'd done just that. The new guidelines now say that vaginal birth is safe for most women who have had a c-section if the cut in the uterus was low and horizontal. The guidelines also say that VBAC after C-section is also okay for most women with twins and who've had more than two c-sections. ACOG also said hospital policies shouldn't force women to have c-sections or deny care to women who want to try it the other way. In 1985, 6.6% of women with prior cesareans were giving birth normally. By 1996, the rate had risen to 28%. But some uterine ruptures were reported, with lawsuits and enormous payments, and the rate began to drop. By 2006, the number of women who had VBAC after a c-section fell to 8.5%. According to Denise Grady of the Times, "opinions vary as to whether the new recommendations will lead to a lift on bans on trial of labor due to various hedges about when 'permission' for vaginal birth is to be granted or denied." One doctor said the guidelines had to be construed in a way to include patients in the risk by building in a clause that they "can't sue the physician if there's a bad outcome." Reported in the New York Times.

ALIEN

We thought we'd recap an earlier news piece about a theory of pregnancy that apparently pits the mother against her infant.* The theory, offered by David Haig, an evolutionary biologist at Harvard, goes like this: "Pregnancy is absolutely central to reproduction, and yet pregnancy doesn't seem to work very well… If you think about the heart or the kidney, they're wonderful bits of engineering that work day in and day out for years and years. But pregnancy is associated with all sorts of medical problems. What's the difference?" The difference, Haig said, is that organs belong to one person but pregnancy involves two unique persons who wage an unconscious struggle over nutrients. Haig said his theory presents an evolutionary view of pregnancy, and that pregnancy presents an evolutionary conflict: Natural selection favors parents who can raise the most offspring. As such, they can't put all their resources into one child. However, the child's own chances for success, including reproductive success, increase as its feeding and care increase. Ultimately, natural selection might favor genes that help the child get more than the parents want to give. The fetus, the article noted, didn't just sit there, but sprouted trophoblasts that "invade its mother's tissues to extract nutrients." At the same time, natural selection also favors mothers who can fight off such incursions yet still bring gene-carrying babies to term. Thus, Haig said, pregnancy was "a tug of war. Each side pulls hard, and yet a flag tied to the middle of the rope barely moves." Specifically, Haig noted that preeclampsia was "an extreme form of strategy used by all fetuses, [which] somehow raised the blood pressure of their mothers so as to drive more blood into the relatively low-pressure placenta." The preeclampsia, he said, occurred when fetuses injected too much of whatever the mystery stuff was that raised mom's blood pressure, perhaps attempting to pig out on nutrients. Haig said his research may well demonstrate how, in turn, maternal defenses to the foregoing have evolved: perhaps mothers shut down some of the genes in their own fetuses, not implausible, since recent studies have shown that more than 70 pairs of parental genes never make a protein or are silenced in particular organs. Recent studies on gene imprinting favor Haig's theory. [*Information and quotes are from the New York Times, reported by Carl Zimmer, March 14, 2006, via the Times internet archives, under "Silent Struggle: A New Theory of Pregnancy."]

FORCED

US News & World Reports recently reported on the case of a six-month pregnant Florida woman who was forcibly hospitalized because her doctor said she was risking a miscarriage if she didn't quit smoking and stay in the hospital on bed rest. A commentator wrote that this was "one of those cases that proves sexism is still alive and well in America... How often are young men forcibly hospitalized for any reason?... The woman took her doctor to court for forcing her to become a ward of the state for the heinous crime of visiting a doctor while pregnant," and a state appellate court recently ruled that the woman's forced hospitalization was "a denial of her constitutional rights." The author wrote that she has "long thought that any major medical decisions need not be made 'by a woman and her doctor,' whether they pertain to pregnancy or not." She added, "Women should make their medical decisions with information provided her by her doctor or doctors," but the "pure power of decision-making should reside with the woman, just as it does with a man." [Bonnie Erbe, "Politics & Policy," U.S. News & World Report, 8/13. Information is from Medical News Today, © 2010 National Partnership for Women & Families. All rights reserved.]

NOT A NEW FAD

An article in Pediatric and Developmental Pathology noted that in cases of fetal akinesia deformation sequence (FADS), the fetus may have been affected by a disrupting injury or unavoidable maldevelopment. FADS encompasses several overlapping disorders that begin with decreased fetal movement and involve degeneration of the brain and spinal cord, joint contractures, and craniofacial anomalies. Researchers hypothesized that there is an often-unrecognized pattern in FADS: a combination of neural and muscular pathology. In a recent study, autopsy cases of fetuses at 20 to 23 weeks gestational age were examined. Out of 18 cases of FADS, seven showed delayed skeletal muscle maturation that would suggest only a muscular disease. However, when four of these cases were more closely examined, they revealed polymicrogyria and evidence of hypoxic/ischemic injury. Polymicrogyria in FADS cases is often attributed only to malformation of the developing brain. A few cases have been described that associate polymicrogyria with central nervous system hypoxic/ischemic injury without the inclusion of a delay in skeletal muscle maturation. Given the four cases found in the study, the authors believe there is a need for complete neuropathologic examinations that can help determine the

frequency of hypoxic/ischemic injury in FADS. For more see "Fetal Akinesia Deformation Sequence with Delayed Skeletal Muscle Maturation and Polymicrogyria: Evidence for a Hypoxic/Ischemic Pathogenesis," Pediatric and Developmental Pathology, Volume 13, Issue 2, 2010.

SAFETY

The Canadian MOREOB patient safety program has a measurable, positive impact on the health of mothers and babies, according to a study in the Journal of Obstetrics and Gynaecology Canada, titled "Outcomes of the Introduction of the MOREOB Continuing Education Program in Alberta." Evidence showed that the program resulted in a significant reduction in severe morbidity for newborns, as measured by the rate of serious complications such as respiratory distress syndrome, sepsis and severe intraventricular hemorrhage. With respect to maternal outcomes, there was a significant reduction in third- and fourth-degree tears and length of stay in hospital. MOREOB (Managing Obstetrical Risk Efficiently) is a comprehensive, three-year patient safety, professional development and performance improvement program for caregivers and administrators in hospital obstetrics units. The program structure is based on the principles of High Reliability Organizations (HROs), including safety as the priority, effective communication, teamwork, decreased hierarchy in emergencies, practice for emergencies, and reflective learning. The program integrates evidence-based professional practice standards and guidelines with current and evolving patient safety concepts, principles and tools. MOREOB is currently implemented in 211 hospitals in Canada, and has involved over 10,000 healthcare professionals. The program is currently being expanded to the United States under an agreement with the Risk Management & Patient Safety Institute.

CRAZY FROM FLU

A study at Temple University has found that children born to mothers who suffered from flu, viruses and other infections during pregnancy have about a 1.5 to 7 times increased risk for schizophrenia. Exposure during pregnancy to certain immune proteins, such as those produced in response to the flu, leads to increased risk for brain abnormalities associated with schizophrenia in offspring. Previous studies had established a link between maternal exposure to flu and increased risk for schizophrenia in offspring, but it was not clear why the link existed, because most infections do not cross the placenta. Researchers then began to look at maternal immune responses to infection, particularly proinflammatory cytokines, which are produced by the body in response to infection. Researchers looked at archived blood samples drawn during the 1950s and '60s from 12,000 pregnant women during each trimester of their pregnancies. The women and their offspring were followed after delivery. Results showed a direct correlation between structural brain changes among offspring diagnosed with schizophrenia and increases in maternal levels of interleukin-8 (IL-8), one of the proinflammatory cytokines produced when fighting infection during pregnancy. Maternal IL-8 levels were not related to any brain changes among a control group of offspring, indicating that vulnerability to schizophrenia needed to be present for the fetal brain to be affected. The researchers said these findings underscored the importance of prenatal contributions

to schizophrenia, with implications for prevention, early intervention, and treatment strategies.

BMC NEWS

Germany's largest scientific organization, the Helmholtz Association, signed a new open access agreement which will cover the article processing charge for any of its researchers wishing to publish in a SpringerOpen or BioMed Central journal using BioMed's membership program. Authors from more than 340 institutions in 39 countries benefit from these memberships taking on full or partial payment of article processing fees.

ACROSS THE STREET

An abortion clinic and a crisis pregnancy center on opposite sides of the street were the subjects of an HBO documentary, "12th and Delaware," which illustrated yet another so-called front line in the abortion-rights debate. The film documented the various strategies used by the Crisis Pregnancy Center (CPC) to persuade clients to continue an unintended or unwanted pregnancy. Time magazine reported that there are more than four thousand such centers in the US, five times the number of abortion clinics, and that many are purposely near abortion clinics, so women wanting abortions sometimes walk into the wrong place. The HBO documentary revealed that CPCs use manipulative practices to influence pregnant women not to get an abortion, such as describing abortion procedures in explicit detail or writing "Hi, Mommy" on an ultrasound image. Time magazine also reported that CPCs frequently lie about abortions increasing a woman's risk for breast cancer, which is not true. A recent report found, for example, that 67% of CPCs in Virginia gave women false information about pregnancies, such as "all condoms have flaws," and telling women that condoms don't protect against pregnancy or HIV. Lawmakers have recently started to look at deceptive advertising by CPCs, and legislation has been introduced to prohibit CPCs from calling themselves abortion providers, which some have done to lure women. The above information is from the Daily Women's Health Policy Report, featured in Medical News Today,

FAT MOM = BIG BABY

A study at Children's Hospital Boston analyzing weight gain during pregnancy of mothers with more than one child revealed that pregnant women who put on additional weight are more likely to have heavier babies. The researchers studied 15 years of birth records in Michigan and New Jersey, using multiple single pregnancies in the same mother so that the genetic element could be excluded. The study looked at more than 500,000 women and their million-plus offspring, and found a consistent association between pregnancy weight gain and birthweight, with each kg gained by the mother in pregnancy increasing the baby's birthweight by 7.35 g. Infants of women who gained more than 24 kg during pregnancy were 150g heavier at birth than were infants of women who gained 8-10 kg. Women who gained more than 24 kg during pregnancy were more than twice as likely to give birth to a child weighing 4 kg or more compared with women who gained 8-10 kg.

NO KIDDING

Relieving poverty during pregnancy reduces the incidence of low birth-weight babies. Researchers at the University of Albany, in their study, Prenatal Poverty on Infant Health: State Earned Income Tax Credits and Birth Weight," tested whether access to state anti-poverty programs diminished the occurrence of low birth weight and at-risk babies. The researchers used EITC programs to determine whether improved income in single mothers suggested improved prenatal health, higher birth weights, and reduced maternal smoking. The study's authors found evidence that participation in state EITCs is directly linked to higher birth weights, including reducing chances that a mother smoked during pregnancy. The study obtained 22 years of data from the US Natality Detail File, a statistical record of nearly every birth in the United States.

RADIATION AND STILLBIRTH

The risk of stillbirth or neonatal death among the kids of women who had radiation therapy (radiotherapy) for cancer when they in turn were kids is higher than the norm, according to researchers at Vanderbilt University and the International Epidemiology Institute. The researchers wondered if radiation-induced damage of human germ cells might be passed on to the offspring of patients, which could have adverse effects on reproduction and the health of the baby. The researchers gathered data from the Childhood Cancer Survivor Study (CCSS), covering more than two dozen institutions, and calculated the risk of stillbirth and neonatal death among the offspring of men and women who had survived childhood cancer. All the CCSS patients were under 21 years of age when diagnosed with cancer and had subsequently survived for at least five years. The researchers studied nearly 5,000 pregnancies. Irradiation of the testes in men and pituitary gland in women and the use of chemotherapy weren't linked to increased risk of stillbirth or neonatal death. However, uterine and ovarian irradiation increased the risk of stillbirth and neonatal death by nine times when doses of more than 10.00 Gy were used. For women treated for cancer before puberty, irradiation in even low doses caused five-times more stillbirths or neonatal deaths. For radiation doses over 2.5 Gy, the risk was 12 times greater. Gonadal irradiation in males didn't seem to make much demonstrable difference. The full study is available from The Lancet. The above is based on an article written by Christian Nordqvist, published online by Medical News Today, copyright Medical News Today.

GET EDUCATED

The Philadelphia Inquirer/Kansas City Star reported, "Most nurse practitioners still have master's degrees, but nursing schools want the doctor of nursing practice degree to be the entry-level degree for advanced-practice nurses by 2015. Enrollment in those programs nationally jumped from 70 in 2002 to more than 5,000 last year." According to the newspaper, the titles of nurses and how they interact with academic degrees are causing some confusion among patients and resentment from doctors, and noted that physical therapists and pharmacists now often have doctorates, and that they're also available to audiologists, PAs and OTs. A fairly recent AMA survey noted that that 38% of patients believed that nurses with doctorates were medical doctors. The AMA wants legislation requiring nurses and other healthcare providers to wear badges with their credentials, which some states already mandate. The above info is from Kaiser, copyright Henry J. Kaiser Family Foundation, via Medical News Today.

APPS FOR ROUNDS

Doctors and nurses making rounds can now use an iPhone app to reference adverse events and feed their info into a database for clinical trials. The Center for Biomedical Informatics (CBMi) at The Children's Hospital of Philadelphia converted CTCAE

reference information into a free downloadable app available through the App Store. From a list of symptoms, users can tap in, for example, "ear pain" and get info from clinical trials that deal with the symptom. Researchers can use this app to quickly access information at the point of care and improve the efficiency of research. Caregivers such as attending physicians and medical students can also use the CTCAE app as an information resource, independent of clinical trials. To download the CTCAE free of charge, users with an iTunes account can search the App Store for "ctcae."

NOTHING TO SNEEZE AT

A Boston University study says that women who take over-the-counter decongestants during their pregnancies are less likely to give birth prematurely. Researchers found that women who took decongestants in their second or third trimesters had a 58% percent reduced risk of preterm delivery compared to women who didn't use them. The researchers analyzed data from 3,271 births over a ten-year period Six percent had preterm deliveries, and 4.2% took decongestants. Women taking them were older, white, married, educated, and had higher incomes. Another previous study, in Sweden, also found a link between decongestant use and preterm delivery. The authors cautioned, however, that the findings do not necessarily imply a cause and effect relationship.

MAN UP, NOT

Fetal exposure to stress could be more harmful to males than females, according to a study at the University of Pennsylvania. When pregnant female mice were exposed to stressful situations, their male offspring were more sensitive to stress than the females. The males also had smaller testes and lower testosterone levels, and these effects were also passed on to the next generation of sons. How come? Researchers believe that the placenta develops in a different way for males, and that sex differences may affect the way that hormones and nutrients pass from mothers to their young through the placenta. Information for the above is from an article copyrighted by Medical News Today.

HERPES DRUGS & DEFECTS

Researchers at the Statens Serum Institut, Copenhagen, found no risk of birth defects for moms using antiviral herpes drugs during the first trimester of pregnancy. Researchers studied 837,795 infants. Among 1,804 pregnancies exposed to acyclovir, valacyclovir, or famciclovir at any time in the first trimester, 40 infants (2.2%) had a diagnosis of a major birth defect, compared with 19,920 of 835,991 infants (2.4%) among the unexposed pregnancies. Additional analyses revealed no associations between antiviral drug exposure and 13 different subgroups of birth defects.

LBW AND ANXIETY

BMC Public Health presented a paper on Indian women depressed or anxious during pregnancy, by Nasreen, et al. According to the authors, there is a high prevalence of antepartum depression and low birth weight in Bangladesh. In high- and low-income countries, prior evidence linking maternal depressive and anxiety symptoms with an infant's LBW is conflicting. The study used a sample of 720 pregnant women assessed for symptoms of antepartum depression and antepartum anxiety and followed them till 6-8 months postpartum. The researchers found that depressive or anxiety symptoms were significantly associated with LBW, as were poverty, malnutrition and lack of support. The authors said the study provided evidence that maternal depressive and anxiety symptoms during pregnancy predict LBW of newborn and replicates results found in other South Asian countries.

WHERE'S THE EVIDENCE

In response to the growing evidence that late preterm infants are at greater risk of complications than babies who are born full term and because these complications have been under-appreciated, AWHONN announced the release of its Assessment and Care of Late Preterm Infant Evidence-Based Clinical Practice Guideline and accompanying Quick Care Guide. The new Guideline is the first of its kind published by a nursing organization. It provides nurses with detailed information about the risks associated with late preterm birth and recommendations for providing comprehensive care and parent education. The project is the central focus of a multiyear initiative launched in 2005 in recognition of the importance of late preterm birth as a significant clinical issue. The Guideline offers 2.3 contact hours toward the CNE and can be purchased through the AWHONN store at www.awhonn.org.

PRODUCTS

PACIFIED

The Babi.Plus Pacifier Adaptor from B&B Medical Technologies is a convenient new way to provide aerosolized medication therapy for babies and children who present with breathing difficulties and are reluctant to relinquish their familiar pacifiers or to wear a mask. The Pacifier Adaptor attaches directly onto the child's pacifier and delivers medication via a small port directed at the nose, which minimizes aerosol or gas directed toward eyes. The Pacifier Adaptor's "U" shaped connector is applied to the pacifier with adhesive tabs for a secure connection. It fits and adheres to a wide variety of pacifiers and holds fast, but can easily be removed after treatment, even while the child still is sucking on the pacifier, helping to maintain comfort for the child. The Pacifier Adaptor can be reapplied to the pacifier for subsequent treatments. The adaptor is latex- and phthalate-free. The Pacifier Adaptor comes packaged with a 15 cm (6") length of 10 mm tubing and a nebulizer adaptor for connection to any small volume nebulizer. Contact www.bandb-medical.com.

A LONG STRETCH

GE Healthcare has received FDA clearance to market the Giraffe Shuttle transportable power source with its Giraffe and Panda families of incubators and warmers for newborn babies, enabling intra-hospital transport. The Giraffe Shuttle, combined with the bed, helps weak babies focus their energy on healing and growing instead of on managing the stress of exposure to cold temperatures and excessive handling. The combined unit helps reduce the potential for clinical problems that can result from interrupted patient thermoregulation, patient nuisance touch, handling and movement—all of which may challenge physiological stability when moving babies to and from a transport incubator. Recharging in just two hours, the Giraffe Shuttle provides up to 45 minutes of electrical power. It also can accommodate accessories and auxiliary equipment such as life support monitors, ventilators and infusion pumps that may be needed during intra-hospital transport. Contact gehealthcare.com/perinatalevent.

FDA CLEARANCE

Instrumentation Laboratory (IL) announced that it has received clearance from the FDA to market the first-ever, rapid point-of-care, lab-quality blood test for measuring total bilirubin (tBili) in newborns. The new tBili assay is performed on IL's GEM Premier 4000 critical care analyzer. It allows clinicians to receive lab-quality test results in 90 seconds from whole blood in the Neonatal Intensive Care Unit, rather than waiting up to an hour for results from the lab, using traditional chemistry methods. tBili assays performed on the GEM Premier 4000 are not affected by moderate turbidity or hemolysis, ensuring accuracy. Additionally, from a single whole blood sample, a full range of analytes can be measured, including blood gas, electrolytes, glucose, lactate and full CO-oximetry, for an efficient and comprehensive assessment of patient status. IL announced the FDA clearance of the tBili assay at the Annual Meeting of the American Association for Clinical Chemistry in Anaheim, CA. At the meeting, IL also introduced GEMweb Plus Custom Connectivity, software for automated information management. GEMweb Plus is the only software to provide system-wide, bi-directional capabilities from any networked PC or GEM Premier 4000 analyzer. GEMweb Plus provides complete control of all networked analyzers, regardless of location, to enhance quality assurance and regulatory compliance. GEM Premier 4000 critical care analyzer provides blood gas, electrolyte and metabolite analysis with integrated CO-Oximetry testing. It features IL's patented Intelligent Quality Management (iQM), a real-time, automated, quality assurance system that continuously detects, corrects and documents, to assure quality results and compliance, 24/7, regardless of operator or testing location. iQM, coupled with its cartridge-based technology and ease of use, allows the GEM Premier 4000 analyzer to provide consistent, accurate, lab-quality results throughout the hospital. Products mentioned above are trademarks of Instrumentation Laboratory Company and/or one of its subsidiaries or parent companies. Contact www.ilus.com.

UPGRADED

Royal Philips Electronics announced the introduction of a newly upgraded line of oral/enteral feeding products. Oral/enteral syringes are part of Philips Children's Medical Ventures' (PChMV) safety and feeding solution products for the neonatal intensive care unit and pediatric intensive care unit. These newly-designed, specialty-use syringes were developed to reduce feeding errors in the NICU and PICU, and to help professional healthcare providers avoid potential tubing misconnections. The new line of oral/enteral syringes (1 ml, 3 ml, 5 ml, 10 ml, 20 ml, 30 ml and 60 ml sizes) includes highly visible text on the barrel that reads "ORAL/ENTERAL ONLY" and an oral-only tip that distinguishes it from medication syringes. It will not attach to a standard luer lock connector. Because standard 1 ml syringes are commonly used to administer medication in the hospital setting, PChMV's 1 ml oral/enteral syringe is a highly noticeable orange color. In addition, the one-piece design eliminates tip separation during filling, and an airtight, brightly colored cap does not allow air or water in, or breast milk to leak out, during prep, storage and warming. The 1 ml, 3 ml and 5 ml syringes include a pointed plunger that fills the tip and eliminates waste by ensuring that all contents of the syringe are delivered. Individual packaging protects the sterile syringe during shipping and is labeled with a barcode for easy inventory management. PChMV oral/enteral syringes are compatible with the most commonly used hospital syringe pumps. Other significant features include individual product packaging that allows the clinician to see the syringe type and size before opening the package and a clear oral/enteral syringe barrel that allows clinicians to easily monitor feeding and check for residuals. Contact philips.com.

APPS-PLICABLE

Philips has introduced the world's first app for noninvasive ventilation, offered free to all clinicians involved in critical care ventilation. The interactive Philips NIV Guide is a valuable reference tool to build or expand ventilation skills. The guide contains physician tips, contraindications, predictors of failure, and successful mask fitting tips. The NIV protocol and process map covers everything from patient selection through initiation, adaptation, monitoring, and weaning. The app's NIV IQ test tests your NIV knowledge. The app also offers educational white papers and articles on NIV. It is available for the iPhone, iPod touch and iPad. Go to the Apple app store to download the guide.

TIE ONE ON

The new Pepper Medical Inc Vent-Tie #401 and Pedi Vent-Tie #401-P are patented ventilator anti-disconnect devices coupled with trach tube neckbands. This unique combination device offers a margin of safety to ventilator-dependent patients and clinicians alike. The easy to use Vent-Tie features a quick release Velcro strap that is compatible with all trach tubes, elbow connectors, and closed suction devices. The integral anti-disconnect strap eliminates the use of rubber bands, shoelaces and tape to secure the ventilator circuitry to the trach tube. The Vent-tie neckband is made of a soft, 100% cotton flannel that offers moisture wicking properties to keep skin dry and cool. This disposable, combination product saves time and money by offering an all-in-one device. It is available in individually packaged boxes of 20 each. Contact peppermedical.com.

CLEARED

Mercury Medical, a leading provider of respiratory products recently received FDA 510(k) clearance to market a new device for use in the Neonatal Intensive Care and Labor & Delivery departments. Neo-Tee is a new, single-use disposable infant T-Piece resuscitator that will help clinicians such as neonatologists, NICU nurses and respiratory therapists provide the best and most appropriate care for their tiny, delicate patients that need respiratory assistance. Neo-Tee is flow controlled and pressure limited. It offers the ability to measure more consistent, targeted Peak Inspiratory Pressure (PIP) and Positive End-Expiratory Pressure (PEEP). Adding the Neo-Tee complements Mercury's infant resuscitation product line (Hyperinflation, CPR & CPR-2 bags), providing hospitals with three choices of therapies for infant resuscitation. Neo-Tee is the only device on the market to offer a built-in manometer "on the Tee" for convenient, in-line viewing of delivered pressure to an infant/patient. Compared with capital equipment T-Piece circuits, the Neo-Tee with a manometer on the Tee offers in-line viewing of delivered pressure to the patient, adding a measure of safety, since the clinician doesn't have to look away from the patient to view the pressure gauge. The NeoTee is disposable and eliminates cross-infection. There's also no cleaning and no capital equipment costs. The controller/built-in pessure relief allows for connection to a flowmeter, and safety pressure relief activates at 40 cm H_2O. It also has a variable PEEP knob, comes in a variety of sizes and styles, and is compatible with other systems. Contact mercurymed.com.

AARC PREVIEW

B&B Medical Technologies

Booth 641

What neonatal/perinatal products will you be presenting?

B&B Medical Technologies will be showcasing our new Babi. Plus product line, which includes the Bubble PAP Valve 0-10 cm H_20 for noninvasive ventilatory support of neonates, premature infants and infants weighing ≤10 kg; Silicone Infant Nasal CPAP Cannula (prongs) for delivery of comfortable nCPAP; and a single or dual pole clamp for both the Bubble PAP Valve and humidifier systems; and Danny Ties for a soft, comfortable fit for tracheostomies.

What products will you be featuring that are of particular current importance, and why?

B&B Medical Technologies will introduce the new **Babi.Plus Pacifier Adaptor** for nebulized medication delivery via the infant's own personal pacifier. The Babi.Plus Pacifier Adaptor is hypoallergenic, latex-free and phthalate-free. The Pacifier Adaptor has been designed to fit and adhere to a wide variety of non-silicone face plate pacifiers. The Pacifier Adaptor holds fast with a specialty adhesive but can be easily removed after treatment, even while the child still is sucking on the pacifier. The Babi.Plus Pacifier Adaptor provides a convenient and cost effective alternative to other methods of nebulized medication delivery for babies and young children. The new **Danny Ties** will be introduced at the booth. Danny Ties are made of a soft, absorbent material that lay smooth at the edges of the collar and significantly minimize skin breakdown beneath the collar. The collar holds its shape, does not fold in half around the neck and does not stretch when it absorbs moisture. The patent pending design of the Danny Ties evenly distributes the padded collar material around the neck to minimize pressure points on the skin. The Danny Ties collar is easy to apply with tapered ends to the collar straps. The ends thread easily through the eyelets of the tracheostomy tube allowing for quick application and changes of the collar on the smallest of infants and the large adult patient. Danny Ties are developed with special care by a dad wanting to "make a difference" for his son and change the quality of life for tracheostomy patients. His engineering expertise and commitment to finding a better solution is found in the Danny Ties. In addition, B&B will present the new preemie-sized **Sil.Flex Stoma Pad** for advanced tracheostomy stoma care for the very smallest infants. B&B Medical Technologies is the first and only company to offer an FDA-cleared, professional Bubble CPAP system specifically designed to deliver precise CPAP pressure in the premature infant population. The **Babi. Plus Bubble Pap Valve** and **Infant Nasal CPAP Cannula** eliminates the need for hospital personnel to invest time and money manufacturing and maintaining the "homemade" bubble devices previously used for nasal CPAP application.

Discuss educational/support/training materials you'll be promoting.

B&B Medical Technologies will have complete product brochures, clinical application guides to assist the clinician in the introduction and education for the complete line of B&B Medical Technologies specialty airway management products.

Why should neonatal/perinatal caregivers visit your display?

B&B Medical Technologies' "signature" giveaway—See's Lollipops—will be available at our booth. Please stop by to see how the New Babi.Plus product line and Danny Ties will provide benefits to your small patients by making your life easier in the clinical setting, and enjoy a lollipop from B&B Medical Technologies.

Bunnell Incorporated

Booth 529

What neonatal/perinatal products will you be presenting?

Bunnell Incorporated is celebrating 25 years in the ventilator industry. The **Life Pulse** High-Frequency Jet ventilator has passed the test of time. Its therapeutic flexibility makes it an indispensable tool in many NICUs. Jet pulse technology, passive exhalation, and an adjustable I:E ratio makes this high-frequency uniquely effective.

What products will you be featuring that are of particular current importance, and why?

The **"WhisperJet"** patient box with sound reduction technology is the most timely product Bunnell will feature at the 2010 AARC Congress in Las Vegas. The most recent sound reduction upgrade has lowered the sound output from 56 to 41 dB.

Discuss educational/training/support materials you'll be promoting.

Bunnell has developed a three booklet pocket reference set that explains *what* high-frequency ventilation is, *why* the Life Pulse is uniquely effective, and *how* the Life Pulse is used to care for patients. The Life Pulse HFV Training DVD will also be available at the AARC Congress. The DVD contains a complete in-service video, a patient management video, an alarms and troubleshooting video and more. It contains everything you need to understand how the Life Pulse works and how to use it. The DVD is organized, for your convenience, into chapters so you can focus in on the information that is important to you. All of these training materials and much more are available on the Bunnell website at bunl.com.

Why should neonatal/perinatal caregivers visit your display?

The number one reason NICU therapists should stop by the Bunnell booth is to hear how quiet HFV can be, just 41 dB. Noise in the NICU has become an important topic of research and debate. Bunnell is committed to continuous improvement and our new "WhisperJet" proves it. Stop by Booth 529; hearing is believing. Whether you currently use HFV or not our clinical specialists can answer all your HFV questions. Stop by and give us a try.

Dräger

Booth 817

What neonatal/perinatal products will you be presenting?

Dräger will be presenting its latest product advancement in the field of neonatal ventilation. Visitors will get a first-hand look at the **Babylog VN500**, a technologically advanced device with

a comprehensive array of therapy options to support infant ventilation. Once again, our customers led the development of the next generation in neonatal ventilation. The Babylog VN500 combines conventional ventilation, nasal CPAP and oxygen therapy in one medical device. Designed with the clinician in mind, its versatility and range of operation makes it well suited for neonatal and pediatric intensive care units.

What products will you be featuring that are of particular current importance, and why?
The Babylog VN500 was designed with the neonatal respiratory therapist, neonatologist, and tiny patient in mind. After over two decades of experience with the former device, the VN500 brings a wealth of technology in mechanical ventilation to the bedside. The **Evita Infinity V500** enters the ventilation marketplace with new tools and options never before available. Features such as APRV with Auto-Release, Variable Pressure Support, Smart Pulmonary View, and configurable SmartCare/PS are some of the examples of new technology that the V500 brings to the respiratory therapist and critical care physician.

Discuss educational/training/support materials you'll be promoting.
Dräger will be promoting a variety of new materials including a booklet on ventilation modes in intensive care, a pocket guide on mechanical ventilation to include a book signing by the author, a continuing education supplement on thermoregulation, and an internet educational platform created to support neonatal doctors and nurses, as well as parents of premature babies. Launched in 2010, **Babyfirst.com** is an online resource where clinicians in Labor and Delivery and the NICU can share their expertise and experience—across a range of neonatal care specialties, including respiratory care and infection control. This interactive website also provides resources to assist clinicians in educating parents about the NICU for a healthy collaboration with professionals towards the growth of their babies. The website is supported by Dräger and NICUniversity, a Web-based medical education center for clinical professionals. Every day during exhibit hours, the first 100 visitors to the booth will be given the "Mechanical Ventilation Pocket Guide" by Dana Oakes. Additionally, Mr Oakes will be onsite for a book signing and interview. See the booth receptionist in advance for details. Visitors to the booth can also request a copy of "Ventilation Modes in Intensive Care," a booklet designed to improve the understanding of contemporary modes of mechanical ventilation. The revised nomenclature is an effort in standardizing common understandings of pressure, volume, and spontaneous ventilation modes.

Why should neonatal/perinatal caregivers visit your display?
Dräger has been in the forefront of ventilation for over 100 years. Our knowledge and experience continues to bring the latest technological advances to caregivers worldwide. Forums such as the AARC allow for sharing of expertise and of course fellowship amongst colleagues, customers, and friends. We invite neonatal and perinatal caregivers to stop by the Dräger AARC booth to see our new Babylog VN500 dedicated infant ventilator and Babyfirst.com interactive website and tell us what you think.

Fisher & Paykel Healthcare, Inc

Booth 701

What neonatal/perinatal products will you be presenting and why are they important?
In addition to the launch of the newly enhanced **Neopuff Infant T-Piece Resuscitator**, F&P is excited to announce that attendees at the AARC Conference will be the first to see the launch of our new family of resuscitation circuits. Among the many benefits of the new resuscitation circuits is the ability for the clinician to provide suction and deliver surfactant during resuscitation. This is another reason to visit our booth. An integral component of the Neopuff Infant T-Resuscitator and family of circuits is the unique line of resuscitation masks, including the first ever micro-preemie mask for very low birth weight patients. The masks are specifically designed to conform comfortably to the infant's face, facilitating a seal for optimum resuscitation. The masks come in five sizes ranging from micro-preemie to pediatric size. Fisher & Paykel will also be exhibiting the first humidified infant resuscitation system using the MR850 respiratory humidifier. The Neopuff Infant T-Piece Resuscitator facilitates the delivery of warm humidified gas to help protect the pulmonary epithelium and reduce heat and moisture loss especially during prolonged resuscitation. Conditioning cold, dry gas to body temperature and saturated with water vapor can help reduce the risk of an inflammatory response occurring in the infant's airway. In addition, Fisher & Paykel is exhibiting our Infant Nasal High Flow System as well as our **Bubble CPAP Interface**. The **Infant Nasal High Flow System** provides humidified oxygen via a nasal cannula from flows of 0.3 to 8 lpm to provide comfortable precise oxygen delivery as well as respiratory support. The Bubble CPAP Interface System provides an alternative approach to help reduce nasal septal breakdown while being versatile and adaptable to a wide variety of patients.

What educational materials will be available at the conference?
We look forward to discussing and demonstrating the Fisher & Paykel Infant Respiratory Care Continuum and sharing CNE opportunities with you. Also, we will be providing flash drives containing Neopuff Infant T-Resuscitator educational material.

Why should neonatal/perinatal caregivers visit your display?
Attendees are invited to experience all of the above-mentioned demonstrations and hands-on stations, including the opportunity to test their resuscitation skills on our simulator. Please join us at the AARC Conference in Las Vegas at booth 701 for a complete review and demonstration of all Fisher & Paykel Healthcare products that include our newly enhanced Neopuff Infant T-Piece Resuscitator and new family of circuits. Fisher & Paykel Healthcare, Inc understands and appreciates the critical role neonatal nurses undertake in infant care. This is the reason Fisher & Paykel is dedicated to improving patient care and outcomes. With over 20 years of worldwide use and acceptance involving millions of safe and effective resuscitations, the Fisher & Paykel Neopuff Infant T-Piece Resuscitator has recently been updated to further enhance functionality and usability while providing optimal resuscitation and continuing to raise the standard of care for infant resuscitation.

Mercury Medical

Booths 428/430

What neonatal/perinatal products will you be presenting?

Mercury Medical will be exhibiting **Neo-Tee**, the industry's first disposable Infant T-Piece Resuscitator with Built-In Pressure Relief and Color-Coded Manometer on the Tee. Mercury will also be showing the neonatal CO_2 detector, **Neo-StatCO2** with expanded weight range of 0.25 kg-6 kgs. Also on display will be Mercury's high-quality hyperinflation and infant CPR bags with and without manometers as well as Mercury's new disposable infant sizes of **air-Q** (Masked Laryngeal Airways): 1.0, 1.5 and 2.0.

What products will you be featuring that are of particular current importance, and why?

The new Neo-Tee will be very important as hospitals begin changing their protocols for safer and more affordable infant resuscitation solutions. The Neo-Tee infant T-Piece resuscitation single-patient-use device allows practitioners to deliver required volumes for neonatal lung expansion with simultaneous patient monitoring of airway and/or PEEP pressures. The new Neo-Tee affords the clinician more consistent PIP and PEEP pressure. Additionally, there is no "bag" to squeeze so the clinician will not experience bag squeezing fatigue. Furthermore, the Neo-Tee includes a built-in pressure relief valve as an added safety measure when releasing high ventilatory pressures over 40 cm of H_2O. The stay-put PEEP valve allows for quick and easy gas flow adjustments, when needed. The adjustable PIP controller, which regulates pressure, is much smaller and compact than competitive capital equipment. Neo-Tee does not require cleaning and it's completely disposable. As compared with expensive capital equipment, Neo-Tee will be affordable for any hospital (small or large) to incorporate at every NICU and L&D bedside.

Discuss educational/training/support materials you'll be promoting.

Full product training will be provided at the booths by Mercury Medical Product Specialists. We will provide Neo-Tee product information brochures with specifications and offer free samples. The samples will be provided by fully trained sales representatives who will provide full product in-servicing at the attendees' facilities.

Why should neonatal/perinatal caregivers visit your display?

Mercury is a leading manufacturer of resuscitation products that commands the number 1 market position in infant CPR resuscitation bags. Mercury pays special attention to customer needs and develops high-quality products to meet those customer requirements. Mercury's slogan, "Your Need... Our Innovation!" sums up the company positioning. Neonatal/perinatal caregivers should visit our display to get a first-hand view and advantages of Neo-Tee, the industry's first disposable infant T-Piece resuscitator with built-in pressure relief and color-coded manometer on the Tee.

COMPANY CASE STUDY

HELPING HANDS

GE has a program for equipping doctors, nurses and clinicians with the equipment and products needed to provide basic medical care to thousands of families in rural communities around the world: "Developing Health Globally." GE is committing $50 million to 13 countries and delivering technology, training and hope. GE employees are volunteering time and expertise through programs like the Hispanic Forum in Honduras, the Asian Pacific American Forum in Cambodia, and the African American Forum in Ghana. GE is also making major investments to develop healthcare products for the individual needs of these markets, including investments in its Maternal-Infant Care business. The company is aligning strategic philanthropy and commercial development with GE's healthymagination initiative, a $6 billion commitment to healthcare innovation, designed in 2009 to help deliver better care to more people at lower cost. The results have touched the lives of nearly five million people.

For example, GE highlighted its efforts in sub-Saharan Africa. GE reported: Although significant strides have been made by expanding immunization and improving water, sanitation and nutrition, child survival remains a major public health concern in most countries in Africa. What's more, the first hour of life is still the most critical time of the most critical month. And for infants in sub-Saharan Africa, it's a perilous time indeed. The majority of deliveries still take place without the basics of a skilled birth attendant equipped with simple midwifery tools, such as a fetoscope, basic linen to dry infants and keep them warm, and basic suction for clearing mucus, enabling babies to take their first breath. At least 50% of global births occur in underserved urban settings where access to affordable technology remains limited. The results are predictable. Every minute, eight infants one month old or younger die, mostly from preventable causes; nearly as many are stillborn. In places with high infant mortality rates, newborn deaths routinely go unrecorded, and those who live are often not named until they have survived that first month. The vast majority of these deaths could be prevented if women and their babies had access to basic skilled care during pregnancy, childbirth and the first days after delivery. According to GE, "Of all the people being impacted by the United Nations' Millennium Development Goals (MDGs), the children of the world are foremost in the minds of GE Healthcare's employees—especially the youngest and most fragile. It is no surprise, therefore, that we are especially focused on MDG 4, 'reducing by two-thirds the under-five mortality rate by 2015.'"

There are already 24 products in GE's healthymagination portfolio; its target is to bring to market 100 such innovations by 2015, many to meet the specific needs of developing nations. One such device is the Lullaby Warmer, developed by GE in Bangalore, India—a system created to address the worldwide problem of neonatal hypothermia, a contributing factor in many of the 3.1 million newborn deaths each year, particularly among low birth weight and preterm infants. The Lullaby Warmer was explicitly designed for operational ease; a simple interface and manual controls allow caregivers to concentrate on their patients instead of complex switches and settings. It allows hospitals and clinics to precisely deliver needed warmth to newborns during the critical early hours of life, often replacing makeshift

Continued on page 20…

A Reason to Flip for Variable Flow

Lorelee Goehle, RRT, MSHS, MBA

Introduction

"Premature births are an enormous global problem that is exacting a huge toll emotionally, physically and financially on families, medical systems and economies. In the United States alone, the annual cost of caring for preterm babies and their associated health problems tops $26 billion," commented March of Dimes President Jennifer Howse.[1]

According to the National Center for Health statistics, over a half a million babies, or 1 out of every 8 live births, are born prematurely.[2] Late preterm babies account for 70% of the premature births.[3] In comparison to term babies, late preterm babies are more likely to suffer complications such as respiratory distress; to require prolonged hospitalization; incur higher medical costs; and to die within the first year of life.[2,3] The average cost of medical care for a premature baby in his first year of life is $49,000.[1]

Incidence of RDS by Weight (NICHD) Neonatal Research[4]

501-750 g	750-1000 g	1001 -125 g	1251-1500 g	501 -1500 g
71%	54%	36%	22%	42%

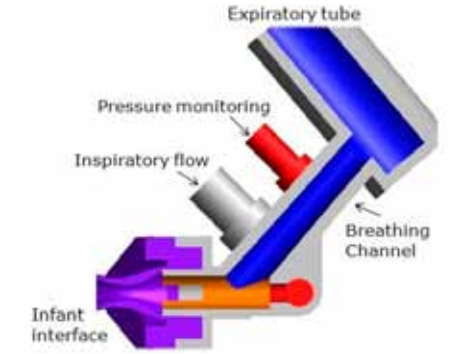

Figure 1. Single jet generator.

Historically, the initial treatment for infants with respiratory problems was mechanical ventilation via an artificial airway. An alternative method is nasal continuous positive airway pressure (nCPAP). Nasal CPAP is an established method for providing noninvasive respiratory support to a spontaneously breathing infant via a nasal mask or nasal prongs. Evidence-based outcomes associated with nCPAP therapy included fewer days on respiratory support and oxygen,[5,6] and avoidance of tracheal intubation up to 70%.[7] Reports have shown that the use of nCPAP may be associated with cost savings in treating infants with RDS.[8]

Lorelee Goehle is employed by CareFusion, manufacturer of the AirLife nCPAP System and Infant Flow System. AirLife and Infant Flow are registered trademarks of CareFusion.

How CPAP Works

During exhalation, premature lungs are vulnerable to airway collapse. This causes increased work of breathing on inspiration to re-expand the lungs. CPAP is a technique that applies continuous positive pressure to the infant's airway throughout the breath cycle. The positive pressure acts as a splint to prevent collapse of the alveoli and terminal bronchioles. CPAP enhances alveolar recruitment decreasing pulmonary vascular resistance; thereby reducing intrapulmonary shunting. By increasing alveolar gas exchange surface area, nasal CPAP decreases ventilation/perfusion mismatch and improves oxygenation. In addition, CPAP stabilizes functional residual capacity and decreases work of breathing.[10,11,12] If an infant is expending energy to overcome work of breathing, they are using precious calories that otherwise could be used for vital recovery and growth processes. The goal of CPAP therapy is to maintain normal lung volumes and oxygenation.

Delivery Method

Nasal CPAP is delivered using two types of technology, continuous flow or variable flow. Continuous flow devices use a constant flow and vary the CPAP level by some mechanism that applies resistance to the expiratory limb of the circuit, eg conventional ventilators and underwater bubble CPAP (bCPAP). In a mechanical ventilator, the clinician changes the CPAP level by varying the expiratory resistance to flow. In bCPAP, the pressure is adjusted by submerging the distal end of the expiratory circuit into a water column the depth of the desired CPAP.

Variable flow CPAP is delivered by a dedicated CPAP driver and a special flow generator with either single (Figure 1) or dual jets. The generator utilizes fluidic gas principles to deliver a constant CPAP at the airway proximal to the infant's nares while maintaining an open expiratory flow path. The level of CPAP created is proportional to the flow provided by the driver (eg 8 LPM of flow provides approximately 5 cmH_2O CPAP).

Regardless of the method used, there are three main components to a CPAP system.

- Gas source: Provides continuous supply of warm humidified and blended gases ie, air and oxygen;
- Pressure generator: Creates the positive pressure in the circuit;

- Patient interface/delivery system: Connects the CPAP circuit to the infant's airway ie, circuit, bonnet, nasal prongs or mask.

Fluidic Technology

Variable flow generators use Bernoulli's principle effect via injector jets directed toward each nasal prong in order to maintain a constant pressure. If the infant pulls additional flow, the venturi action of the injector jets entrains additional flow from either the source gas or atmosphere. With the single jet design generator, on passive exhalation there is a decrease in the forward velocity of air flow. This allows the Coanda effect to dominate and flip the jet stream away from patient nares (Figure 2) and exit through the expiratory limb, reducing patient effort on exhalation. This "flip" is accomplished by the Coanda effect, which is "the tendency of a gas or liquid coming out of a jet to travel close to the wall contour even if the wall's direction of curvature is away from the jet's axis."[17] The residual gas pressure is provided by the continuous gas flow, which enables a stable CPAP pressure delivery throughout the respiratory cycle.[11,12]

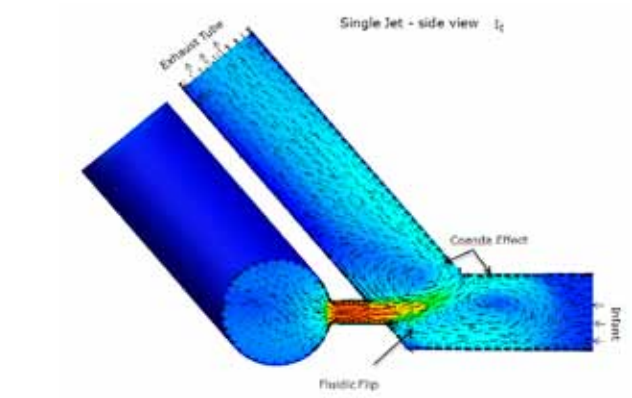

Figure 2. Fluidic flip and Coanda Effect.

A dual jet generator utilizes two low-momentum jets per nare and vortices to help reduce work of breathing (WOB) during inhalation and exhalation. Vortices are a spiral motion of fluid or gas within a limited area that pulls everything toward its center. The jets of gas impinge inside the generator to form a stable jet pump that exerts a constant positive pressure in the patient's airway.[15]

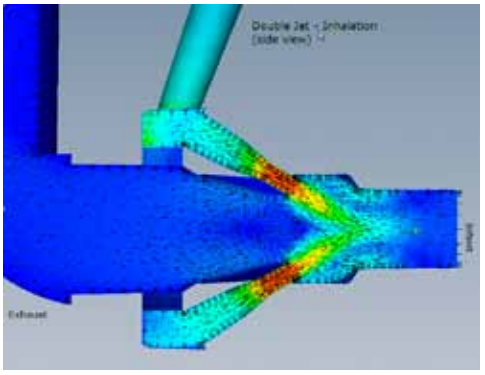

Figure 3. Side view. Inspiratory phase.

During inhalation (Figure 3) the jet pumps are able to maintain a constant CPAP and meet the patient's inspiratory flow demand. If the patient's peak inspiratory flow exceeds the flow provided by the driver, then the generator's jet pumps efficiently entrain additional flow to match the demand and provide a stable CPAP.

As the patient begins to exhale, and throughout the expiratory phase, the low momentum jets are easily deflected away

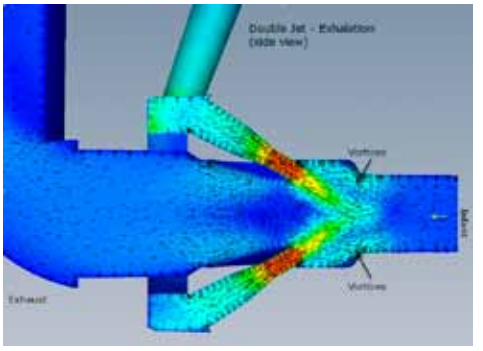

Figure 4. Expiratory phase, vortices shedding.

(flipped) from the impingement point, disrupting the jet pump and the pressure it exerts. As the jets disrupt, they shed vortices that spiral outwardly, combining with the patient's exhaled breath to create an organized, efficient flow path toward the exhaust ports (Figure 4). This effectively provides a lower flow resistance, like breathing through a larger tube, and helps reduce the imposed WOB. This is a fluidic mechanism, like the Coanda effect, that is used to help make variable-flow CPAP devices work more efficiently.

Variable flow generators operate with an "open" exhalation path and do not require an exhalation valve to maintain CPAP pressure. The jet pumps create the pressure based on momentum and the exhalation path is always open. The fluidic mechanisms that actively reduce exhalation resistance operate over the entire range of set pressure levels, whether nCPAP or BiPhasic mode.

Evidence has demonstrated that fluidic technology is associated with decreased WOB. On continuous flow CPAP devices, the infant must exhale against the flow resistance of incoming air. With variable flow devices, the direction of the flow is dependent on the patient's respiratory cycle. On inhalation, the flow rate is supplemented by entrainment when necessary to meet inspiratory demand. When the infant exhales, the flow "flips" away from the nares to reduce the imposed WOB, and then "flips" back as the exhalation phase ends. The response is almost instantaneous as it occurs at the patient nares. Klausner reported the WOB via variable flow nasal prongs to be one-fourth that of continuous-flow CPAP.[13] Pandit assessed WOB in premature infants and found the WOB to be significantly less with variable flow devices versus continuous flow devices.[14]

Conclusion

Premature babies are more susceptibly to respiratory problems due to their underdeveloped lungs. Common neonatal respiratory conditions include respiratory distress syndrome, apnea of prematurity, transient tachypnea of newborn, meconium aspiration syndrome, pulmonary edema, and post-extubation support. These are often associated with decreased pulmonary compliance and functional residual capacity.[10,11] Approximately 50% of neonates born at 26 to 28 weeks gestation develop respiratory distress syndrome, in comparison, to only 30% of premature neonates born at 30 to 31 weeks gestation.[10]

To treat respiratory disorders in the spontaneous breathing infant, nCPAP is standard of care in NICUs worldwide. Noninvasive CPAP therapy is associated with improved outcomes for neonates requiring additional respiratory support. Fewer intubations, reduced days on respiratory support and oxygen therapy reduce costs in treating preterm infants.

There are several options available to the clinician on the

delivery method from bCPAP to conventional ventilators. By redirecting gas flow in direct response to patient breaths, variable-flow nCPAP offers lower imposed WOB than continuous flow devices. Dedicated variable-flow nCPAP drivers provide a measurable therapy with system alarms to help ensure safe and effective therapy for the smallest patient.

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News–Company Case Study…continued from page 17
heaters improvised from 60-watt light bulbs—and to do so at a significantly lower cost than its more sophisticated predecessors, while meeting all international quality and safety standards.

In too many countries, equipment goes unused because there's no one to operate it, maintain it, or replenish consumables or spare parts. In fact, equipment that can't be used is a common sight in public hospitals and rural health clinics in developing countries. GE is addressing this challenge in a variety of ways. For example, to promote proper application, maintenance and repair, GE makes education and training available for every piece of equipment it delivers, whether through commercial contracts or philanthropic donation.

Members of the GE Healthcare Maternal-Infant Care team have been working to educate the medical community in developing nations on specific infant-care processes and procedures—for instance, preventing hypothermia by keeping newborns warm. GE experts have conducted seminars on such subjects for doctors and nurses at conferences in South Africa, and have provided hands-on training in nations such as Namibia and Kenya.

Education is not just for doctors and nurses, however. As part of the Developing Health Globally program, GE is building biomedical technology training programs to enable the repair of vital, lifesaving equipment, to help ensure its longevity, and to optimize its utilization over its intended lifetime. And to reinforce formal training, GE is also creating a series of training videos. Caregivers and maintenance staff alike will be able to learn at their own pace about everything from using our products to ensuring that they are operating at peak performance.

Much of the attention on achieving the UN's Millennium Development Goals has focused on the delivery of proven solutions such as vaccination, contraception or mosquito nets. These approaches are attractive because they have a direct impact on urgent health challenges and can be delivered on any scale.

Building on these programs, GE is partnering with a wide range of organizations to deliver comprehensive solutions that promote the safety of mother and child alike in clinics and hospitals worldwide—and especially in developing-world nations. Toward that end, we are now focusing our efforts on implementation, in order to make today's progress part of each nation's infrastructure, and part of each healthcare worker's routine to bridge the "know-do" gap.

Through healthymagination, Developing Health Globally, innovative product development, and comprehensive educational initiatives, we are committed to helping nations worldwide achieve dramatic and sustainable improvements in infant survival rates. For more on the above, visit healthyimagination.com.

Poractant and Beractant

A recent study compared animal-derived surfactant treatments of preemies using beractant and poractant alfa. Results showed that there are benefits to larger initial doses of poractant alfa than beractant in extremely premature infants. The study appeared in Journal of Perinatology (2010), copyright 2010 Nature Publishing Group, and compared Survanta and Curosurf. Beractant is used in initial and subsequent doses of 100 mg kg-1. Poractant is used in initial dosage of 200 mg kg-1 and subsequent doses of 100 mg kg-1, in <30 week ventilated infants with RDS. The researchers studied 52 infants. Twenty-five received poractant alfa and 27 received beractant. The researchers concluded: Infants in the poractant alfa group had a greater number of extubations at 48 and 72 hours than the beractant group. The authors reported that the prevalence of PDA and air leaks was less in poractant alfa-treated infants than in those receiving beractant.

Previous studies had demonstrated that treatment with poractant alfa caused more improvement in oxygenation and ventilator support a day after administration, that poractant treatment led to a shorter ventilatory course, that infants needed less oxygen for a shorter period of time, and had shorter hospital stays (Speer, Baroutis). Other studies had shown a decrease in mortality when using poractant alfa, but this may have been due to the larger initial dose. The specific goal of the study was to find out if the level of lower ventilator support was maintained during the first three days of the infants' life using poractant alfa vs beractant, and to find out if such differences in ventilator support affected chronic lung disease or mortality.

Infants in the trial were placed on an Evita XL (Draeger) ventilator with a tidal volume of 5 ml kg-1, 35 breaths min-1, inspiratory time .35 s and peep 5. FIO_2 saturation was 85 to 92%. Initial dosages were administered right and left-laterally for MAPx6 cm H_2O, >30% FiO_2. Secondary doses of poractant were administered every 12 to 24 hours and beractant, every 6 to 12 hours. After the course of treatments, infants were extubated and ventilator settings were recorded every four hours. Arterial and venous blood gases were tracked every 5 hours in the babies' first 24 hours, and then every four to 12 hours. Data were collected to evaluate the use of Survanta or Curosurf.

Between 2005 and 2007, 25 patients were treated with poractant alfa and 27 with beractant. Patients treated with poractant alfa required a lower MAP to maintain oxygenation. According to the researchers, "Patients treated with poractant alfa required a lower MAP to maintain adequate oxygenation than those infants treated with beractant, beginning at 12 h after the initial dose with differences persisting through the first 72 h of life." Neither surfactant caused a significant difference in FiO_2. "Very premature infants with RDS treated with poractant alfa required less respiratory support during the first 3 days of life than infants treated with beractant, allowing a greater number of patients to be electively extubated at 48 and 72 h of life." While there was no difference in FiO_2 using the two treatment modalities, MAP differed because more infants were extubated to NCPAP or oxygen in the poractant group. Initial differences in patient responses to both surfactants didn't affect later differences in BPD or mortality. A lower trend, however, was noted for BPD and/or death in infants treated with poractant alfa vs beractant. Those treated with both surfactants had similar lengths of ventilation and nCPAP. The length of stay for both groups was about the same. As such, the researchers noted a trend toward less chronic lung disease and death among the poractant group. Pulmonary air leak was also lower in the poractant alfa group.

The authors noted, "this is the first prospective randomized control trial to report a prolonged early difference between poractant alfa and beractant, associated with a difference in the frequency of hemodynamically significant PDA." While the results of this study didn't always mesh with the results of previous studies, the authors remarked that differences might be due to different dosing regimens or surfactants. Less air leaks with poractant alfa, they noted, might have been "due to a more rapid improvement in the pulmonary status, and lower level of ventilator support in the infants treated with poractant alfa." The authors concluded, "poractant alfa induced a greater early and persistent improvement in pulmonary function in very premature infants with RDS, compared with infants treated with beractant... In the infants who received poractant alfa, there was a concomitant reduction in the number of infants with PDA and air leak syndrome, compared with those treated with beractant."

Poractant alfa and beractant treatment of very premature infants with respiratory distress syndrome, A.M. Fujii, S.M. Patel, R. Allen, G. Doros, C-Y Guo, S. Testa, Journal of Perinatology 2010, 1-6. Original article provided to Neonatal Intensive Care by Cornerstone Therapeutics.

Surfactant and NCPAP

A recent study revealed that prophylactic surfactant was not superior to nCPAP and early selective surfactant in decreasing the need for mechanical ventilation in the first 5 days of life and the incidence of main morbidities of prematurity in spontaneously breathing very preterm infants on nCPAP. The study, by Sandri et al and published in the Journal of Pediatrics, investigated whether prophylactic surfactant followed by nCPAP compared with early nCPAP application, with early selective surfactant reducing the need for MV in the first 5 days of life.

In the study, 208 infants at 25 to 28 weeks' gestation were given prophylactic surfactant or nCPAP within their first thirty minutes, and results were collected for the first five days. Thirty three babies in the surfactant group required mechanical ventilation compared with 34 in the nCPAP group. Death and survival were similar at 28 days and 36 weeks postmenstrual age. About 78% of infants in both groups survived at 36 weeks and were able to breathe on their own.

Previous trials have established that early surfactant therapy (as opposed to delayed therapy) improves outcomes for high-risk preemies. Nasal CPAP is often used instead of intubation and mechanical ventilation in very small preemies. Studies have shown that nCPAP, then intubation, the administration of surfactant, and the use of mechanical ventilation only if nCPAP fails, reduces the need for MV, and this protocol reduces the incidence of BPD without increased mortality.

The babies selected to participate in the study were intubated with 200 mg/kg of Curosurf and manually ventilated, then extubated to nCPAP within an hour if they evinced respiration. (If not, they were placed on mechanical ventilation.) Infants extubated to nCPAP after their dose of surfactant were mechanically ventilated if nCPAP failed. (Failure criteria included inability to maintain viable oxygen saturation, apnea, and respiratory acidosis.) Nasal CPAP was delivered by the Infant Flow nasal prong/mask at a pressure of 6-7 cm H_2O, and a subsequent 100 mg/kg dose of surfactant was administered to infants on MV if indicated. Extubation and placement on nCPAP was determined by FiO_2 of 0.4 to maintain pulse oximetry readings of 85-92%, and evidence of low ventilator pressures. Infants in both groups reached primary outcomes in the hour after surfactant was administered.

Information for this article is from the paper, "Prophylactic or Early Selective Surfactant Combined With nCPAP in Very Preterm Infants," by Fabrizio Sandri, Richard Plavka, Gina Ancora, Umberto Simeoni, Zbynek Stranak, Stefano Martinelli, Fabio Mosca, José Nona, Merran Thomson, Henrik Verder, Laura Fabbri, Henry Halliday and for the CURPAP Study Group. The original article was published by Pediatrics, (published online May 3, 2010). PEDIATRICS is the official journal of the American Academy of Pediatrics. PEDIATRICS is owned, published and trademarked by the American Academy of Pediatrics, copyright 2010 by the American Academy of Pediatrics. All rights reserved. Original article provided to Neonatal Intensive Care by Cornerstone Therapeutics.

The researchers predicted that half of the 25 to 28 week gestation age infants would require mechanical ventilation. The goal was to see if using prophylactic surfactant reduced this to 30%.

Two hundred eight newborns were enrolled at 24 European NICUs. Thirty-three infants in the prophylactic surfactant group required mechanical ventilation in their first five days, compared to 34 in the nCPAP group. Ten of 105 babies couldn't be extubated after surfactant administration; 19 of 50 who received surfactant in the nCPAP group couldn't be extubated; reintubation was necessitated for 23 of 95 in the surfactant group and 15 of 31 in the surfactant plus nCPAP group. The median range of hospitalization days was 68 in the surfactant group and 71 in the nCPAP group. Hours on mechanical ventilation were 128.8 in the former and 183.8 in the latter. Fifty infants (nearly half) in the nCPAP group needed early surfactant at a median age of four hours; Fourteen babies in the surfactant group needed a second dose, compared with 11 in the nCPAP group.

The authors found that early nCPAP, surfactant treatment and mechanical ventilation are complementary strategies, and stated, "Our study shows that, in spontaneously breathing preterm newborns who were treated with nCPAP, prophylactic surfactant given within 30 minutes of birth was not superior to early selective surfactant in terms of requirement of MV in the first 5 days of life. Prophylactic surfactant treatment within 15 minutes of birth reduced mortality compared with later selective surfactant treatment… Our findings suggest that in spontaneously breathing newborns of 25 to 28 weeks' GA, it is possible to initiate nCPAP and treat with surfactant later only when they show signs of RDS… In summary, our results show that nearly one-third of infants who were intubated for surfactant administration can be successfully extubated to nCPAP at these low GAs." The study revealed good respiratory outcome overall, with a 78-79% survival rate for infants without supplemental oxygen or ventilatory support at 36 weeks postmenstrual age. Incidences of BPD were 14.3 and 11.7% in the surfactant and nCPAP group, respectively. Said the authors, "the respiratory management used in our study combining extensive use of nCPAP with either prophylactic or early selective surfactant seems to be both safe and efficacious in spontaneously breathing infants of 25 to 28 weeks' GA." Other complications related to prematurity were insignificant in the two groups, and the length of mechanical ventilation and hospitalization in the two groups was also similar. Additional surfactant dosing after the initial dose also didn't produce different results.

The authors recommended that nCPAP "should be started soon after birth in spontaneously breathing infants of 25 to 28 weeks' GA and early selective surfactant should be given once signs of respiratory distress have developed." Using this strategy, half of infants will need just nCPAP, 48.5% will need to be intubated and receive surfactant, and a third will need mechanical ventilation during their first five days.

Cancer, Infant Mortality and Birth Sex-Ratio in Fallujah, Iraq 2005-2009

Chris Busby, Malak Hamdan, Entesar Ariabi

Abstract: There have been anecdotal reports of increases in birth defects and cancer in Fallujah, Iraq blamed on the use of novel weapons (possibly including depleted uranium) in heavy fighting which occurred in that town between US led forces and local elements in 2004. In Jan/Feb 2010 the authors organised a team of researchers who visited 711 houses in Fallujah, Iraq and obtained responses to a questionnaire in Arabic on cancer, birth defects and infant mortality. The total population in the resulting sample was 4,843 persons with and overall response rate was better than 60%. Relative Risks for cancer were age-standardised and compared to rates in the Middle East Cancer Registry (MECC, Garbiah Egypt) for 1999 and rates in Jordan 1996-2001. Between Jan 2005 and the survey end date there were 62 cases of cancer malignancy reported (RR=4.22; CI: 2.8, 6.6; p<0.00000001) including 16 cases of childhood cancer 0-14 (RR=12.6; CI: 4.9, 32; p<0.00000001). Highest risks were found in all-leukemia in the age groups 0-34 (20 cases RR=38.5; CI: 19.2, 77; p<0.00000001), all lymphoma 0-34 (8 cases, RR=9.24;CI: 4.12, 20.8; p<0.00000001), female breast cancer 0-44 (12 cases RR=9.7;CI: 3.6, 25.6; p<0.00000001) and brain tumors all ages (4 cases, RR=7.4;CI: 2.4, 23.1; P<0.004). Infant mortality was based on the mean birth rate over the 4 year period 2006-2009 with 1/6th added for cases reported in January and February 2010. There were 34 deaths in the age group 0-1 in this period giving a rate of 80 deaths per 1,000 births. This may be compared with a rate of 19.8 in Egypt (RR=4.2 p<0.00001) 17 in Jordan in 2008 and 9.7 in Kuwait in 2008. The mean birth sex-ratio in the recent 5-year cohort was anomalous. Normally the sex ratio in human populations is a constant with 1,050 boys born to 1,000 girls. This is disturbed if there is a genetic damage stress. The ratio of boys to 1,000 girls in the 0-4, 5-9, 10-14 and 15-19 age cohorts in the Fallujah sample were 860, 1,182, 1,108 and 1,010 respectively suggesting genetic damage to the 0-4 group (p<0.01). Whilst the results seem to qualitatively support the existence of serious mutation-related health effects in Fallujah, owing to the structural problems associated with surveys of this kind, care should be exercised in interpreting the findings quantitatively.

Chris Busby is with the Department of Molecular Biosciences, University of Ulster. The co-authors reside in London. The authors wish to thank Abdulmunaem Almula and Eva Ehrstedt and the members of the team in Fallujah who obtained the results and to all of those individuals who answered the questionnaires. Reprinted from BioMed Central, International Journal of Environmental Research and Public Health,

Introduction

There have been several media reports of apparent excess rates of cancers and birth defects in the town of Fallujah in Iraq, some 50 miles west of Baghdad.[1-3] In 2004, one year after the end of the second Persian Gulf War in March 2003 there was heavy fighting between US led occupation troops and Iraqi elements in this town. Little is known about the types of weapons deployed, but reports began to emerge after 2005 of a sudden increase in cancer and leukemia rates.

Concerns have been expressed for some time about increases in cancer, leukemia and congenital birth anomalies in Iraq. These have been blamed[4] on mutagenic and carcinogenic agents (like depleted uranium) employed in the wars of 1991 and 2003. Increases in childhood leukemia in Basra have recently been investigated[5] and the findings confirm that there has indeed been a significant increase since 1991. Unfortunately, since many reports from Iraq and Fallujah have been anecdotal, and have rarely been backed up by any population-based epidemiological evidence, it is difficult in these cases to assess the validity of the various assertions. Questionnaire survey studies have a long history of use in areas where there are difficulties obtaining accurate population numbers or illness rates.[6] Epidemiology in post-conflict areas where official population, cancer and birth data are not available can use questionnaire survey methods developed and used earlier in a number of areas of the UK and Ireland. The method is described fully with a sample questionnaire in Busby 2006[7] where breast cancer rates in the town of Burnham on Sea, Somerset were reported. The study was later investigated by the official South West Cancer Intelligence Service and was shown to have given an accurate result for the breast cancer incidence rates.

For these reasons we decided to conduct such a survey study in Fallujah.

Method

Between Jan 20th and Feb 20th 2010 a team of 11 researchers visited houses in an area of Fallujah Iraq. They administered a questionnaire in Arabic on cancer and birth outcomes including infant mortality. It was explained that the purpose of the project was to obtain information which would show what the rates of cancer and birth effects were, that all personal information would remain completely confidential and that the results would be made available when the study was completed. The interviewer and the household member then filled out the questionnaire together. The interviewee then gave their

Table 1. Sex and 5-year age group population in the Fallujah response sample; also calculated is the Sex ratio (males per 1000 females) in the four groups aged 0-19.

Age Group	Males	Females	Sex Ratio
0–4	234	272	860
5–9	481	407	1,182
10–14	388	350	1,109
15–19	393	389	1,010
20–24	166	213	
25–29	182	224	
30–34	129	106	
35–39	157	93	
40–44	71	133	
45–49	144	67	
50–54	61	58	
55–59	31	13	
60–64	31	10	
65–69	9	6	
70–74	17	0	
75–79	3	1	
80–84	1	2	
85+	1	0	
Total	2,499	2,344	

Table 2. Cancers reported in responses from January 1st 2005 to January 31st 2010.

Cancer	Males	Females	Total
All malignancy all ages	28	34	62
Childhood cancer ages 0–14	6	10	16
Leukemias all ages	16	6	22
Lymphomas all ages	9	1	10
Brain tumours all ages	2	2	4
Breast cancer (f) all ages	0	13	13

Table 3. Infant deaths reported from 2004.

Year reported died (Approximate birth year)	Number of infant deaths 0–1 years
2004 (2003)	1
2005 (2004)	0
2006 (2005)	8
2007 (2006)	4
2008 (2007)	6
2009 (2008)	10
2010 first 2 months only (2009)	6

personal identification number and the address of the house was recorded. In general people were anxious to cooperate in order to discover the true level of cancer and birth problems in the area. This has generally been found to be the case in other surveys of this type.[7] However, it was found that in some areas there was considerable distrust and fear that the questions were part of some secret-service operation and householders refused to participate; on one occasion the interview team was physically attacked. Following this, the teams were always accompanied by a local person of some reputation or standing in the community. It is estimated that the final refusal rate per house visited was less than 30%. However this 30% was almost entirely from one single area where the locals were particularly suspicious and where the teams had visited early in the survey period without a local person to vouch for the study. The final number of houses responding to the questionnaire was 711 and the total population in the resulting sample was 4,843 persons.

The ethical aspects of conducting such a study were considered in some depth. In contemporary Iraq it would have been impossible to obtain ethical committee approval even if such a body existed, which it does not. The authorities have consistently avoided examining the health of communities which have complained of increases in ill health, and little has been done by the international community. Indeed, shortly after the questionnaire survey was completed, Iraqi TV reportedly broadcast that a questionnaire survey was being carried out by terrorists and that anyone who was answering or administering the questionnaire could be arrested. In general, the provisions of the Helsinki protocol were followed insofar as no one was coerced and all confidentiality was assured.

The questionnaire method has strengths and weaknesses. Its main strength is that it obtains the sex and age breakdown of the current population: in this aspect it is essentially a census of the study population at the time of the survey. No official census data would be as accurate as this, and in a post war situation no accurate census to this level of resolution exists. It also obtains the cancer data in the study population in the last ten years; the questionnaire asks for details of all cancers in the household (sex, age at diagnosis, site or type of cancer, name of clinic or doctor which diagnosed and survival).

One weakness of this type of study is population leakage due to migration. Although ten years is used on the questionnaire, from analysis in earlier studies of this kind[7] it has become clear that there is leakage of cases (due to deaths and subsequent population movements) and so the recent five year period is employed. However, as a consequence of such a population leakage it is clear that the result will show the minimum cancer rates existing in the study group. In earlier studies this effect was especially found for lung cancer which has a high mortality to incidence ratio. One other weakness is that the questionnaire could in principle be manipulated by those who do not honestly report the cancer cases in the household: no independent confirmation of the cases is made, although in principle it would be possible to do this since the individuals give their identity numbers and names of the doctors or clinics where they were treated. Our belief is that those in the present study group gave accurate answers to the questionnaire since in present day Iraq the public would be fearful of giving both misleading data and also at the same time their identities.

The population at the time of the questionnaire is used as a surrogate for the mean population over the 5-year study period and this may introduce some inaccuracies into the analysis. The question of selection bias does not arise in this case since the questionnaires were administered to a random sample of those houses in the study area selected by the interviewees and responses were random. However, the 30% who refused to respond were all from one area initially visited before it was decided to bring a local person to vouch for the study, and so it is not thought that their exclusion introduced bias. These structural problems listed above are accepted and should be borne in mind. They may be used to place limits to the accuracy of the results and we will therefore return to examine this in the Discussion Section.

Table 4. Relative Risks of cancer in Fallujah 2005–2010. Reported (Rep) and expected (Exp) numbers of cases and statistics for main classes of cancer and leukaemia/lymphoma observed. Expected numbers calculated on the basis of rates for 1999 in Egypt and checked against rates reported for Jordan 1996–2001.

Cancer	Rep	Exp	RR	95% CI	Chisq	p-value <
All malignancy all ages	62	14.7	4.2	2.8 < RR < 6.6	50.9	0.00000001
Childhood cancer 0–14	16	1.27	12.6	4.9 < RR < 32	46.3	0.00000001
Breast cancer (f) all ages	13	2.46	5.3	2.4 < RR < 11.8	20.75	0.00002
Breast cancer (f) 0–44	12	1.24	9.7	3.6 < RR < 25.6	30.9	0.00000002
Leukaemia all ages	22	0.99	22.2	12.1 < RR < 41	212	0.00000000
Leukaemia 0–35	20	0.52	38.5	19.2 < RR < 77	287	0.00000000
*Lymphoma all ages	9	2.11	4.27	1.3 < RR < 14	6.95	0.008
*Lymphoma 0–35	8	0.865	9.24	4.12 < RR < 20.8	43.8	0.00000000
Brain tumours all ages	4	0.542	7.4	2.4 < RR < 23.2	16.2	0.004

*The class Lymphoma may be contaminated with lymphatic metastases of common tumours.

Table 5. Infant deaths and births 1st January 2006 to 28th February 2010 with comparisons with Egypt, Jordan and Kuwait. Mean annual birth rate is calculated from the reported 0–4 population.

Birth and deaths information	Value
0–4 population reported	506
Mean Annual birth rate	101.2
Births in the period 2006–2010+ (50 months)	425
Reported deaths in the period	34
Rate per thousand births in Fallujah 2006–2010+	80
Reported deaths in the period 2009–2010+ (14 months)	16
Rate per thousand births in Fallujah 2009–2010+ (14 months)	136
Rate in Kuwait 2008	9.7
Rate in Egypt 2008	19.8
Rate in Jordan 2008	17

Infant mortality

The questionnaire investigated infant mortality by asking each household if any child aged 0-1 had died in the previous ten years; again a 5-year period was employed in the analysis. The cause of death was also asked for. Researchers found that interviewees were very sensitive to the question about birth defects since there is a stigma attached to admitting to such an event in the family; a similar situation has been reported for the Hiroshima survivors.[7] There was no apparent problem with admitting an infant death, without explaining the cause, and therefore in this study, infant mortality is a better indicator of the birth outcomes than the answer to the cause of infant death and this is what was employed. For infant mortality, the mean annual birth rate was assessed from the population data as 1/5th the 0-4 population and the number of infant deaths per thousand births was obtained. This was compared with infant mortality in Egypt, Jordan and in Kuwait. Sex ratio was calculated from the population data directly. The population data in 5-year age groups was used to examine the sex ratio in 5-year birth cohorts.

The national cancer rates in Iraq are not currently available; use of earlier Iraq cancer rates would bias the results since the whole country has been affected by post-war contamination following the 1991 and 2003 conflicts to various putative carcinogens, including oil fires, heavy metals and uranium from weapons. Therefore the cancer relative risks were calculated by applying 5-year sex and age group rates from the Middle East Cancer Registry (Gharbiah)[8] in Egypt for 1999 to the study group population to give an expected number of cases of all malignancies, breast cancer, leukemia, lymphoma and brain tumors in 5 years. The reported number in the previous 5-year period in the study group was then divided by this expected number to give a relative risk RR for the cancer. Standard contingency table statistical methods were employed to assess the results. The MECC Egypt age and sex specific rates were compared with the rates in Jordan[9] to check that there were no anomalous rates in Egypt which might bias the results. Age specific incidence rates for the cancers studied were broadly similar in Egypt and in Jordan.[9] The rates in Kuwait were not used since it was thought that the standard of living in Kuwait and also its proximity to contamination from the 1991 and 2003 Gulf Wars might make its use as a standardizing population questionable.

Results and Discussion

The population base obtained from the questionnaires was 711 households with 4,843 persons. The sex and age breakdown by 5-year groups is given in Table 1. Reported cancers from Jan 1st 2005 to the end of January 2010 are given in Table 2. Cancers reported before 2005 were not included. All cancer and infant death cases reported were checked against duplicate sex and age patterns to ensure there was no double reporting; if there was any doubt, data was discarded (one such instance was found). Table 3 shows the infant mortality cases reported from 2004 and includes reports of deaths in the first two months of 2010.

In Table 4 the reported numbers of cancers are compared with expected numbers for 5-year period 2005 to the sample cutoff date in 2010. The expected numbers are calculated by applying the sex and 5-year age group rates obtained from the Middle East Cancer Consortium[8] for Egypt 1999 and also checked against rates in Jordan[9] 1996-2001.

Table 5 shows the mean infant mortality rate per 1000 births for the period 2006-2010 including deaths reported in the first two months of 2010. Also shown are rates for the period from 1st January 2009 and comparisons are made with infant mortality rates in Jordan, Egypt and Kuwait.

The responses show that there is an anomalous sex ratio in the 0-4 age group. There are 860 males to 1000 females, a significant 18% reduction in the male births from the normal expected value of 1,055 (267 boys expected, 234 observed; $p<0.01$) Perturbation of the sex ratio is a well known consequence of exposure of mutagenic stress and results from the sensitivity of the male sex chromosome complement to damage (the females have two X chromosomes whereas the males have only one). A number have studies have examined sex-ratio and radiation exposure of mothers and fathers. Of relevance is the study of Muller et

al.[10] of the offspring of 716 exposed fathers who were Uranium miners. There was a significant reduction in the birth sex ratio (fewer boys). Lejeune et al. (1960)[11,12] examined the offspring of fathers who had been treated with pelvic irradiation; at high doses there was an increase in the sex-ratio, but this reversed in the low doses (around 200 mSv). Schull et al. 1966[13] found a reduction in the sex ratio in A-Bomb survivor fathers (mothers "unexposed") for children born 1956-1962 a reversal of an earlier finding by Schull and Neel 1958[14] of a positive effect in the 1948-1955 births. It should be noted that there were external and internal irradiation effects in these groups, with the internal effects predominating in the later years. Yoshimoto et al. 1991[15] found an overall reduction in the sex ratio for A-Bomb survivors for children born 1946-1984. Thus the evidence suggests that exposure to ionising radiation at low doses and specifically exposure to Uranium may cause a reduction in the sex ratio.

It is clear that the 0-4 population, born in 2004-2008, after the fighting, is significantly 30% smaller than the 5-9, 10-14 and 15-19 populations. This could be a result of lower fertility or early foetal losses in this cohort. It has been pointed out by a referee that it might also in principle be a result of the deaths of men in the 2004 fighting but this does not seem to be supported by the sex ratios in the men and women aged 25 and over. The infant mortality numbers reported by year point to sudden increase in deaths in 2006 (Table 3). There was only one death reported for the two years 2004 and 2005 in the sample population. For the period from 2006 to the end of the survey there was a mean death rate of 80 per 1,000 births, more than 4 times the rate in Egypt and in Jordan ($p<0.00001$) and some 9 times the rate in Kuwait. The rate seems to have increases markedly after 2009 to a rate of 136 per 1,000 births. These results support the many reports of congenital illness and birth defects in Fallujah and suggest that there is evidence of genetic stress which appeared around 2004, one year before the effects began to show.

The results for cancer show some alarming rates in the 5-year period. Relative Risk based on the Egypt and Jordan cancer rates are significantly higher for all malignancy, leukemia, lymphoma, brain tumors and female breast cancer. Between January 2005 and the survey end date there were 62 cases of cancer (all malignancies) reported (RR=4.22; CI: 2.8, 6.6; $p<0.00000001$) including 16 cases of childhood cancer 0-14 (RR=12.6; CI: 4.9, 32; $p<0.00000001$). Highest risks were found in all leukemia's in the age groups 0-34 (20 cases RR=38.5; CI: 19.2, 77; $p<0.00000001$), all lymphomas 0-34 (8 cases, RR=9.24;CI: 4.12, 20.8; $p<0.00000001$), female breast cancer 0-44 (12 cases RR=9.7;CI: 3.6, 25.6; $p<0.00000001$) and brain tumors all ages (4 cases, RR=7.4;CI: 2.4, 23.1; $P<0.004$). These results for cancer also support the idea that there has been exposure to some mutagenic agent at some time in the past. Could this have been around 2004 when the fighting occurred? The answer depends upon whether it is plausible to accept such a short time lag between exposure and clinical expression of the cancer, leukemia or lymphoma. It is commonly believed that the lag between initiation and expression of cancer is a significant period: for exposure to acute external low LET radiation the onset of leukemia is stated to be about 5 to 7 years, and for breast cancer and solid tumors as high as 15 to 20 years. However, genetic damage expansion models for cancer[16,17] hold that it is the acquisition of a key number of mutations which lead to final clinical expression. This is then seen as purely probabilistic so long as the mutagenic stresses are constant; in this way the exponential increases in cancer rates with age are explained as are cancer rates and initiation expression lags in cell populations with different natural replication rates. However, such an explanation makes it also clear that the sudden (spike) introduction of a mutagenic stress could supply a final key mutation in those individuals who already carry almost the full necessary complement of mutations for the specific cancer.[18] This idea explains many observations of increases in cancer shortly (a few years) after an exposure. For example, there seems to have been a rapid increase in lymphoma in Italian peacekeepers potentially exposed to depleted uranium in the Balkans.[19] Tondel et al have reported increased cancer risk in Northern Sweden peaking less than 5 years after the Chernobyl contamination and significantly associated with the levels of Caesium-137 fallout in municipalities.[20] Despite the assertions of the studies of the Japanese A-Bombs (which did not begin until 1952) that the first increases in leukemia in the study group appeared more than 5 years after the bomb, leukemia in victims of Hiroshima and Nagasaki was reported beginning only months after the explosion, and even in those who had not been exposed to the prompt radiation but to fallout and uranium in the bombed city debris.[21] Furthermore, the onset lag for internal exposure to high LET radiation (eg, Uranium) has not been determined and it can be argued that this lag cannot be deduced from the external low LET studies that make up the current radiation risk model. On the other hand, it may be that the increases in cancer found here for some individuals are the result of some earlier exposure, perhaps during the 1991 Gulf War. The origin and time of introduction of the carcinogenic agent causing the effects found here will be the subject of a separate report. However it does not seem unreasonable to conclude that the causes of the infant deaths and the cancer increases are one and the same.

We must finally address the earlier listed shortcomings of the interview questionnaire survey method. These might have been of concern had the findings been less clear but since the Relative Risks for the various indicators were extremely high, it can hardly be possible that these results could have occurred through errors introduced through any of the potential problems outlined in the Methods Section. A 100% error in the population would only halve the relative risks. The levels of cancer and infant mortality which have been found are too great to be accommodated by any hypothesis except that a significant proportion of those interviewed completely invented the results, and for the reasons already given i.e., that they had given names, addresses and identities and the names of the doctors and clinics involved in an area where the consequences of giving misleading responses to questions are severe, this seems highly unlikely.

Conclusions

This study was intended to investigate the accuracy of the various reports which have been emerging from Fallujah regarding perceived increases in birth defects, infant deaths and cancer in the population and to examine samples from the area for the presence of mutagenic substances that may explain any results. We conclude that the results confirm the reported increases in cancer and infant mortality which are alarmingly high. The remarkable reduction in the sex ratio in the cohort born one year after the fighting in 2004 identifies that year as the time of the environmental contamination. In our opinion, the magnitude of these effects make it difficult to question them on the basis of any of the hypothetical shortcomings of the study type which we have considered although these must be borne in mind. However, owing to the various constraints placed by circumstance on the methods employed, we must emphasise that the results of this study should be interpreted with those

aspects in mind. Finally, the results reported here do not throw any light upon the identity of the agent(s) causing the increased levels of illness and although we have drawn attention to the use of depleted uranium as one potential relevant exposure, there may be other possibilities and we see the current study as investigating the anecdotal evidence of increases in cancer and infant mortality in Fallujah.

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Health Implications Resulting from the Timing of Elective Cesarean Delivery

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Abstract

Background: The literature is nearly unanimous in recommending elective cesarean delivery at 39 weeks of gestation because of the lower rates of neonatal respiratory complications compared to 38 weeks. However, elective cesarean delivery at 39 weeks or more may have maternal and other fetal consequences compared to delivery at 38 weeks, which are not always addressed in these studies.

Discussion: Between 38 and 39 weeks of gestation, approximately 10%-14% of women go into spontaneous labor; meaning that a considerable number of women scheduled for an elective cesarean delivery at 39 weeks will deliver earlier in an unscheduled, frequently emergency, cesarean delivery. The incidence of maternal morbidity and mortality is higher among women undergoing non-elective cesarean deliveries than among those undergoing elective ones. Complications may be greater among women after numerous repeat cesarean deliveries and among older women. Other than reducing the frequency of non-elective cesarean deliveries, bringing forward the timing of elective cesarean delivery to 38 weeks, may occasionally prevent intrauterine fetal demise which has been shown to increase with increasing gestational age and to avoid other fetal consequences related to the emergency delivery. All these considerations need to be weighed against the medical and the economic impact of the increase in neonatal morbidity resulting from births at 38 weeks compared to 39 weeks.

Summary: Until prospective randomized trials are conducted, we are unlikely to be able to precisely answer all risk:benefit questions as to the best timing of scheduled elective cesarean delivery. Older women, and women with numerous prior cesarean deliveries, are of particular concern. It is reasonable to inform the pregnant women of the risk of each of the above options and to respect her autonomy and decision-making.

Background

The literature is nearly unanimous in recommending elective cesarean delivery at 39 weeks of gestation because of lower rates of neonatal respiratory complications compared to 38 weeks. However, elective cesarean delivery at 39 weeks or more may have maternal and other fetal consequences compared to delivery at 38 weeks, which are not always addressed in these studies. Delaying delivery for an additional week increases the time that the woman and her fetus is vulnerable to a number of unexpected complications and increases the proportion of women who will deliver by non-elective cesarean delivery rather than an elective one.

The outcome of this particular group of women is less addressed in the literature when discussing the advantages of elective cesarean deliveries since the majority of published studies on elective cesarean delivery exclude from statistical analysis women who delivered non-electively before the scheduled date of delivery. Other studies combined this cohort of patients with those that delivered electively so that it is impossible to isolate the contribution of non-elective delivery to the outcome. A design centered on the actual delivery route will allow investigators to distinguish between labored and unlabored cesarean deliveries. In studies limited to unlabored cesareans, women who present in labor before their scheduled date of delivery are, by definition, excluded. Excluding these women may overestimate potential benefits and also potential harms because the studies then cannot account for any effect that labor has on outcomes of interest. Landon et al[1] investigated maternal and perinatal outcomes among women who underwent an elective repeat cesarean delivery. Women who were designated for an elective cesarean delivery but presented in early labor were excluded from the study. The authors stated that exclusion from the study of women who presented in early labor and subsequently underwent repeated cesarean delivery probably lowered the risk of complications in the group of women undergoing elective repeated cesarean delivery.[1]

Thomas et al reported that 10% of women go into spontaneous labor between 38 and 39 weeks of gestation.[2] Obstetrical data from 25,533 women delivered between the years 2003 to 2008 in our delivery ward (Obstetrics and Gynecology Department, HaEmek Medical Center in Afula, Israel, a university teaching hospital) revealed that 14% of ongoing pregnancies went into spontaneous labor between 38 to 39 weeks (unpublished data). The meaning of these numbers is that over 10% of elective cesarean deliveries scheduled to 39 weeks will likely convert to non-elective ones between 38 to 39 weeks.

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A search of PubMed, MEDLINE, EMBASE, and Cochrane Library databases up to December 2009, did not detect any randomized controlled trial that compared the timing of elective cesarean delivery at 38 or 39 weeks and which investigated both perinatal and maternal outcomes.

In this report we address some of the maternal and perinatal consequences resulting from scheduling elective cesarean delivery at 39 weeks rather than 38 weeks. We claim that scheduling elective cesarean delivery at 38 weeks is a viable alternative with potential benefits particularly for older women and women with numerous prior cesarean deliveries.

Discussion

Women assigned to an elective cesarean delivery may go into labor prior to the scheduled date of surgery. Laboring women might present during the early stages of labor, with or without membrane ruptures, or alternatively they may present during advanced stages of labor. Maternal and neonatal outcomes may be adversely affected when cesarean delivery is preceded by labor, even if labor is not advanced.

Fetal and neonatal consequences: The implication of scheduling delivery to 39 weeks is that a proportion of elective cesarean deliveries will convert to non-elective ones, which may increase the risk of traumatic injury to the fetus/newborn.[3] The reported incidence of iatrogenic fetal trauma during cesarean delivery is 0.1% to 1.9% of births.[4] Several risk factors for fetal injury at the time of the cesarean delivery have been identified through various case reports. These include lack of surgical experience, labor with thinning of the lower uterine segment exposing the fetus to injury with the scalpel, and a lack of amniotic fluid secondary to rupture of the membranes making the underlying fetal parts more accessible.[5,6] Fetal lacerations, finger injuries and amputations, penetrating brain injuries, skull fractures and long bone fractures have all been reported from the use of the scalpel or scissors at the time of cesarean delivery.[3] Although traumatic delivery is still associated with cesarean delivery, it is almost unheard of with elective cesarean delivery of the vertex fetus at term.[3]

In the term breech trial, 6% of women who were assigned to a planned cesarean delivery, delivered vaginally because cesarean delivery was not possible due to imminent vaginal delivery.[7] Delaying an elective cesarean delivery scheduled for breech presentation may expose some of the fetuses to preventable morbidity and mortality associated with vaginal breech delivery in cases where vaginal delivery is imminent at admission.

An accumulative increased risk of intrauterine fetal death has been reported with increasing gestational age. The timing of fetal death for stillborn infants born between 23 and 40 weeks is evenly distributed with nearly 5% of all stillbirths occurring per week of gestation.[8] This is important when considering all stillborn infants at 38 weeks and beyond, where significant complications of prematurity would be very rare if only these fetuses had simply been delivered earlier. Furthermore, it has been reported that a fairly stable rate of fetal death of 0.6 per 1000 live births occurs from 33 weeks to 39 weeks of gestation. However, at 39 weeks, the rate increases significantly to 1.9 per 1000 live births.[9] De la Vega and coworkers in a mixed risk population with unrestricted access to testing for fetal wellbeing and sonographic evaluations concluded that, despite intensive surveillance, they were still unable to reduce the rate of fetal death. The investigators suggested that this is probably due to occurrence of acute placental and cord accidents that cannot be detected through antenatal fetal surveillance and are simply unavoidable.[10] The sudden death of a fetus in utero has medical, social and economic implications. It is particularly tragic when it occurs shortly before the expected date of delivery.

Table 1. Neonatal and current clinical characteristics of the 35 children born extremely preterm

Number of boys, n (%)	13 (37)
Gestational age (weeks)[a]	26.7 (1.7)
Birth weight (grams)[a]	933 (204)
Impaired hearing, n (%)	2 (5.7)
Epilepsy, n (%)	3 (8.6)
ADHD b), n (%)	2 (5.7)
Mild mental retardation, n (%)	5 (14.3)
Intraventricular hemorrhage grade 1-2, n (%)	8 (22.9)
Maternal infection, n (%)	11 (31.4)
Prenatal steroid treatment, n (%)	15 (42.9)
Neonatal steroid treatment, n (%)	10 (28.6)
Days on ventilator[a]	8.3 (11.8)
Oxygen treatment (days)[a]	57.4 (48.0)
Boys *	81.7 (59.9)
Girls *	43.0 (33.1)
Bronchopulmonal dysplasia	
- none; n (%)	9 (25.7)
- mild[c]; n (%)	14 (40.0)
- moderate/severe[d]; n (%)	12 (34.3)
Age when assessed (years)[a]	10.5 (0.4)

a) Mean (standard deviation)
b) Attention Deficit Hyperactivity Disorder
c) Requirement for oxygen treatment at age 28 postnatal days
d) Requirement for oxygen treatment at 36 weeks postmenstrual age
*Boys vs. girls p-value = 0.047 (independent sample t-test)

Maternal consequences: Hansen et al reported in a cohort study that a significant reduction in neonatal respiratory morbidity may occur if elective caesarean delivery is postponed to 39 weeks. Carrying out elective cesarean deliveries at a later gestational age resulted in higher rates of laboring cesarean deliveries since some women went into spontaneous labor. Twenty-five percent of women entered labor before the 39th week in their cohort. They also stated that compared with elective cesarean deliveries, laboring cesarean deliveries may carry an increased risk of complications such as uterine rupture, infections, or even maternal mortality.[11]

Severe maternal morbidities including deep vein thrombosis, pulmonary embolism, amniotic fluid embolism, puerperal infection, severe hemorrhage, uterine rupture or inversion and intestinal obstruction have been reported to be significantly more frequent in non-elective than in elective cesarean deliveries. Operative interventions after delivery were also significantly more frequent after a non-elective cesarean delivery.[12] Operator experience and the emergency nature of the cesarean delivery were found to be risk factors for bladder injury during cesarean delivery.[13]

The overall risk of uterine rupture among women who go into spontaneous labor is higher compared to women who had an elective cesarean delivery. The risk of rupture is greater among parous women with multiple prior cesarean

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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 proteins 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 and 25% 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 15,500 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 no discharge for all treated patients from this treatment trial are shown in

Table 1- Infasurf vs Exosurf Neonatal®: Treatment Trial

Efficacy Parameter	Infasurf® (N=570) %	Exosurf Neonatal® (N=556) %	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]	1	1	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 853 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=435) %	Exosurf Neonatal® (N=422) %	p-Value
Incidence of RDS	15	27	<0.001
Incidence of air leaks[1]	10	15	0.01
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 427 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 fractions of inspired oxygen (FiO_2) 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 (16%), 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=1011) %	Exosurf Neonatal® (N=978) %	Infasurf® (N=553) %	Survanta® (N=566) %
Apnea	61	61	56	56
Patent ductus arteriosus	47	48	45	48
Intracranial hemorrhage	29	31	36	36
Severe intracranial hemorrhage[1]	12	10	9	7
IVH and PVL[2]	7	5	5	5
Sepsis	20	22	28	27
Pulmonary air leaks	12	22	15	15
Pulmonary interstitial emphysema	7	17	10	10
Pulmonary hemorrhage	7	7	7	6
Necrotizing enterocolitis	5	5	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 615 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). HOLD 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 respiratory 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 $PaO_2 \geq 80$ 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, dislodgement 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 61938-456-03) and 6 mL (NDC 61938-456-06) 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

Table 2. Adjusted [a]mean differences in CHQ-PF 50 [b]scores between preterms and matched control children

CHQ sub-scales	Boys Mean (95% CI)	Girls Mean (95% CI)	Interaction p-value gender × preterm/ control
Roles/social emotional	-21.7 (-35.1, -8.3)	-1.8 (-12.1, 8.5)	0.01
Parental impact-time	-19.4 (-31.3, -7.5)	-4.5 (-13.6, 4.6)	0.04
Parental impact-emotional	-25.8 (-41.5, -10.2)	-4.1 (-16.1, 7.9)	0.02
Behavior	-22.3 (-35.6, -9.1)	-4.5 (-14.7, 5.7)	0.02
Psychosocial summary score	-11.0 (-17.9, -4.1)	-2.2 (-7.5, 3.0)	0.03
	With learning or attention problems Mean (95% CI)	**Without learning or attention problems Mean (95% CI)**	**Interaction p-value attention/learning × preterm/control**
General health	-20.5 (-31.7, -9.3)	-2.0 (-16.1, 12.2)	0.02
Parental impact-time	-17.1 (-26.5, -7.8)	2.9 (-9.6, 15.4)	0.01
	Adjusted[a] results without interaction Mean (95% CI)		
Physical functioning	-3.9 (-8.1, 0.4)		
Role/social physical	1.4 (-6.2, 9.0)		
Bodily pain	5.0 (-5.2, 15.3)		
Self-esteem	-3.4 (-12.3, 5.5)		
Mental health	-4.0 (-9.6, 1.8)		
Family activities	-9.2 (-19.3, 0.9)		
Family cohesion[c]	-8.7 (-19.7, 2.3)		
Physical summary score	-1.4 (-5.3, 2.4)		

a) Results are presented adjusted for gender, physical activity, learning and/or attention problems and forced expiratory volume in the first second (% predicted), including the interaction term when this was significant.

b) Child Health Questionnaire-Parent Form 50; scale range 0-100 (except summary scores = norm based values with mean of 50 and standard deviation of 10)

c) Single item score

deliveries, a situation commonly encountered in some regions.[14] Other than maternal morbidity, a ruptured uterus carries a greater risk for perinatal morbidity and mortality.[14]

Although uterine rupture occurs primarily among women during a trial of labor, women assigned to an elective cesarean delivery will occasionally present in the advanced stages of labor before their scheduled date of operation.

Failed intubation and pulmonary aspiration are the leading causes of anesthesia related maternal morbidity and mortality. Fasting for a period of six to eight hours is recommended before an elective cesarean delivery.[15] Women scheduled for an elective cesarean delivery and who go into spontaneous labor may present while not in the fasting state. Performing an immediate operation because the woman is in labor may increase anesthesia related morbidity and mortality. Alternatively, delaying the procedure six to eight hours may increase the likelihood of progression into advanced labor which may further complicate the operation. Furthermore, in women whose indication for a cesarean delivery is human immunodeficiency virus infection or genital herpes, the risk of neonatal infection may increase if abdominal delivery is delayed.

Women with severe urinary incontinence have a marked deterioration in their quality of life, most substantially curtail activities, many become homebound, and for some, urinary incontinence is the defining event that prompts nursing home admission. In the United States each year, an estimated 135,000 women undergo surgery for urinary incontinence.[16] An estimate of direct costs for urinary incontinence in the United States has been reported to be $16 billion per year.[17] Given the substantial public health burden of pelvic floor disorders, much research has been focused on identifying risk factors, especially modifiable risk factors, for the development of pelvic floor disorders. Retrospective and cross-sectional studies implicate childbirth as a major risk factor for urinary incontinence in younger women.[18] Whether, and to what degree, cesarean delivery may protect child-bearing women from developing urinary incontinence is an unresolved issue. Several prospective studies evaluated the risk of postpartum urinary incontinence by delivery type, grouping all cesarean deliveries together and reported inconsistent results. In one study, however, elective cesarean deliveries were separated from non-elective ones. Chin et al assessed the impact of delivery on the pelvic floor and to what degree cesarean deliveries could prevent pelvic floor injury. Five hundred thirty nine women were divided into three groups according to the delivery method adopted: elective cesarean delivery, non-elective cesarean delivery, and vaginal delivery. Only elective cesarean delivery was protective. They concluded that the key to the best protection against postpartum urinary incontinence seems to lie in the timing of the cesarean delivery; that is, the cesarean delivery has to be performed before labor or uterine contractions have commenced.[19]

Delaying delivery until 39 weeks may increase the risk for pregnancy complications such as gestational hypertension, preeclampsia, and eclampsia that are known to increase in incidence from 37 to 43 weeks when calculated according to ongoing pregnancies.[20]

Data suggests an increased risk of maternal mortality with non-elective cesarean deliveries as compared with elective ones. The Report on Confidential Enquiries into Maternal Deaths, 1997 to 1999, reported a significantly higher maternal mortality rate with emergency and urgent cesarean deliveries.[21] Another publication reporting on deliveries in Israel between 1984 and 1992 compared maternal mortality among vaginal deliveries, emergency and elective cesarean deliveries. The authors reported maternal mortality rates of 2.8, 3.6, and 30 per 100,000 deliveries for elective cesarean delivery, vaginal delivery, and emergency cesarean delivery, respectively.[22]

Advance maternal age: More women are postponing pregnancy into the fourth and fifth decades of life for a variety of reasons. Advanced maternal age, traditionally defined as over 35 years,

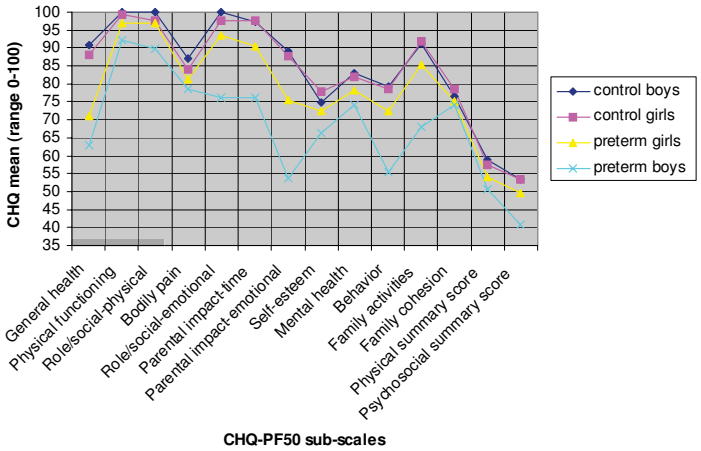

Figure 1. Current clinical and sociodemographic characteristics of the preterm cohort and their matched controls.

The data provided represent the statistical analysis of McNemar, a nonparametric method, and t-test for paired samples to explore group differences between preterm and matched control children on clinical and sociodemographic characteristics.

has been associated with increased obstetric morbidity and interventions. Older women are more likely to have elective cesarean deliveries.[23] The risk for severe complications in non-elective cesarean deliveries is even higher among older women than in younger ones.[12] Furthermore, perinatal complications are reported to be higher among this population.[24] Intrauterine fetal death and perinatal mortality are significantly higher in older women even after excluding deaths due to congenital malformations and adjusting for existing illnesses or pregnancy complications.[25] The highest rate of stillbirth was reported to occur among older women after 38 weeks of gestation.[26]

Health Care Provider Type and Professional Resources:
The availability of resources, such as operating rooms and staff, may influence a health care provider's decision regarding when to schedule the date of the elective cesarean delivery. Non-elective cesarean deliveries, which by definition are poorly timed, may result in a patient that presents in the non fasting state, at a time that the hospital is staffed with less experienced surgeons and anesthetists whose skills are further compromised due to demanding working hours. All these factors present additional challenges to the patients' safety. One of the advantages of scheduled operations is the greater ease of balancing staffing levels with clinical volume. Inadequate levels of staffing, as well as fatigue among health care providers, may contribute to increased patient morbidity.[27,28]

Summary

Multiple chance events may influence outcome. For example, an elective cesarean delivery at 38 weeks may result in the delivery of an iatrogenically premature infant at risk for respiratory morbidity. On the other hand, delaying delivery to 39 weeks may result in an unexplained stillbirth, or spontaneous onset of labor with intrapartum complications that may compromise maternal and neonatal well-being. Decision analysis is a quantitative methodology for evaluating competing strategies under conditions of uncertainty.

According to our data, 14% of all women booked for an elective cesarean delivery at exactly 39 weeks and 0 days, would be expected to go into spontaneous labor between 38 to 39 weeks (unpublished data). For an average hospital with 4500 births a year, such as ours, and a 10% elective cesarean delivery rate, scheduling delivery at 38 weeks rather than 39 weeks will result in an additional 10 neonates with respiratory morbidity a year, assuming an additional 2% neonatal morbidity for those delivered at 38 weeks.[29] On the other hand, 63 non-elective cesarean deliveries will be prevented. In fact, since it is not feasible to book all women to exactly 39 weeks and 0 days, particularly in public medical centers, the number of non-elective operations that would be prevented may actually be higher. Other than decreasing the risk of non-elective cesareans, scheduling elective cesarean deliveries to 38 weeks may prevent cases of fetal death especially among older women.

Until prospective randomized trials are conducted, we are unlikely to be able to precisely answer all risk:benefit questions as to the best timing of scheduled elective cesarean delivery. We believe that if dating is confirmed with an ultrasound study prior to 20 weeks of gestation, scheduling cesarean delivery to 38^{+0-6} weeks may be another reasonable and alternative option to 39 weeks. This is particularly true among a selected group of women, namely older women and women where a complicated cesarean delivery is anticipated. It is reasonable to inform women of the risks entailed with each of the above options. The clinician's role should be to provide the best evidence-based counseling possible to the woman, and to respect her autonomy and decision-making.

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Health Related Quality of Life After Extremely Preterm Birth

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Abstract

Background: The majority of infants born before the last trimester now grow up. However, knowledge on subsequent health related quality of life (HRQoL) is scarce. We therefore aimed to compare HRQoL in children born extremely preterm with control children born at term. Furthermore, we assessed HRQoL in relation to perinatal and neonatal morbidity and to current clinical and sociodemographic characteristics.

Method: The Child Health Questionnaire (CHQ-PF50) and a general questionnaire were applied in a population based cohort of 10 year old children born at gestational age ≤28 weeks or with birth weight ≤1000 grams in Western Norway in 1991-92 and in term-born controls, individually matched for gender and time of birth. The McNemar test and paired t-tests were used to explore group differences between preterms and matched controls. Paired regression models and analyses of interaction (SPSS mixed linear model) were used to explore potential effects of sociodemographic and clinical characteristics on HRQoL in the two groups.

Results: All 35 eligible preterm children participated. None had major impairments. Learning and/or attention problems were present in 71% of preterms and 20% of controls (odds ratio (OR): 7.0; 95% confidence interval (CI): 2.2 to 27.6). Insufficient professional support was described by 36% of preterm vs. 3% of control parents (OR: infinite; CI: 2.7 to infinite). Preterms scored lower on eight CHQ-PF50 sub-scales and the two summary scores, boys accounting for most of the deficits in areas of behavior, psychosocial functioning and parental burden. HRQoL was associated with learning and/or attention problems in both preterm and control children, significantly more so in preterms in areas related to health and parental burden. Within the preterm group, HRQoL was mostly unrelated to perinatal and neonatal morbidity.

Conclusions: HRQoL for children born extremely preterm, and particularly for boys, was described by parents to be inferior to that of children born at term, and sufficiently poor to affect the daily life of the children and their families. Learning and/or attention problems were reported for a majority of preterms, strongly influencing their HRQoL.

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Background

To the benefit of all seriously ill newborns, substantial improvements have occurred in neonatal intensive care during the last decades. In parallel with this development, the survival rates for extremely preterm infants have increased substantially. If resuscitated, approximately 80% of these infants will grow up.[1] One may envision two possible cohort effects from this scenario: Less sequelae due to better treatment or more sequelae due to increased survival of more vulnerable individuals. Repeated and comprehensive long-term follow-up studies are therefore needed to identify areas of concern in this very special population. In this context, one must bear in mind that preterm birth is not a disease entity in itself, but a risk factor for subsequent functional deficits of partly unknown qualities and quantities. Importantly, few of the disorders that have been linked to preterm birth are specific for this population but may somehow be observed also in children born at term, although less prevalent and often with somewhat different appearances. These issues are not well understood, impeding evidence based adjustments of the neonatal treatment and adequate follow-up measures throughout childhood.

Major disabilities (eg cerebral palsy) are generally recognized early, and referred to relevant remedial programs. However, to recognize and foresee the significance of milder impairments may be more difficult.[2] When tested, preterm children generally score poorer on areas related to behavior, emotional health and learning capacity, influencing psychosocial functioning.[3-5] Also with respect to general health, preterm children are at risk of deficits with potential functional consequences, eg reduced lung function and exercise capacity.[6-8] However, the impact from such deficits on the overall well-being of the child and the family is not well described. A systematic review of health related quality of life (HRQoL) research in children born preterm, concludes that preschool children who are born preterm tend to be scored lower by their parents, but that the literature in school-aged children is scarce and the issue therefore important to address.[9]

Interestingly, in the few studies available on adolescents, subjects born preterm report their HRQoL quite similar to peers born at term, while their parents' assessment is significantly lower.[10-12]

HRQoL is a multidimensional construct of physical, psychological and functional well-being, ie subjective information beyond morbidity, as observed from the perspective of a parent or from the child itself, or better, both.[13,14] Even though quality of life (QoL) and HRQoL are related and often used interchangeably they are not identical, as QoL is a broader concept referring more to a child's feelings and appraisal with his or her life while HRQoL somewhat refers to a child's functional status.[15] Functional status may be defined as "the child's ability to perform daily activities that are essential to meet his or her basic needs, fulfill roles, and maintain health and well-being" (Drotar p. 358).[16]

The aim of the present study was to assess HRQoL in 10 year old children born extremely preterm compared to children born at term, and to assess if and how perinatal and neonatal morbidity and current clinical and sociodemographic characteristics were related to HRQoL.

Methods

Subjects: The subjects participated in a comprehensive follow-up study assessing different long-term outcome measures, of which some have been described in detail elsewhere.[6] Briefly, eligible children were born at a gestational age (GA) ≤28 weeks or with a birth weight ≤1000 g in 1991-1992 within a defined region in Western Norway. Of 47 eligible infants admitted to the NICU, 12 (26%) died (seven girls, three boys, two unknown sex). All the 35 survivors participated in this study. Medical care had been provided at the only regional neonatal intensive care unit (NICU) at Haukeland University Hospital, Bergen.

For each preterm, the temporally nearest term born infant of the same gender with birth weight between 3 and 4 kg (Norwegian 10^{th} to 90^{th} centile)[17] was recruited as control. If one potential control subject declined to participate, the next born subject was approached, and so on until one term born child was recruited for each enrolled preterm.

Methods: One pediatrician (TH) assessed current health status in all subjects through a standard medical history and physical examination. Current pulmonary function was described by forced expiratory volume in the first second (FEV_1), measured with Sensor Medics Vmax 22 spirometer (Anaheim, CA, USA) and transformed to percentages of predicted with a standard reference equation.[18] All relevant medical information for preterm and control subjects alike, was available from hospital records. Perinatal and neonatal characteristics were described in terms of maternal infection, use of antenatal corticosteroids, birth weight ratio (ratio between birth weight and the $50^{th.}$ percentile for gestational age) and selected markers of early morbidity, ie cerebral hemorrhage, days on mechanical ventilation, and severity of lung disease (severity of bronchopulmonary dysplasia (BPD) and duration of oxygen treatment).

HRQoL was assessed with the Child Health Questionnaire-Parent Form 50 (CHQ), a validated, generic instrument that measures functional health and well-being of a child through the eyes of a parent. The physical, emotional and social well-being of the child and the perceived burden of the child's health on the family is addressed.[19] The questionnaire follows the definition of health, given by The World Health Organization as "a state of complete physical, mental, and social wellbeing and not merely the absence of disease or infirmity."[20] Health is assessed over several domains including: general health perceptions, physical functioning, role/social physical functioning, bodily pain, role/social emotional and behavioral functioning, parent impact-time and parent impact-emotional, self-esteem, mental health, behavior, family activities and family cohesion. All scales except family cohesion and general health use a recall period of the preceding four weeks. The responses are indicated along an ordered 4 to 6 point Likert-type scale specifying level of agreement to a certain categorical statement such as "very often" to "not at all." The items within each scale are summarized and linearly transformed into a scale of 0 (poor) to 100 (optimal) for each dimension. The instrument also consists of two summary scores, physical and psychosocial, constructed from factor analyses of ten different sub-scales, and standardized based on means and standard deviation (SD) from a combined US population and linearly transformed, yielding a mean score of 50 and a SD of 10. The Norwegian version of this instrument had been validated in a pediatric population with juvenile arthritis with good internal consistency (Cronbach's alpha=0.84), and capacity to discriminate towards healthy subjects and to be sensitive to clinical changes.[21-23] Differences of 5-10 points on a 100-point scale are regarded as clinically significant.[24]

Information on sociodemographic characteristics and the children's functioning were obtained through the CHQ and a questionnaire to the parents, which was developed for the study. Data included parents' education, parents' assessment of their child's school performance and learning or attention problems as reported to them by health professionals or teachers, participation in sport and social activities, extent of professional, academic and psychological support, perceived adequacy of support and counseling from professional bodies or remedial programs during childhood, and financial support through the National Insurance Scheme. The questionnaires were completed by the parent while the child was examined by health personnel, allowing a relaxed atmosphere and ample time. The same nurse supervised the procedure, assuring that similar information was given to all parents completing the questionnaires.

Statistical analyses: Cronbach's alpha was used to determine internal consistency of the CHQ-PF50 scores.

The McNemar test and the t-test for paired samples were used to explore group differences between preterms and matched controls on categorical and continuous demographic variables, respectively. Differences between preterm and control subjects on the CHQ-PF50 scores were examined with the Wilcoxon signed rank test and the paired sample t-test, as appropriate. The mixed linear model[25] was used to study potential differences in HRQoL between the premature and the matched term born control children, adjusted for potential confounders, ie gender, physical activity, learning and/or attention problems and FEV_1. Analyses of interaction were used to assess if effects from gender or learning/attention problems on the CHQ scores differed between preterm and control children.[26]

In the preterm group, simple linear regression analysis was used to study associations between CHQ scores and the following perinatal and neonatal variables: maternal infection, antenatal

corticosteroids, birth weight ratio (ratio between birth weight and the 50th. percentile for gestational age) and selected markers of early neonatal morbidity ie cerebral hemorrhage, days on mechanical ventilation, duration of supplemental oxygen and corticosteroid treatment for BPD.

A priori power calculation for this particular part of the overall follow-up study was difficult to perform, as the distribution of the variables of interest was not readily available for preterm children. By performing this study, we learned that one standard deviation (SD) for the psychosocial summary score was 10.3 for preterms and 4.8 for control subjects. With this information at hand, we have in retrospect calculated that the study had 80% power to detect group differences between preterm and control subjects of approximately 5.5 points, providing that the level of significance was set at 0.05. All statistical analyses were done with SPSS version 16/17 for Windows, except McNemar's test, which was done in StatXact.

Results

Subjects: All the 35 surviving and eligible preterms consented to participate in the study. On average, 1.3 potential control children had to be invited to find one willing match for each preterm index subject. All but two subjects (both born preterm) were Caucasians. Questionnaires were completed by 30 biological mothers, one foster mother and four fathers in the preterm group and by 31 biological mothers and four fathers in the control group.

Demographic and clinical variables: Compared to the mothers of controls more preterm mothers had never married and were living single (4 vs 1), while fewer parents of preterms had divorced or separated (1 vs 4).

Within the preterm group, none had cerebral palsy or were blind or deaf, but 20%, (four boys and three girls) had minor impairments (Attention Deficit Hyperactivity Disorder, epilepsy, mild mental retardation or hearing impairment requiring hearing aid) (Table 1). All seven were living normal childhood lives, also reflected by their ability to take fairly complex instructions in relation to lung function testing and to complete a maximum exercise treadmill test.

Compared to the term born controls, significantly more preterms had problems related to academic and social functioning. As many as 71% of the preterms vs 20% of those born at term (odds ratio (OR): 7.0; 95% confidence intervals (CI): 2.2 to 27.6) had learning and/or attention problems, 38% vs 3% (OR: infinite) were assessed to perform academically below average of their classmates and 65% vs. 20% (OR: 8.5; CI: 2.2 to 51.5) received academic and/or psychological support in school. The parents of 36% of the preterms vs 3% of those born at term (OR: infinite) felt that they had received insufficient professional support when raising their children. Fewer preterm children participated in organized extracurricular physical activities, while participation in other social activities, such as choirs, bands, scouts, and various social clubs, did not differ between the groups.

Child Health Questionnaire-PF50: Cronbach's alpha (internal consistency) for the sub-scales ranged from 0.70 to 0.94 for the two groups as a whole, except for mental health, which had an alpha of 0.55. In eight of the sub-scales and the two summary scores, parents of preterms scored their children significantly lower than did parents of control children (Figure 1). Preterm children were described as more juvenile and oppositional in their behavior (mean difference: -13; CI: -21.1 to -4.9), to have more limitations in role/social functioning due to behavior and emotional problems (mean difference: -11.4; CI: -20.0 to -3.0), and to have poorer general health (mean difference: -21.2; CI: -30.2 to -12.1). Their health and behavioral difficulties limited and interrupted family activities and caused more family tension (mean difference: -12.8, CI: -22.2 to -3.4). Compared to parents of term-born children, parents of preterms more often experienced emotional worries (mean difference: -21.0; CI: -31.1 to -11.0) and limitations in time available for personal needs (mean difference: -12.4; CI: -19.5 to -5.3) due to their children's physical and psychosocial health. However, relationships in general within the families (family cohesion) were assessed fairly equal in the two groups, as were the domains role/social physical functioning, bodily pain and self-esteem.

Differences between the preterm and term born children were mainly explained by the results for the preterm boys, and this modifying effect from gender was statistically significant (test of interaction) for four of the CHQ sub-scales as well as for the overall psychosocial summary scores (Table 2 and Figure 1). Learning and/or attention problems were associated with poorer HRQoL in all participants. However, this association was stronger for the preterms, particularly in areas related to general health perception and impact on parental time (Table 2), but there was no gender difference (tests of interaction, data not shown).

There were differences between the preterm and the term born control group with respect to participation in organized physical activity, maternal education and lung function (FEV_1). These potential confounding factors did not alter the conclusions from the regression models.

Within the preterm group, those who had received neonatal steroid treatment for BPD scored poorer in the domain for role/social functioning related to emotional and behavioral problems (p=0.027). Otherwise, none of the assessed perinatal or neonatal variables significantly influenced subsequent quality of life scores (simple linear regression). The boys required more days of oxygen treatment than girls (Table 1). In a multiple linear regression model, male gender and not neonatal oxygen treatment, was significantly associated with poor HRQoL outcomes.

Discussion

Being born extremely preterm was associated with inferior health related quality of life at the age of ten, particularly for the boys. Nearly three out of four preterms had problems related to school performance, compared to one out of five born at term. Academic concerns were related to quality of life in all participants, but more strongly in preterms.

Strengths and limitations

The major strengths of this study were the population-based design and the complete participation. Since there were no subjects with major impairments, there were no exclusions in the analyses, increasing the study's validity for prematurely born children expected to follow a normal social progress during childhood. On average, only 1.3 term born subjects had to be approached to recruit a complete control population, limiting potential sample bias. The same team conducted all parts of the study, limiting inter-observer variability. The major

weakness of the study was the relatively low overall number of participants, which made it susceptible to statistical type II errors and thus weakening particularly negative conclusions. However, the reported associations were marked and consistent, and appeared statistically robust. Control subjects were selected with the intention to create a group as similar to the preterm group as possible, with one exception only, the gestational age at birth. Preterm birth has been associated with socioeconomic shortcomings,[27] and one may argue that a control population should reflect this. However, the Norwegian society is characterized by a fairly egalitarian sociodemographic structure, and therefore we opted to match control subjects on gender and the timing of birth only. In this study, we observed a tendency for a lower educational level in mothers of preterms compared to mothers of control subjects, but no such tendency for the fathers. These factors did not influence the conclusions of the study.

Knowledge about HRQoL in school-aged children who were born extremely preterm is relatively scarce. Assessment of a subjective phenomenon like quality of life through information provided by others, in this study the parents, has limitations. However, when self-reported data are difficult or impossible to obtain, this is a valid method to generate information.[9,13] Also, parental reports will reflect the challenges of these children and of their families such as they are perceived by the most important person in the life of a child—the parent.

The potential burden of raising a preterm child starts the very minute the parent(s) leave the NICU. Thereafter, a continuously changing panorama of new circumstances and potential difficulties will materialize with the growth of the child, challenging the family structure and its members. A positive finding from the present and similar studies was that parents of the preterm children reported overall family relationships to be good,[10,28] and that fewer parents in the preterm group had divorced. These findings seemingly contradict the observed CHQ-PF50 scores, which indicate an increased burden of parenting. This result suggests that some forms of adjustment, acceptance, or coping mechanisms are activated within the family by the uncertainty of raising these children. One third of preterm parents reported insufficient societal professional support. Recent reports from the USA and Denmark support this finding.[29,30] Lack of professional support may be another factor increasing the observed burden of parenting. Alternatively, there may be inherent challenges involved in the process of parenting many preterm children, making it difficult to offer or receive outside help. It is of considerable interest in this context that two quite different social welfare systems, namely those of Norway and the USA, both seem to fail in providing adequate help for these families.

The school is an arena of utmost importance for both academic and social success in life. As preterm children were reported to have more learning difficulties and/or attention problems, they naturally received more support, both academically and psychologically. In a previous study from our institution, eleven year old children with birth weights less than 2000 g without major disabilities had twice as many school problems and were referred to the School Psychological Services two to three times more often than children born at term.[31] In the present study, this ratio approached four times that of their matched peers born at term, probably because our preterm cohort was more immature at birth. Similar concerns with respect to academic performance have also been expressed by others examining populations relatively similar to ours.[32-34] The observed association between learning and/or attention problems at school and quality of life was present in all participating subjects, but was more prominent among those born preterm. Why academic shortcomings had a greater negative influence on the quality of life in children born preterm and their parents cannot be answered within the frame of this study since we did not assess the nature and the extent of the learning and attention problems.

Physical activities and sports are important elements of a normal childhood, influencing subsequent physical as well as social development. Neurosensory and cognitive abilities, neuromotor skills, aerobic capacity and personal ambitions influence the extent of individual success. Compared to term born controls, the preterms took less part in physical activities and sports, while they participated to a similar extent in other nonphysical, extracurricular activities. We are not aware that others have reported this pattern. Typical features of children born preterm, e.g. a sense of insecurity, clumsiness, attention problems and reduced physical capacity[3,35,36] may limit their ability and subsequent interest in physical activities. Participation in non-physical social activities might provide an important alternative arena for psychosocial training. Considering the well described tendency towards behavioral problems and reduced social competence in this group of children,[4,37-39] this finding is encouraging. At the age of ten, parents have a strong influence on the choice of activities and lifestyle of their children and one explanation may be that parents of preterms acknowledge their children's physical limitations and therefore encourage them to take part in activities felt to be appropriate and within their physical and mental abilities. A contributing factor to the high rate of participation in non-physical social activities might be that at this age the full impact from potential limitations was not sufficiently obvious to discourage participation.

The excess of concerns and poorer HRQoL scores among the preterm children were mainly explained by the poorer results for the boys. This finding is in line with previous studies on preterm subjects, but contradicts similar studies in unselected populations of similar ages.[10,40,41] Male gender is a well known risk factor for neonatal mortality and morbidity in preterm neonates. In the present study, the boys had a neonatal history characterized by nearly twice as many days of oxygen supplementation compared to the girls. Statistical handling of this situation is difficult, ie which is the "true" explanatory factor: gender or prolonged oxygen requirements. However, within the frame of the present study, male gender and not neonatal oxygen treatment appeared as the most important and most robust explanatory variable. It has been suggested that a poorer prognosis in terms of survival and early morbidity for boys also extends to their later development, even for survivors without major disabilities.[42,43] Hintz et al propose that there may be a gap in the societal support offered to boys in their first two years of life.[30] Why males are more vulnerable than females may partly be explained by a biological fragility of the male fetus, possibly reinforced by an attitude from society that boys are, or must be mademore resilient than girls, thus adding "a social insult to the biologicalinjury" (S. Kraemer p. 1609).[44] Based on the present study, one might suggest that this should have implications also for the clinical management of males in a NICU setting, as well as for the upbringing of male children born extremely preterm.

Within the preterm group, subjects who had received neonatal

corticosteroid treatment scored poorer in the domain of social functioning. In this context one must bear in mind that corticosteroids are used to treat severely ill neonates with a number of potential risk factors for poor outcome. However, the observation agrees with an accumulating number of reports that neonatal treatment with corticosteroids is associated with an increased risk of impairments.[45] Apart from this notable exception, there were no associations between the assessed neonatal and perinatal variables and subsequent HRQoL outcomes. This contradicts findings reported by our own group and by others regarding physical outcomes such as lung function and pulmonary CT scans.[6,46] One may argue that impact from a diverse postnatal environment will influence multidimensional outcomes such as HRQoL more than unidimensional physical outcomes. Additionally, the neonatal history of extreme preterms varies considerably and most medical problems somehow tend to be interrelated, complicating research on subsequent cause and effect relationships. Also, the limited sample size may have precluded our ability to detect potential associations that might be present. In fact, neonatal treatment with corticosteroids has been reported to have an adverse effect on academic achievement at the age of eight and maternal infection has been reported to predict neurodevelopmental impairments.[2,47] Randomized long-term follow-up studies must be performed to explore these issues.

Conclusion

Being born extremely preterm was associated with inferior HRQoL at the age of ten, particularly for boys, affecting the child as well as the family. The majority of parents of preterms reported that their children had learning and/or attention problems, and one third experienced insufficient professional support. Learning and/or attention problems at school were associated with inferior HROoL in all participants, but this association was stronger among preterms. Treatment and support offered to preterm children and their families needs to be addressed in future studies, particularly if the child is a boy.

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Atypical Perceptual Narrowing in Prematurely Born Infants is Associated with Compromised Language Acquisition at 2 Years of Age

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Early auditory experiences are a prerequisite for speech and language acquisition. In healthy children, phoneme discrimination abilities improve for native and degrade for unfamiliar, socially irrelevant phoneme contrasts between 6 and 12 months of age as the brain tunes itself to, and specializes in the native spoken language. This process is known as perceptual narrowing, and has been found to predict normal native language acquisition. Prematurely born infants are known to be at an elevated risk for later language problems, but it remains unclear whether these problems relate to early perceptual narrowing. To address this question, we investigated early neurophysiological phoneme discrimination abilities and later language skills in prematurely born infants and in healthy, full-term infants.

Our follow-up study shows for the first time that perceptual narrowing for non-native phoneme contrasts found in the healthy controls at 12 months was not observed in very prematurely born infants. An electric mismatch response of the brain indicated that whereas full-term infants gradually lost their ability to discriminate non-native phonemes from 6 to 12 months of age, prematurely born infants kept on this ability. Language performance tested at the age of 2 years showed a significant delay in the prematurely born group. Moreover, those infants who did not become specialized in native phonemes at the age of one year, performed worse in the communicative language test (MacArthur Communicative Development Inventories) at the age of two years. Thus, decline in sensitivity to non-native phonemes served as a predictor for further language development.

Our data suggest that detrimental effects of prematurity on language skills are based on the low degree of specialization to native language early in development. Moreover, delayed or atypical perceptual narrowing was associated with slower language acquisition. The results hence suggest that language problems related to prematurity may partially originate already from this early tuning stage of language acquisition.

Basic auditory skills constitute a foundation for language development. Healthy infants possess well-developed auditory capabilities from birth, allowing the perception of a wide range of auditory material, as indexed by behavioral[3-5] and electrophysiological methods of testing. Perceptual development, however, undergoes a process of narrowing and specialization for almost all socially relevant stimuli—voices, faces, and speech sounds. During the first months of their lives, infant's sensory systems are broadly tuned to any type of auditory material, and they are able to discriminate speech sounds regardless of whether these sounds belong to the surrounding adult language or not. Language-specific discrimination abilities improve between 6 and 12 months of age for native, and decline for unfamiliar phoneme contrasts[13-15] as the brain tunes itself towards optimal perception of the native spoken language. Several studies have suggested that improved native-phoneme discrimination skills are good predictors of later language performance, while the opposite has been observed to hold for the non-native phoneme discrimination. Atypically long lasting sensitivity to non-native speech contrasts may indicate poor brain commitment to a native language, and has been previously demonstrated to result in slower language development at the age of 2 years.

Most children develop language skills without effort, following a typical sequence of development. However, some children, including those born very prematurely, may have great difficulties in acquiring language. Of those prematurely born children who survive, roughly half have language and learning disabilities, representing a growing public interventional and educational concern. An atypical auditory processing has been demonstrated in prematurely born infants which has been linked to atypical language and cognitive development at school age. However, there is currently no clear model which would provide information on stages of language, and auditory processing development in prematurely born infants through the first 2 years of life. Event-related potentials (ERPs) are a safe and reliable method to investigate language related auditory processing in infants long before their language production abilities can be assessed.

The ERP component called the mismatch negativity (MMN) is elicited by potentially discriminable changes in repeated auditory stimuli, and its latency and amplitude are correlated to behavioural discrimination accuracy. Cheour et al found that amongst six-month-old monolingual Finnish infants, the non-native õ elicited higher MMN amplitudes than the native ö, presumably due to the higher acoustic contrast compared to repeated native/e/. In contrast, at the age of one year,

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these infants showed a diminished MMN for the non-native but an increased MMN for the native, indicating long-term memory traces for native speech sounds formed between the ages of six months and one year. These studies provide an electrophysiological evidence for neural tuning to familiar spoken material, and suggest it to be predictive of later language development.

The present study examined 1) the ability of prematurely born and full-term, healthy six-month-old infants to discriminate between native (rare native Finnish/ö/amongst repeated native/e/ phoneme), and between native and non-native phonemes (rare non-native/õ/phonemes amongst repeated native/e/ phoneme), as reflected by the MMN; and 2) the development of this ability during the subsequent period of six months; 3) language development at the ages of one and two years, and 3) an association of the development of neural discrimination ability with language abilities at two years of age. We recorded the MMN from 11 very prematurely born monolingual infants (GA<32 weeks), and 13 full-term, healthy infants at the age of six months (±1 week), and at the age of one year (±1 week) to investigate whether these two groups of children differ from each other in their ability to discriminate between phonemes. Gestationally corrected age was used for the prematurely born infants. Language skills (vocabulary development, the use of morphological structures in spoken language, and the mean length of the three longest utterances=MSL) of the full-term and prematurely born infants were assessed at the ages of one and two years using MacArthur Communicative Development Inventories (CDIs).

At the age of 6 months, there was no significant difference between the two groups in the MMN amplitude in response to non-native phoneme contrast (Table 1). Consistent with the theory of perceptual narrowing and previous studies,[9,10,12] the amplitude of the MMN response to the non-native phoneme contrast, however, diminished between 6 and 12 months of age in full-term infants (F(1,24)=3.288, P=0.082; Figure 1; Table 1). In contrast, in the prematurely born children, this reduction was not observed, and at the age of one year, the MMN amplitude in response to the non-native phoneme contrast was significantly higher in prematurely born children than in the children born full-term (F(1,22)=5.453, p=0.029). Furthermore, there was a tendency for a Right-Left × Group interaction (F(1,22)=4.125, P=0.055) which was due to more enhanced MMN in the left hemisphere in children born premature than in the controls (Figure 1).

At the age of 6 months, repeated measures ANOVA revealed no significant difference in the MMN amplitude in response to native phoneme contrasts between the two groups of infants. However, the MMN latency was significantly shorter in children born full-term than in children born premature (F(1,22)=5.602, P=0.027; Table 1, indicating faster discrimination of native phonemes by the former. In the children born premature the MMN latency tended to shorten between 6 and 12 months of age (F(2,20)=4.178, P=0.054) while no such changes in the MMN latency were observed in the children born full-term. At the age of one year, no significant difference in the MMN latency was found between prematurely born and full-term infants anymore. Neither was there any significant difference in the MMN amplitude. The results indicate that the formation of long-term memory traces for native phonemes was already well-developed by the age of 6 months in the children born full-term, while in the very prematurely born children, the native-language phoneme discrimination still continued to develop up to the age of 12 months.

The language measures at 12 months did not yield any significant differences between the groups. At the age of two years, however, the prematurely born children produced significantly less words (F(1,19)=8.522, P=0.009), and had shorter MSL, as indexed by the number of morphemes produced in sentences (F(1,19)=6.819, P=0.017) than the full-term children. Furthermore, the morphological structures of the sentences were less developed in the prematurely born children than in the full-term children (F(1,19)=5.270, P=0.033), as also reported in earlier studies.

To explore whether phonetic discrimination abilities, as reflected by the MMN, are associated with behaviorally measured language skills, as reflected by the CDI, a correlation analysis was performed. The correlation analysis revealed that the larger was the MMN amplitude in response to the non-native phoneme at the age of one year, the less the child produced words (r^2 0,199, P=0.048; Figure 2), the less developed the morphology (r^2 0,268, P=0.019), and the shorter the MSL was (r^2 0.376, P=0.004) at the age of two years. The findings indicate that those infants who did not acquire neural long-term representations specific to native-language phonemes at the age of one year, performed also worse in all subtests of the CDI language test at the age of two years.

In this study we examined the association between native and non-native phonetic discrimination in a group of monolingual, full-term, healthy children, and in a group of very prematurely born children. Consistent with the previous studies we showed

Table 1 MMN latencies and mean amplitudes in response to native and non-native phoneme contrasts at the ages of 6 and 12 months.

Condition and age	Latencies ms					Amplitudes μV				
	Premature Mean (SD)	Controls Mean (SD)	F	Df	P	Premature Mean (SD)	Controls Mean (SD)	F	Df	P
Native phoneme										
6 months	227 (40)	194 (29)	5,602	1.22	.027	-1.039 (2.12)	-.571 (1.24)	0,277	1.22	.604
12 months	200 (16)	188 (41)	0,777	1.22	.387	-.498 (2.58)	-.819 (2.79)	0,124	1.22	.728
Non-native phoneme										
6 months	216 (27)	197 (33)	2,216	1.22	.151	-.575 (2.15)	-.541 (1.24)	0,002	1.22	.962
12 months	198 (16)	199 (29)	0,020	1.22	.889	-1.061 (1.70)	+.323 (1.19)	5,453	1.22	.029

Thevalues represent the corresponding means and standard deviations over six electrodes. The P-values represent the result of the ANOVA analyses, indicating the significance of the between- group differences over all the electrodes.

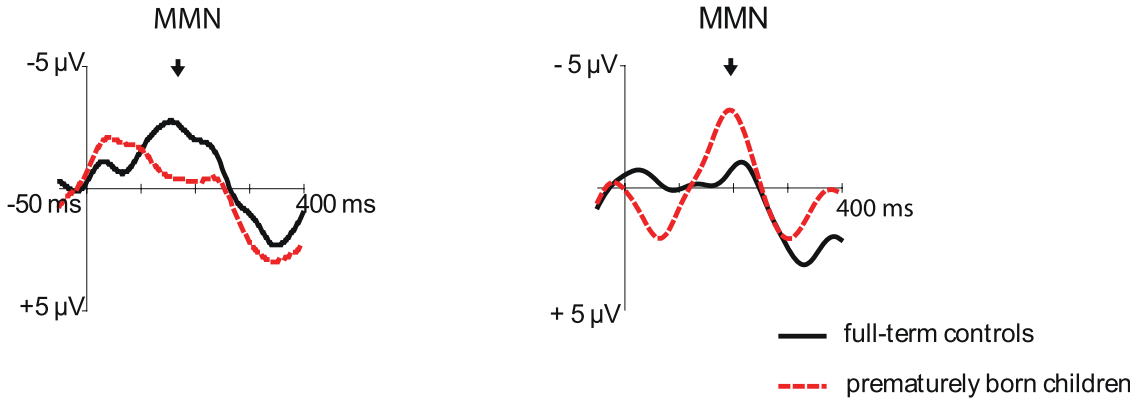

Figure 1 Mismatch negativity (grand average, infrequent-frequent difference waveform) reflects the development of language specific memory traces (left-hemisphere C3 in the figure). Frequent phoneme was/e/, infrequent phoneme was non-native, Estonian/õ/. The MMN amplitude in response to non-native phoneme contrast diminished from the age of 6 months (on the left) to the age of 12 months (on the right) in the full-term controls, while in the prematurely born children this kind of reduction was not observed.

that long-term memory traces for native phonemes are well-developed in infants born full-term by the age of 6 months. In contrast, prematurely born infants continued to develop this ability up to the age of one year, as indexed by the shortening of the MMN latency. The most striking finding in these children, however, was that the discrimination of non-native phoneme contrasts strengthened from 6 to 12 months of age, which was negatively associated with several measures of linguistic skills at the age of two years. Thus, the prematurely born infants appeared to continue to maintain their ability to discriminate accurately non-native phonemes at the age of one year. In contrast, children born full-term showed a decrease in their ability to discriminate non-native vowels, as is typical for normal development.

The stimuli [for the study] were Finnish vowels /e/ (frequent) and /ö/ (infrequent) as well as Estonian /õ/ (infrequent) which is non-native to Finnish infants. The acoustic difference between the /e/ and /õ/ is bigger than /e/ and /ö/. The stimuli were presented through closed-type headphones (Please, see detailed information of the stimuli ref. 10).

The EEG measurements were performed in an acoustically and electrically shielded room. During the measurements, the infants were seated in a safety seat, and an assistant entertained the infant with soundless toys to keep the infant relaxed and satisfied during the experiment. The stimuli, 400 ms (with 10 ms rise and fall times) were binaurally presented through headphones (75 dB SPL) with a 650 ms sound-onset asynchrony from onset to onset. The electroencephalogram (on-line bandpass 0.05-70 Hz, sampling rate 500 Hz) was recorded at the F4, C4, P4 (right hemisphere) and F3, C3, P3 (left hemisphere) sites, according to the international 10-20 system, using NeuroScan 4.0 amplifiers and software. Electro-ocular activity was recorded with two electrodes, one attached below the outer cantus of the left eye, and the other above the outer cantus of the right eye. Epochs (-100 to 500 ms) exceeding 200 µV in amplitude at any electrode were omitted from averaging. During the recording, the reference electrode was at FCz. After averaging, the data was re-referenced to the ipsilateral mastoids. Frequencies higher than 15 or lower than 1 Hz were digitally filtered out off-line. The MMN was analyzed from the difference waveform (the response elicited by the standard stimulus subtracted from that elicited by the deviant stimulus). The MMN was identified as the most negative peak within the time window of 150-300. The mean amplitudes were measured from the difference waves with a 100 ms window centered at the peak amplitudes of these waves (±50 ms). The between group differences (prematurely born children, full-term children) were tested separately for native and non-native phonemes at six electrodes using repeated measures ANOVA with Group as a between-subject factor and Hemisphere [Right (F4, C4, P4) & Left (F3, C3, P3)] × Anterior-Posterior [(Frontal (F3, F4) & Central (C3, C4) & Parietal (P3, P4)] as within-subject factors. Developmental change for each phoneme were performed separately for the prematurely-born infants' data and for the control data by the ANOVA with Age [6 & 12 months] as a between-subject factor and Hemisphere [Right (F4, C4, P4) & Left (F3, C3, P3)] × Anterior-Posterior [(Frontal (F3, F4) & Central (C3, C4) & Parietal (P3, P4)] as within-subject factors. The Huynh-Feldt Correction was applied when appropriate.

Language development, comprehension and production, was assessed at the ages of one and two years by using the MacArthur Communicative Development Inventories (CDIs) which is a questionnaire designed to assess both language comprehension and production in children between ages 8-30 months. In the CDI Words and Gestures (for 8-16 month old infants, used here for 12 month olds), parents document the child's understanding of early vocabulary items separated into semantic categories such as animal names, household items, and action words. Parents report the words understood and the words used by the infant, and the forms yield separate indexes of understanding and production. In the CDI Words and Sentences (for 16-30 month old children, used here for 24 month olds), parents report the child's production and use of words divided into semantic categories. In addition, the parents are asked to answer, whether the child uses certain morphological structures in spoken language (like plural and verb forms), and provide written examples of the child's three longest sentences or words that the child has used. In this study the CDI questionnaire was sent to parents two weeks before the MMN measurements were performed at the age of 12 months, and the CDI questionnaire was received from them at the MMN measurements. At the age of 24 months, questionnaires were sent and received from the parents by mail. Questionnaires were not received from parents of two prematurely born children and two control children. A One-Way ANOVA was used to compare the language test results between the groups, and correlations between the MMN and CDI values were tested using Spearman's Correlation Coefficients.

The subjects were 13 full-term (average gestational age: 40 weeks; SD 1,3 weeks; birth weight average 3720 g, SD 530 g)

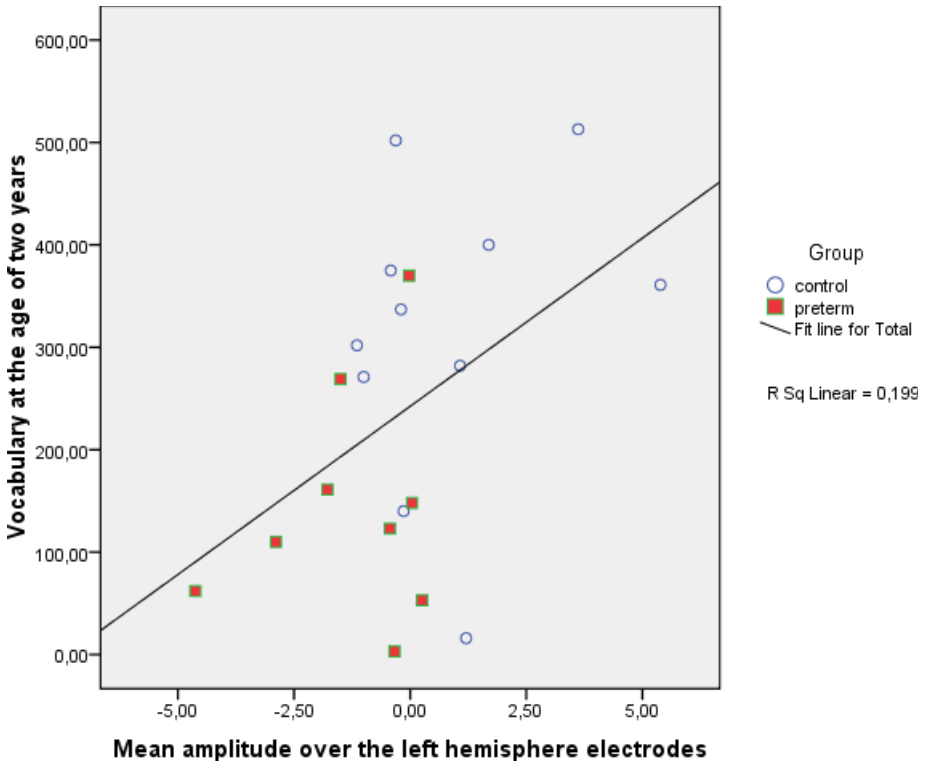

Figure 2. Correlation between the MMN mean amplitude over the left hemisphere electrodes (F3, C3, P3) in response to non-native phoneme at the age of 1 year and the number of words produced by the children at the age of 2 years. Correlations are over both groups. Horizontal line is the MMN mean amplitude over the left hemisphere electrodes, vertical line the number of words produced by each child as shown by the MacArthur Communicative Development Inventories (CDI). The result showed that the more negative the mean amplitude indicating better discrimination of non-native phoneme, the less the child produced words at the age of two years.

children and 11 children born very prematurely (gestational age <32 weeks, average 29 weeks, SD 1.7 weeks; birth weight average 1291 g, SD 411 g) served as participants. The postnatal ages were calculated on the basis of the post conception age of 40 weeks. All the children had normal hearing in each ear, as indexed by transient otoacoustic emissions, and normal auditory brainstem responses in prematurely born children at the stimulus level of 40 dB. The study was approved by the ethical committee of Oulu University Hospital.

The theory of native-language neural commitment suggests that normal language development involves plastic changes while the brain tunes itself to native phonemes at the expense of its ability to process unfamiliar phonemes. Our study shows that this tuning is delayed or atypical in prematurely born infants. In prematurely born infants, an acoustically larger but non-native contrast evoked a larger brain response, suggesting that lower-level processing of physical acoustic characteristics is still dominating over language-specific processing at the age of one year. The result is in accordance with previous studies indicating a higher sensitivity to larger acoustic contrasts in infants born premature. Thus, the finding of the present study suggests that language problems in prematurely born children may partially originate already from this early tuning stage of language acquisition.

There is a possibility that children born premature have not only a deficit in perceptual narrowing but also a more general auditory processing deficit. Further studies are needed to investigate the specificity of this deficit to native and non-native vowel contrasts. A new method, optima or multifeature paradigm,[33] enables the use of different deviants in the same paradigm, and would therefore be a valuable method to define auditory processing deficits in prematurely born children in more detail. It would also be interesting to follow-up the same group of children from infancy to later age to investigate whether children born premature and showing deficits either in auditory processing or language development ever catch up their peers.

Premature birth constitutes a set of health risks for the infant. Minor but common deficits, like atypical auditory processing and slight delays in language development, are in most cases not diagnosed. Nevertheless these deficits may lead to later language and learning disabilities. Information provided by this study might be crucial for the early identification of infants at-risk for later language and learning deficits. Thus, prematurely born infants would benefit from information concerning their early language-related brain plasticity for early identification of infants at-risk for later language and learning deficits, and for introducing them to early interventions always when needed.

The results of our follow-up study show for the first time that perceptual narrowing for non-native phoneme contrasts found in the healthy controls at the age of one year was not encountered in very prematurely born infants. Moreover, our results showed that this delayed or atypical perceptual narrowing was associated with slower language acquisition. The results hence suggest that language problems in prematurely born children may partially originate already from this early tuning stage of language acquisition. Further studies are, however, needed to investigate whether this deficit is specific to perceptual narrowing or whether it is related to a more general auditory processing deficit and whether these children ever catch up their peers.

Risk Factors and Obstetric Complications of Large for Gestational Age Births with Adjustments for Community Effects

Shu-Kay Ng, Adriana Olog, Anneliese B. Spinks, Cate M. Cameron, Judy Searle, Rod J. McClure

Abstract

Background: High birth weight has serious adverse impacts on chronic health conditions and development in children. This study identifies the social determinants and obstetric complications of high birth weight adjusted for gestational age and baby gender.

Methods: Pregnant women were recruited from three maternity hospitals in South-East Queensland in Australia during antenatal clinic visits. A questionnaire was completed by each participant to elicit information on eco-epidemiological exposures. Perinatal information was extracted from hospital birth records. A hierarchical mixture regression model was used in the analysis to account for the heterogeneity of birth weights and identify risk factors and obstetric complications of births that were large for gestational age. A generalized linear mixed model was used to adjust for (random) "community" effects.

Results: Pre-pregnancy obesity (adjusted OR=2.73, 95% CI=1.49-5.01), previous pregnancy (adjusted OR=2.03, 95% CI=1.08-3.81), and married mothers (adjusted OR=1.85, 95% CI=1.00-3.42) were significantly associated with large for gestational age babies. Subsequent complications included the increased need for delivery by caesarean sections or instrumental procedures (adjusted OR=1.98, 95% CI=1.10-3.55), resuscitation (adjusted OR=2.52, 95% CI=1.33-4.79), and transfer to intensive/special care nursery (adjusted OR=3.76, 95% CI=1.89-7.49). Communities associated with a higher proportion of large for gestational age births were identified.

Conclusions: Pre pregnancy obesity is the principal modifiable risk factor for large for gestational age births. Large for gestational age is an important risk factor for the subsequent obstetric complications. The findings improve the evidence-base on which to base preventive interventions to reduce the impact of high birth weight on maternal and child health.

Background

Increased numbers of high birth weight infants (>4000 g) and large for gestational age (birth weight above the 90th percentile for gestational age) have been reported in North America and Europe. Macrosomia, defined by the American College of Obstetricians and Gynecologists, as birth-weight >4000 or >4500 g irrespective of gestational age is associated in the literature with numerous perinatal and maternal complications. Macrosomic infants are at an elevated risk of shoulder dystocia and associated brachial plexus injury, perinatal asphyxia, meconium aspiration, hypoglycaemia and fetal death. Associated maternal complications include prolonged labour, labour augmentation with oxytocins, caesarean delivery, prolonged hospital stay and higher mortality from coronary heart disease for the mother.

Children born large for gestational age are prone to induce neonatal complications and develop insulin resistance, obesity, diabetes and early cardiovascular disease later in life. High birth weight has also been associated with increased future risk of cancer such as leukemia, breast, prostate and colon cancer. Large for gestational age births have increased from 9.2% to 10.8% in male infants and from 9.1% to 11% in female infants from 1990 to 2005.

High birth weight is also associated with subsequent childhood and adult obesity. The long-term chronic disease consequences of childhood overweight or obesity are of serious public health concern. The proportion of overweight or obese children in Australia has been increasing at an accelerating rate since the 1980's, with obesity increasing 2-4 times, and being overweight increasing by 60-70%. The reported prevalence of overweight or obesity in an Australian population is 34%. The increased prevalence has lead to obesity being recognized as a national health priority risk factor in Australia.

Ng and Cameron are with the School of Medicine, Griffith University, Meadowbrook; Olog is with the Department of Obstetrics and Gynaecology, Gold Coast Hospital; Spinks is with the Commonwealth Scientific & Industrial Research Organisation; Searle is with the Health Workforce Divisiion, Department of Health & Ageing; McClure is with the Monash University Accident Reserch Centre, Victoria, Australia. The authors wish to thank the Editor of BMC Public Health and three referees for helpful comments on the paper. The authors are grateful to Queensland Health and New South Wales Health for providing the birth data in the study region during 2006, which allows comparisons between cohort participants and the general population. The authors also thank Rani Scott, Ryan Thwaites and Sunghwa O'Mahony for managing the recruitment and databases of the Environments for Healthy Living birth cohort study. We gratefully acknowledge the hospital antenatal and birth suite midwives of the participating hospitals for their valuable contributions to the study. Reprinted from BioMed Central, BMC Public Health, This article has been slightly edited for our readers. For references, go to BioMed Central and type the full title.

Table 1 Baseline characteristics of the cohort and comparisons with all births in the study region

Characteristics	Frequency (percentage[a])		P-value[c]
	Birth cohort sample (Years 2006 to 2008) n = 1565	Deliveries in region[b] (Year 2006) n = 8608	
Gender of infant			
Male	764 (49.9%)	4462 (51.8%)	0.079
Female	782 (50.1%)	4145 (48.2%)	
Missing data	19	0	
Maternal age			
<20 years	87 (5.7%)	512 (5.9%)	0.239
20-24 years	325 (21.1%)	1608 (18.7%)	
25-29 years	424 (27.6%)	2388 (27.7%)	
30-34 years	427 (27.8%)	2515 (29.2%)	
≥35 years	274 (17.8%)	1584 (18.4%)	
Missing data	28	0	
Birth weight			
<2500 g	39 (2.5%)	450 (5.5%)	<0.0005
2500-3999 g	1266 (81.7%)	7073 (82.2%)	
≥4000 g	244 (15.8%)	1060 (12.3%)	
Missing data	16	2	
Gestational age at birth			
<28 weeks	0 (0.0%)	59 (0.7%)	<0.0005
28-36 weeks	38 (2.4%)	536 (6.2%)	
37-41 weeks	1505 (97.2%)	7963 (92.5%)	
≥42 weeks	6 (0.4%)	45 (0.5%)	
Missing data	16	4	
Plurality			
Singleton	1532 (98.5%)	8388 (97.4%)	0.016
Multiple	24 (1.5%)	220 (2.6%)	
Missing data	9	0	
Outcome			
Live birth	1554 (99.9%)	8547 (99.3%)	0.007
Stillbirth	2 (0.1%)	61 (0.7%)	
Missing data	9	0	

[a]Percentages are calculated based on the available (non-missing) data.
[b]Data for the study region (Logan, Gold Coast, Beaudesert, Tweed) are provided by Queensland Health and New South Wales Health.
[c]Chi-square test for comparing proportions between birth cohort sample and the general population.

The use of risk factor information to identify mothers at risk of having large for gestational age births is an important clinical tool as the accuracy of weight estimation in the third trimester, whether by clinical estimation or ultrasound is poor. Although some causes for large for gestational age births (such as maternal obesity and diabetes) are known, some causes of large for gestational age births are of unknown origin. Previously identified risk factors in the literature associated with increased birth weight are maternal obesity, multiparity, advanced maternal age, ethnicity, excessive weight gain, marital status, smoking, prolonged labour. However, the extent to which each of these factors influence birth weight is unclear. There remains substantial variation in the literature regarding the strength of association between each of the identified risk characteristics and macrosomia.

In this paper, we aim to refine knowledge of the social determinants of large for gestational age births and assess the subsequent obstetric complications adjusted for gestational age and baby gender, on the basis of the first three phases of a new 'Environments for Healthy Living' birth cohort study using a hierarchical mixture regression model. The identification of modifiable risk factors of large for gestational age births may contribute to the development of public health interventions to reduce the escalating burden resulting from high birth weight in Australia.

Methods

The birth cohort study "Environments for Healthy Living" was launched in November 2006 to quantify the relationship between social, environmental and behavioural factors and the health and development of children in South East Queensland, Australia. The study area contains an estimated population of over 1,300,000 people or approximately 4% of Queensland's population. The study region is markedly heterogeneous with respect to age and socioeconomic distribution.

Eligible participants were infants of mothers who gave birth at one of three maternity hospitals (Logan, Gold Coast and The Tweed Hospitals) in South East Queensland between November 2006 and August 2008. All women waiting for third trimester antenatal clinic appointments at each of the locations were approached by research trained midwives, provided with a detailed explanation of the study aims and invited to participate in the study. A questionnaire was completed by each participant to elicit information on demographics, socioeconomic status, family structure and relationship, neighbourhood and community connectedness, maternal smoking and drinking behaviour, and the usage of supplements and recreational substances during pregnancy. Perinatal information was extracted from hospital birth records. The Environments for Healthy Living study is based on an ecological model of causation, which attempts to investigate effective social and economic approaches for improving the health of disadvantaged populations and contributing to overall health and wellbeing of populations. A wide variety of health-related exposures and outcomes are measured at baseline and during subsequent follow-up period. The present research extracts variables collected at baseline under the following eco-epidemiological headings: (1) Demographics; (2) Socio-economics; (3) Psychological and behavioural; (4) Social network and neighbourhood; (5) Birth procedures; and (6) Neonatal. The first four eco-epidemiological categories are potential risk factors for large for gestational age births. Variables in the last two categories are adopted to assess potential obstetric complications of delivering large for gestational age babies. All these variables are included in the subsequent analyses.

Identification of risk factors for large for gestational age births is usually undertaken using a logistic regression approach with dichotomous outcomes of large for gestational age defined by birth weight percentile for gestational age. The large for gestational age variable is usually defined on the basis of local growth charts specific for gender and gestational age and thus the definition of large for gestational age infants is subjective to the reference adopted. As mean birth weight has continuously increased in the United States, Canada, Europe, and Asia, an up-to-date local reference may not be always available. The adoption of an inappropriate reference can result in misleading inference, with the consequent possibility of invalid findings. Moreover, the logistic regression approach is not able to account for heterogeneity as well as variability of birth weights simultaneously. In this paper, a hierarchical mixture regression model has been adopted to simultaneously account for the

Table 2 Categories of risk variables and adjusted odd ratios for large for gestational age (n = 1440)

Variable category	Frequency (percentage[a]) or Mean (SD)	Adjusted odd ratios (90% CI)
Demographics:		
Maternal age	28.90 (5.83)	0.96 (0.92, 1.01)
Pre-pregnancy (BMI) obesity[b]	211 (16.1%)	2.73* (1.64, 4.55)
Born in Australia	1039 (72.2%)	1.55 (0.85, 2.82)
Previous pregnancy	845 (58.7%)	2.26* (1.32, 3.88)
Married	732 (51.1%)	2.33* (1.36, 3.99)
Maternal work status (employed)	680 (47.6%)	1.22 (0.75, 1.97)
Missing data[c]	144 (10.0%)	
Socio-economics:		
House owned	619 (43.3%)	1.23 (0.74, 2.02)
Mother (education level)		
Not complete high school	281 (19.6%)	1.12 (0.63, 1.98)
Complete high school/TAFE (Reference)	883 (61.5%)	Reference
University degree	271 (18.9%)	0.45* (0.20, 1.00)
Household income		
Low (<$19,999)	81 (6.5%)	0.27 (0.05, 1.55)
Middle ($20,000-$80,000, Ref.)	835 (67.5%)	Reference
High (>$80,000)	322 (26.0%)	0.99 (0.54, 1.80)
Missing data	209 (14.5%)	
Psychological/Behavioural:		
No smoking during pregnancy	1100 (76.9%)	5.20* (2.12, 12.8)
Frequency of alcohol (at least weekly)	122 (8.5%)	0.72 (0.28, 1.90)
Vitamin supplements intake[d]	1085 (75.3%)	0.96 (0.58, 1.58)
Maternal mental health (very high risk[e])	82 (5.8%)	0.17 (0.01, 5.13)
Missing data	51 (3.5%)	
Social network/Neighbourhood:		
Neighbours friendly or very friendly	975 (68.3%)	0.89 (0.52, 1.51)
Satisfied/very satisfied with community	1245 (86.8%)	1.08 (0.44, 2.67)
Community felt like home (agree)	1045 (73.3%)	1.17 (0.61, 2.23)
Get help when need it (agree)	1021 (71.3%)	0.93 (0.53, 1.63)
Get services need (agree)	1114 (78.3%)	0.96 (0.51, 1.82)
Feel safe (agree)	1128 (79.3%)	1.69 (0.75, 3.83)
Active in community (agree)	306 (21.6%)	0.93 (0.54, 1.62)
Moved home in past 1 year	632 (44.3%)	0.65 (0.40, 1.08)
Missing data	46 (3.2%)	

[a]Percentages are calculated based on the available (non-missing) data.
[b]BMI= (weight in kg)/(square of height in meter) ≥30.
[c]Number of individuals with incomplete data within each category of risk variables
[d]Any of supplements (Iron, Zinc, Calcium, Folic acid, Multi-vitamin, Vitamin C & E).
[e]Very high risk based on Kessler scale [45] (Kessler 6 scale >12)

heterogeneity of birth weights (via mixture modelling) and adjust for risk factors and complication variables (via logistic regression).

With the hierarchical mixture regression model, a generalized linear mixed model (GLMM) was used to adjust for inter-community variations (via multilevel modelling), where the community is represented in terms of postal area codes of participating mothers. The impacts of communities on the proportion of large for gestational age births are evaluated based on the "predicted" random effects. A positive random (community) effect indicates an increased proportion of large for gestational age births in a community.

For the mixture regression modelling, we first estimated the unknown parameters in the component densities with the adjustment for gestational age and baby gender. Based on the fixed estimated parameters in the component densities, risk factors were then included into the logistic regression function in steps, where each step corresponds to a single category of risk variables detailed in the study design above. Interactions between variables were considered at each step. For each category of risk variables, we performed the analysis included only individuals for which all variables in the category were present. Variables that were significant at 10% level (two-sided) within each category were entered into the final model for the determination of risk factors on the proportion of large for gestational age births. Obstetric complications of large for gestational age births were then determined by including the complication variables into the final estimated hierarchical mixture regression model via logistic regression.

The proportion of large for gestational age births in each community was calculated by averaging the estimated posterior probability of large for gestational age for all individuals in that community; see the Appendix. The estimated proportion of large for gestational age births was then compared to the unadjusted proportion of large for gestational age births, which was the estimated proportion of large for gestational age births in all regions without adjusting for the risk factors. Communities with more than ten participants and the proportion of large for gestational age births being higher than the unadjusted proportion of large for gestational age births were identified. These communities were associated with a higher

Table 3 Determinants of risk and obstetric complications of large for gestational age

Variable	Coefficient	Adjusted odd ratios (95% CI)
Determinants of risk of large for gestational age - Demographics, Socio-economics, Psychological and Behavioural risk factors (n = 1294):		
Pre-pregnancy (BMI) obesity	1.006	2.73* (1.49, 5.01)
Previous pregnancy	0.707	2.03* (1.08, 3.81)
Married	0.614	1.85* (1.00, 3.42)
Mother education (university degree[a])	-0.897	0.41 (0.16, 1.02)
No smoking during pregnancy	1.427	4.17* (1.43, 12.1)
Obstetric complications of large for gestational age - Birth procedures (n = 1235):		
Onset of labour		
Spontaneous (Reference)	Reference	
Induced	0.496	1.64 (0.85, 3.18)
Planned Caesarean section	-0.001	1.00 (0.42, 2.36)
Presentation (vertex)	-0.356	0.70 (0.46, 1.06)
Foetal distress	0.502	1.65 (0.52, 5.30)
Mode of delivery (Caesarean section or instrumental procedure)	0.683	1.98* (1.10, 3.55)
Obstetric complications of large for gestational age - Neonatal factors (n = 1282):		
APGAR score (5 minutes)	0.026	1.03 (0.97, 1.09)
Congenital anomaly	0.036	1.04 (0.31, 3.42)
Resuscitation procedures required	0.925	2.52* (1.33, 4.79)
Intensive or special care nursery	1.324	3.76* (1.89, 7.49)
Baby hospital length of stay >1 week	0.595	1.81 (0.52, 6.37)

[a]Relative to "no university degree" (not complete high school or complete high school/TAFE)
*Significant results at the 5% level.

than average proportion of large for gestational age births. Their characteristics in twelve pre-determined community profiles were explored based on the 2006 Australian Census of Population and Housing Community Profile data and the matching digital boundary base maps in generic Geographic Information System format.

Results

During the first three recruitment phases of the study (November 2006 to August 2008), the total number of mothers approached was 3321, of whom 1553 women (46.8%) agreed to participate and 1565 babies have been registered with the study (including twelve sets of twins).

The baseline characteristics of the recruited cohort are displayed in Table 1. The corresponding details of all births in the study region during 2006 are also presented to allow comparisons between cohort participants and the general population. The birth cohort sample did not differ significantly from the general population for maternal age or infant gender (Table 1). However, the percentage of infants with low birth weight (<2500 g) was approximately half that of babies born in the general population, due to the prospective mothers being recruited in the study towards the end of the third trimester. For the same reason, our sample did not include any infants born before 28 weeks gestation, and had a smaller proportion of infants born between 28 and 36 weeks gestation. In addition, the percentage of twins was approximately half of that in the general population, and our sample had a very small proportion of stillbirths. As the low birth weight and low gestational age groups in our sample are not good representatives of the population in general, the group of low birth weights (39, 2.5%), gestational age less than 37 weeks, and twin pregnancies are excluded from the analysis. There are a total of 1440 singleton babies with complete information on birth weight, gender, and maternal gestational age for the analysis.

Birth weight: The adjusted mean birth weights at gestational age of 40 weeks for the first subgroup (corresponding to a group of infants of normal birth weight) are 3619 g (95% CI=3580-3659) for males and 3488 g (95% CI=3451-3524) for females. For the second subgroup (corresponding to a group of large for gestational age newborns), they are 4394 g (95% CI=4231-4556) and 4249 g (95% CI=4039-4458) for males and females, respectively. For comparison, we quote the 90th and 95th percentiles of Australian national birth weights at gestational age of 40 weeks from 1991 to 1994, which are 4170 g and 4340 g, respectively, for singleton males, and 4000 g and 4170 g, respectively, for singleton females.

Proximal risk factors: The adjusted odds ratios of large for gestational age births for each category of risk factors are provided in Table 2. Several demographic (Pre-pregnancy obesity; Previous pregnancy; Marital status), socio-economic (Education level), and behavioural (Maternal smoking) factors have impact on risk of large for gestational age births. These five risk factors were entered into the final mixture model. The final results of determinants for risk of large for gestational age births are presented in Table 3.

There is an increased likelihood to have a large for gestational age baby (adjusted OR=2.73, 95% CI=1.49-5.01) for mothers who are categorized as obese during pre-pregnancy based on maternal pre-pregnancy BMI (Table 3). The likelihood of having a large for gestational age baby is also increased for mothers who have had a previous pregnancy (adjusted OR=2.03, 95% CI=1.08-3.81) and mothers who are married (adjusted OR=1.85, 95% CI=1.00-3.42). For mothers who did not smoke during pregnancy, there was an increased likelihood for giving birth to a large for gestational age baby (adjusted OR=4.17, 95% CI=1.43-12.1). The likelihood of having a large for gestational age baby is, however, decreased for mothers who have higher education level, though this result was only marginally significant at the 10% level. The assessment of subsequent obstetric complications of large for gestational age births is presented in Table 3. It was found that delivery of large for gestational age baby increases the chance of requiring caesarean section or instrumental procedure (adjusted OR=1.98, 95% CI=1.10-3.55). Also, newborns who are large for

Table 4 Characteristics of the communities with a high proportion of large for gestational age births

Characteristics	Postal area[a]									Others[b] (n = 25)	P-value[c]
	2486	4127	4128	4129	4207	4209	4213	4223	4280		
Population density (person/km^2)	242 (11)	727 (16)	1357 (23)	659 (15)	**125 (6)**	**196 (9)**	**109 (5)**	**318 (12)**	**92 (3)**	1109 (21)	0.026
Indigenous persons	**3.1% (31)**	1.6% (21)	0.7% (4)	1.6% (20)	2.6% (28)	1.8% (22)	1.1% (12)	1.6% (19)	1.8% (23)	1.3% (15)	0.391
Other language spoken (home)	3.2% (3)	11% (25)	7.9% (19)	6.5% (16)	5.8% (11)	5.5% (10)	6.1% (12)	**3.4% (4)**	**3.6% (5)**	9.3% (21)	0.042
Family income ($/week)	921 (3)	1212 (27)	**1412 (34)**	**1229 (29)**	1107 (15)	1210 (26)	1181 (24)	1110 (16)	1198 (25)	1095 (13.5)	0.110
Household size (person)	2.4 (9.5)	2.7 (17)	3.0 (29)	2.9 (25)	2.7 (17)	3.0 (29)	3.0 (29)	2.5 (11)	3.2 (34)	2.7 (17)	0.105
Married persons	54% (28)	48% (15)	55% (29)	52% (23)	48% (14)	50% (18)	56% (31)	50% (21)	58% (32)	47% (13)	0.039
Volunteer	15% (27)	15% (28)	16% (29)	14% (18)	14% (23)	13% (11)	18% (33)	**15% (26)**	**15% (24)**	13% (14)	0.017
Unpaid domestic work (> 5 hours - females)	73% (28)	69% (20)	71% (25)	72% (26)	**71% (24)**	**76% (33)**	**71% (23)**	64% (13)	77% (34)	65% (14)	0.008
Age 20-39 ever born	66% (27)	55% (13)	58% (17)	59% (18)	66% (28)	65% (26)	63% (23)	57% (16)	73% (34)	55% (14)	0.086
One-parent family with children < 15	9.4% (17)	11% (26)	7.5% (5)	11% (24)	12% (27)	12% (29)	9.3% (15)	9.3% (16)	8.0% (6)	9.6% (18)	0.785
Labour force participation	**48% (2)**	68% (28)	**74% (34)**	**70% (31)**	62% (17)	72% (33)	67% (25)	59% (12)	67% (26)	61% (15)	0.051
Migrant lived at different address 1 year ago	**16% (3)**	17% (11)	**16% (6)**	**17% (8)**	17% (12)	38% (34)	17% (9)	**16% (5)**	**15% (1)**	20% (21)	0.008

[a]Values in parentheses are the rankings am ong the total of 34 communities.
[b]Median values (ranks) are presented among the 25 other communities.
[c]Mann-Whitney test for comparing medians between the nine communities and the others.

gestational age have a significantly higher likelihood of needing resuscitation procedures (adjusted OR=2.52, 95% CI=1.33-4.79) and admission to an intensive or special care nursery (adjusted OR=3.76, 95% CI=1.89-7.49).

Community effect: The unadjusted estimated proportion of large for gestational age births was 10.3%. We identified nine communities (postal code areas of participating mothers) that are associated with a higher proportion of large for gestational age births. These nine communities (Figure 1) have a higher proportion of mothers who possess some of those identified risk factors for large for gestational age babies. Of substantial importance is the finding that three of the communities (postal areas 2486, 4127, and 4280) have a large positive community effect (adjusted ORs are ranged from 1.7 to 2.2), that accounts for unknown adverse effects from the community other than those identified risk factors. The twelve pre-determined characteristics of the nine communities are presented in Table 4. Comparing to other communities, postal areas 4128 and 4129 have higher family incomes, higher labour force participations, but lower percentages of migrants moved in the community within a year. On the other hand, postal areas 4207, 4209, and 4213 have a lower population density but a higher proportion of females doing unpaid domestic work. The postal areas 4223 and 4280 have lower population densities and lower proportions of persons speaking other languages at home. They also have lower proportions of migrants moved in the community within a year. The postal area 2486 is unique; it has a higher percentage of indigenous persons but lower labour force participation.

Discussion

In this study, two sub-populations of infants were identified, with the first subgroup corresponding to a group of infants of normal birth weight and the second subgroup corresponding to a group of infants with large birth weight adjusted for gestational age and baby gender. We identified several risk factors that significantly increase the chance of having a large for gestational age baby. The findings improve the evidence-base regarding determinants and obstetric complications involving large for gestational age births. High maternal pre-pregnancy BMI has been shown to be related to high birth weight. The association with parity, maternal age and region of birth was recently shown. Our research findings indicate the adverse effect of maternal smoking on birth weights and support previously reported results that reduced smoking prevalence among pregnant women partly explains the temporal increase in proportion of large for gestational age births. Similar findings on the association between maternal smoking and low birth weight are demonstrated in the recent cohort studies conducted in Australia and the UK. Our results also confirm that the delivery of a large for gestational age infant is associated with an increased risk of obstetric complications such as caesarean delivery or instrumental delivery for mothers and the needs of resuscitation procedure or intensive/special care nursery for infants.

The identification of risk factors that are associated with large for gestational age infants has important public health implications. In the short-term, it is essential to target those pregnancies that have a high risk of having a large for gestational age infant and concomitant increased likelihood of obstetric complications. The large for gestational age infants will also have a higher risk of complications in the immediate post-delivery period. Hence they will require more intensive monitoring in the newborn nursery or neonatal intensive care unit. There has been evidence that large for gestational age infants may have long-term health issues in addition to the short-term health complications mentioned above. These include an increased risk of suffering chronic diseases later in life such as diabetes, hypertension, and asthma.

We have identified nine communities that have a higher proportion of large for gestational age births. These communities

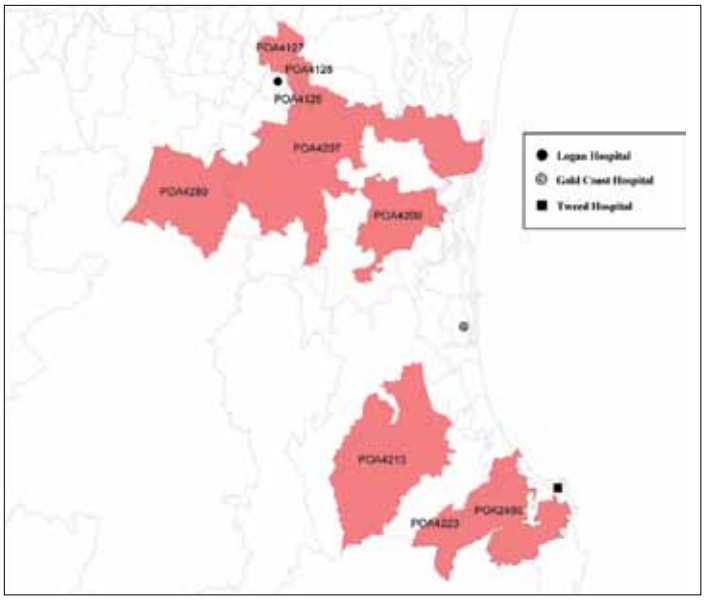

Figure 1. Nine communities, designated by postal area (POA) codes, with a higher proportion of large for gestational age births.

have certain distinguishable characteristics from other communities in the study. They tend to have a higher proportion of females doing unpaid domestic work (except postal area 4223) but a lower proportion of migrants moving in the communities (except postal area 4209). Of substantial importance is the finding that three of the communities had a large positive community effect even after controlling for identified risk factors. While these findings will have the potential to pinpoint where improvements can be made within the community to reduce the impact of high birth weight on chronic health conditions and development in children, further validation on the findings are required when more data become available. The fourth-recruitment phase of the Environments for Healthy Living study has been completed and subsequent recruitment is scheduled for future years. This new birth cohort will help targeting interventions to reduce the escalating burden resulting from high birth-weight in Australia. It will also enhance the power to explore further the ecological determinants of large birth-weight and confirm research findings in other populations worldwide.

Strengths and limitations

In this study, the mixture model assumed that the observed birth weights came from a population that consisted of two components corresponding to the appropriate for gestational age and large for gestational age subgroups. Thus we circumvented a major limitation in previous research in that the mixture modelling approach requires no prehoc threshold to define large for gestational age infants. In contrast to the logistic regression approach that works on dichotomous outcomes of large for gestational age, the mixture modelling method attempts to model directly the birth weights, which are more informative relative to dichotomized outcomes for examining effects of risk factors. Another limitation of the logistic regression approach is that a pre-defined cut-off point for large for gestational age offers only a "hard" classification of infants to large for gestational age and non-large for gestational age subgroups. This means that the estimated effects of the risk factors will be biased when there are substantially overlapping subgroups. The mixture modelling approach, on the other hand, offers a probabilistic classification of infants in the estimation of unknown parameters, and hence will provide less biased estimation of effect sizes.

Given there was complete follow up of subjects between the antenatal ascertainment of explanatory variables and the birth weight and obstetric outcomes the internal validity of the project is strong. The external validity of the results may be compromised by the sample recruitment method that did not engage women who are at risk for delivering babies with low birth weight. Similarly, women using private maternity services (normally those from higher socioeconomic backgrounds) and those with high risk pregnancies referred to specialist care are not captured in the sample. These shortcomings have been addressed in the analysis as described in the methods section by eliminating the group of low birth weights or gestational age smaller than 37 weeks.

In the analysis, we did not include maternal morbidities such as diabetes and hypertension as this information was not available for approximately 30% of the cohort due to differences in hospital perinatal data collection. As the national prevalence of these maternal co-morbidities are generally quite low (such as, 4.6% for gestational diabetes), the number of women in our study sample who would have been affected would have been quite small. The association of diabetes and large birth weight has been demonstrated in previous cohort studies. Moreover, it has been shown that weight gain during pregnancy is also related to large birth weight. As this information was not available for approximately 55% of the cohort, it was not possible to perform multivariate analysis of large for gestational age births and potential risk factors with the inclusion of the weight gain during pregnancy without inducing serious bias in the estimation of adjusted odd ratios.

Conclusions

Pre pregnancy obesity is the principal modifiable risk factor for large for gestational age births. Large for gestational age is an important risk factor for the subsequent obstetric complications. The findings from this new cohort study in Australia improve the evidence-base on which to base preventive interventions to reduce the impact of high birth weight on maternal and child health, and confirm research findings in other populations worldwide.

Legislative Watch: HIPAA, HITECH, and EHR Meaningful Use: An Overview of Major Legal Changes 2009-2010

Carol Brass

The sheer number of acronyms floating around the healthcare atmosphere lately could easily give anyone a headache: from HIPAA to HITECH, EHR to CMS, and ARRA to PPACA, the last two years have been a time of significant legal and regulatory changes for healthcare providers. To best understand these changes, keep in mind Congress' overarching goals: encouraging the adoption and meaningful use of electronic health records (EHR) across the US and assuring patients that their personal health information will continue to be protected as medicine enters the digital era.

Background – HIPAA

In 1996, the US Congress enacted the Health Insurance Protection and Accountability Act (HIPAA), and since then few healthcare providers or their attorneys have heard the term "HIPAA" without feeling a slight chill of apprehension. Under HIPAA, certain covered entities (including healthcare providers, both as individuals (eg, nurses) and organizations (eg, hospitals) are responsible for ensuring that patient safety information is kept confidential. Traditionally, physician-patient confidentiality is protected by judicial evidentiary rules developed by state courts, but patient relationships with other types of healthcare providers are not considered legally protected confidential relationships, nor is physician-patient confidentiality privileged at the federal level. Thus, HIPAA is in a sense the federal legislative equivalent of the state physician-patient relationship, extended to entities such as hospitals and hospital employees.

Ultimately, the goal of HIPAA is to assuage patient concerns that the conditions they disclose to their healthcare providers will be disclosed to outside parties; the rationale is that if patients know their information is protected, they will be comfortable confiding in these healthcare providers and as a result will receive superior healthcare. While this goal is certainly laudable, HIPAA has unfortunately gained a reputation for being overly complex and sometimes harsh in its attempt to protect information. For example, even inadvertent disclosures can be the basis for penalties, regardless of whether any patient was harmed by the disclosure. CVS Caremark recently settled with the FTC for $2.5 million over allegations that it had improperly disposed of paperwork containing private patient information in unsecured dumpsters, despite the fact that there was no evidence that any patient had been harmed. Because the potential penalties for HIPAA violations can be quite large, many healthcare providers have adopted extreme measures to safeguard against disclosure of patient information. While this outcome is in some senses a positive one, it is also inefficient in many cases because providers are hesitant to provide care in what may be the most effective way because they fear HIPAA repercussions. As a result, much of HIPAA's impact has been felt in the adoption of overly protective measures by covered providers. In other words, because of the confusing nature of the regulatory structure, some providers have taken extreme measures—often not mandated by the act itself – to ensure compliance. For example, there was great concern after HIPAA's enactment that announcing a patient's name in a hospital waiting room would violate HIPAA protections, and as a result some hospitals cautioned their employees not to do this. However, HIPAA itself provides an exception for actions such as this in 45 CFR 164.502(a)(I)(iii). In response to the widespread concerns, the Department of Health and Human Services itself stated on its website that: "Covered entities, such as physician's offices, may use patient sign-in sheets or call out patient names in waiting rooms, so long as the information disclosed is appropriately limited." In many similar situations, the confusing regulatory structure has led healthcare providers to take more extreme measures than necessary to protect patient privacy, ultimately at financial expense to healthcare institutions. The reason for this conservative approach is the severe penalties prescribed by HIPAA; for knowing and willful wrongful disclosures of protected health information, individuals could potentially be fined $50,000 and imprisoned up to a year (and for a disclosure with the intent of selling the information or using it for personal gain, the penalties go up to $250,000 and 10 years of imprisonment). Even so, few prosecutions have ever actually been made under HIPAA; up until 2008, only 4 cases were criminally prosecuted under HIPAA. As in many other fields of healthcare however, the fear of accruing legal liability has resulted in extreme responses to laws and regulations that go beyond what is required for legal compliance.[1]

ARRA and HITECH – What changes now?

The HIPAA regulatory structure, which defines the uses and disclosures for which an authorization is required, the uses and disclosures requiring an opportunity for the individual to agree or object, and the uses and disclosures for which an authorization or opportunity to agree or object is not required remains largely the same at this point. What has changed is

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primarily due to the adoption of new legislation under the American Recovery and Reinvestment Act (ARRA). ARRA, otherwise known as the Stimulus Act of 2009, contained within it a section known as the Health Information Technology for Economic and Clinical Health Act (HITECH), as well as sections that expand HIPAA's reach even further into the realm of privacy. These new sections are primarily concerned with two goals: (1) enhancing the existing privacy protections put in place by HIPAA, and (2) creating financial disincentives for organizations that fail to adopt electronic health record systems. ARRA is relevant to healthcare providers, including individual practitioners as well as institutions, in two ways. First, it sets out fairly aggressive new enforcement guidelines for HIPAA breaches. Recall that a HIPAA breach is fairly broadly defined and does not require intent—for example, a respiratory therapist who loses a work Blackberry on the train home may be liable (as well as her employer) if the Blackberry is not password protected at the time of loss, even if the phone is returned to the hospital a few days later. Under ARRA, patients must be notified of any inadvertent disclosure of their information, regardless of whether they were harmed by it or not. Further, ARRA suggests that enforcement will become far more stringent; while previously there were only a handful of criminal prosecutions under the HIPAA statute, prosecutions may be a more common occurrence now. Further, certain penalties have now become mandatory. For example, if a disclosure was made and the provider was found to have acted with "willful neglect," then a penalty will be mandatory. The dollar values for penalties have also been enhanced, and the Act also mandates HHS to conduct audits to ensure compliance with the Act's terms. Recently, responsibility for HIPAA security rule enforcement has been transferred to HHS's Office for Civil Rights. Previously, such enforcement was the responsibility of CMS. Many believe that this switch indicates a future trend towards more rigorous enforcement, as CMS's enforcement of the rule was notoriously lax. Overall, it does appear that these penalties indicate an even stronger commitment by Congress to penalize the unlawful dissemination of private health information.

The second way that ARRA is relevant to healthcare providers is in the electronic health record (EHR) context. The HITECH Act, a section of ARRA, creates new incentives for the adoption and meaningful use of electronic health records (EHR). EHR and, more generally, the use of technology in healthcare, have been touted as solutions to many of the problems currently plaguing healthcare institutions. For example, e-prescription technology would ensure that patients do not receive multiple pharmaceuticals that may adversely interact with each other; similarly, electronic health records help ensure that physicians do not forget to ask potentially crucial diagnostic questions when they diagnose their patients. Others feel that utilizing EHR technology hampers physicians' ability to interact with the patient on a personal level and unduly restricts the physician's ability to make notations on charts and perform examinations in a way that intuitively makes sense for each patient.

Regardless of the perceived benefits and downfalls of EHR, the reality is that the HITECH Act has made adoption of EHR virtually a mandate for many hospitals and eligible providers (EPs). HITECH does this by utilizing both a carrot and a stick. Hospitals and EPs that are able to adopt and meaningfully use EHR technology will be rewarded with incentive payment awards for their use of EHR technology. On July 18, 2010, CMS released its new rules on what constitutes "meaningful use" of electronic health record technology. These rules are quite complex and ultimately it is predicted that many providers will not be able to take full advantage of the incentive payment awards because they simply are not prepared to move to electronic health records technology yet. The Wall Street Journal reported that an American Hospital Association survey of 3,100 members found only 12% currently using electronic records – and only 2% would have met the requirements drafted by the federal government to receive incentive payments. In other words, the vast majority of hospitals that have already adopted EHR would not even qualify for meaningful use incentive payments. The incentive payments will only be available for a short time: for example, providers enrolled in the Medicare EHR incentive program may not receive incentive payments if they commence use after 2015. After 2015, the carrot turns into a stick, and providers that still have not adopted and begun to meaningfully use certified EHR will be penalized with schedule-based fee reductions. Very generally, for EPs, fee reductions will consist of 1% off each year; in other words, an EP would likely receive a payment adjustment of 99% of the schedule-based fee in calendar year 2015 and 98% in 2016. Given that schedule-based fees are already the subject of much legislative scrutiny and potential cuts, these percentage cuts may fall on top of fees that have already been reduced significantly. In that case, failure to meaningfully use EHR could be the difference between financial life and death for a healthcare provider that is already financially unstable.

Future Forecast: Stormy Seas Ahead

Many commentators expect that future HIPAA enforcement will be far more stringent than it has been in the past. The passage of the HITECH Act and its more stringent penalties signals a strong Congressional intent to enhance the protections provided for patient safety. Further, the enhanced financial penalties and the mandatory nature of some penalties under HITECH gives the OCR an enhanced incentive to prosecute cases to their completion. Non-compliance with HIPAA will also now endanger a healthcare organization's future ability to receive the reimbursement incentives in place for EHR adoption. One major concern is that provisions of HIPAA that have not been enforced in the past will now be enforced given the more stringent standards and mandatory penalties. As a result, each individual provider's careful compliance with HIPAA rules and regulations is more important than ever.

1 See, eg, The evolution of HIPAA: the only constant is change, Kirsten Ruzic Wild. 12 No. 2 J. Healthcare compliance 33 (2010).

Challenges in Targeting SpO_2 in Extremely Premature Infants

Tom Bachman

Summary
As early as 1780, oxygen was applied therapeutically to an infant. It was a century later when its neurological and pulmonary toxicity was reported. Nevertheless oxygen therapy for infants in incubators became common. In the early 1950s its use was associated with blindness. In the early 1960s an understanding evolved that limiting inspired oxygen, while reducing blindness, resulted in higher morbidity and mortality.

While SpO_2 monitoring became the standard of care in the NICU in the '90s, its use was focused on detecting significant oxygen desaturations. There was little concern about the need to minimize excess. In 2001 Anderson and colleagues reported an association of increased incidence of ROP in centers that set the high SpO_2 alarm higher. Several studies supported the hypothesis that targeting a lower SpO_2 range could reduce retinopathy of prematurity (ROP) and chronic lung disease (CLD), without increased mortality or developmental morbidity. Currently three mega randomized-trials are being undertaken (each enrolling over a 1000 infants), to identify the best possible guideline for the appropriate target range for SpO_2, and hopefully a standard of care. When fully evaluated, there will more likely be some consensus. The current thinking is that a target of 88%-93% is an appropriate guideline.

Initial studies showed that neonates spend only about half the time in the intended SpO_2 target range and further more unstable infants are likely to spend less time in the intended target range. Studies also found significant gaps in nurse knowledge, practice and unit policy. While a better understanding of the most appropriate target range, and continuing training as to its proper application is important, there are certainly real clinical realities of bedside management. Even with 1:1 staffing it seems unlikely that adjustments could be made more frequently than every minute. It also seems unlikely to expect every severe hypoxemic and hyperoxemic episode to be addressed promptly over an 8 or 12-hour shift. This problem could be addressed with automation and commercial closed loop control systems are currently under development. One of these systems, the Avea $CLiO_2$ (CareFusion, Yorba Linda, CA), is commercially available outside the US and has been evaluated in two studies. The data from these evaluations of the automated system showed promise of increased time in the prescribed target range, decreased time of severe hyperoxemia, reduced alarms with a decrease of manual FiO_2 adjustments.

In conclusion, careful selection of SpO_2 targets and alarm levels, effective education as to the risks of oxygenation extremes and automation all have a critical role to play.

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Introduction

The history of the use of oxygen in infants was recently presented by Silverman and characterized as "the albatross of neonatal medicine."[1] Priestly discovered oxygen in 1774. Shortly thereafter, in 1780, oxygen was applied therapeutically to an infant. It was a century later when Bert and Smith separately reported on oxygen's neurological and pulmonary toxicity. With little regard for this information, in the 1940s oxygen therapy for infants in incubators became common to treat cyanosis and disordered breathing. It was not until the early 1950s that its use was associated with blindness. A large collaborative study suggested that this could be mitigated by reducing the level of inspired oxygen, resulting in the adoption of a "40% is OK" guideline. In the early 1960s an understanding evolved that limiting inspired oxygen, while reducing blindness, resulted in higher morbidity and mortality. With the understanding of the trade-off between too little and too much oxygen and the availability of the blood gas analyzer, infants could be given the right amount of oxygen – though the right amount has never been carefully characterized. Transcutaneous measurement of PaO_2 and $PaCO_2$ made continuous monitoring practical in the late 70s. The refinement of the pulse oximeter, that is, making it useable with neonates, resulted in its widespread adoption a decade later.

Targeting SpO_2

While SpO_2 monitoring became the standard of care in the NICU in the 90s, its use was focused on detecting significant oxygen de-saturations. Evaluation of gas exchange and acid-base balance remained the domain of the periodic arterial analysis. Having forgotten the lessons of the past, there was inadequate concern about the need to minimize excess oxygenation. In 2001 Anderson and colleagues surveyed the SpO_2 alarm-setting practices of 145 leading neonatal centers in the US, and found most (87%) had SpO_2 alarm guidelines.[2] Among those units, however, she reported that 1/3 used an upper level of 97% or higher. Such SpO_2 alarm levels are consistent with PaO_2s in excess of 100 mmHg; clearly recognized then as excessive. She

also reported an association of increased incidence of ROP in centers that set the high SpO_2 alarm higher. Two important observational studies, one retrospective and one prospective, supported the hypothesis that targeting a lower SpO_2 range could reduce retinopathy of prematurity (ROP) and chronic lung disease (CLD), without increased mortality or developmental morbidity.[3,4] This hypothesis was confirmed by the large multicenter randomized BOOST Trial.[5] Nevertheless two recent studies comparing SpO_2 and PaO_2 reiterate that there is no ideal practical SpO_2 range that insures elimination of both hypoxemia and hyperoxia and thus, targeting becomes a tradeoff between the two extremes.[6,7] The STOP-ROP SpO_2 targeting trial preceded the BOOST trial.[8] It found no benefits of higher SpO_2s in treating established ROP, but increased morbidity. However the related HOPE-ROP observational study suggested some possible benefit in subgroups.[9]

With the practical benefit of SpO_2 targeting established, work began on exploring appropriate targets. Three mega randomized-trials were undertaken cooperatively with the intent of an eventual collaborative meta-analysis. Each is enrolling over a 1,000 infants and includes neonatal and long-term developmental outcomes assessment. The preliminary results from the first, SUPPORT, were just reported.[10] They indicate a continued reduction in ROP and CLD associated with the lowest SpO_2 target range (85%-89%), but also a small increase in mortality. The Canadian Oxygen Trial (COT) and BOOST-II (UK, Australia, New Zealand) are ongoing and preliminary results not available at this time. When fully evaluated, there will more likely be some consensus about the appropriate target range for SpO_2, and hopefully a standard of care. The current thinking is that a target of 88%-93%, a range between the high and low targets of the mega-trials, is an appropriate guideline.

Obstacles to Implementation

While there are often scientific challenges in clarifying clinical imperatives, their implementation into clinical practice at the bedside is often also daunting. As described above a major research collaborative emerged. These include patient stability, training/bias, and attentiveness.

To the surprise of some, two studies reported that neonates spend only about half the time in the intended SpO_2 target range. Laptook and colleagues reported that 74 infants at their center spent 27% of time below the target range, 15% above and 58% in range.[11] Hagadorn and colleagues confirmed this finding in 14 centers, reporting that 16% of the time the infants were below the target range, 36% above and 48% in range.[12] There was also considerable variation among and within sites. It is interesting to note the difference between the proportions above and below the target in the two studies, suggesting some operator bias. A careful review of the literature supports the obvious; that the percentage of time in range is correlated negatively with the number of significant de-saturations of the infant. Less obvious, but also important, is that because de-saturations are associated with temporary increases in FiO_2, they can also lead to increased time above the target range. So more unstable infants are likely to spend less time in the intended target range, other things being equal. Most importantly, one needs to remember that the therapeutic effect of oxygen is associated, not with its target range but rather with the actual oxygen exposure.

Three recent studies found significant gaps in nurse knowledge, practice and unit policy. In a retrospective review of the management of 144 consecutive VLBW infants, Clucas and colleagues reported that while the low alarm was set correctly 90% of the time, the high alarm was set higher than the policy nearly three-quarters of the time.[13] Furthermore, it was set at 100% a quarter of the time. Nevertheless they reported a tendency to be more compliant with guidelines with sicker more vulnerable infants. Nghiem and colleagues surveyed 2,805 neonatal nurses who worked in 59 different NICUs.[14] They found that less than a quarter of the nurses even knew their unit's policy. Armbruster and colleagues reported that alarm limits were set correctly for about three-quarters of the infants enrolled in a multicenter targeting trial, and further suggested their performance was better than other centers in the trial.[15] This seems consistent with the findings of Nghiem and Clucas, as you would expect better compliance when part of an international randomized trial. Nevertheless, even setting the alarms correctly three-quarters of the time does offer opportunity for improvement. Correspondingly, Armbruster also surveyed the staff to determine what issues they perceived as important to trigger improvement. The most common were education, providing priority to FiO_2 control including prompt response, staffing ratio and root-cause analysis at the bedside. The challenging shift in practice patterns can be accomplished. In addition to the report of Delofuet, Sink and colleagues have recently reported on their successful transition to a much lower target range, facilitated by a significant education program, "Oxygen With Love."[16]

Another important point has become clear with the publication of more targeting trials that needs to be highlighted. There is a tendency for the SpO_2 to be set higher than intended, even in controlled trials. As an example, in the recently published SUPPORT trial, both groups' median SpO_2s were significantly above the midpoint of the target range. It is not clear whether this is an inherent bias associated with avoiding low saturation alarms, or a lack of understanding of the risks associated with high SpO_2. This tendency would result in excess time above the target range as seen in Hagadorn's report, and must be considered when implementing SpO_2 targeting policy.

While a better understanding of the most appropriate target range, and continuing training as to its proper application is important, there are certainly clinical realities of bedside management. Monitoring SpO_2 and titrating FiO_2 is only one of the tasks facing nurses. Bitan and colleagues undertook an observational study in one unit to determine factors associated with how neonatal nurses react to alarms.[17] Excluding alarms that lasted 5 seconds or less, they found that on average there were 8 alarms per hour for each patient, or one every 2-3 minutes per nurse. Saturation alarms were the most common (83%), followed by heart rate (14%) and respiration (3%). They found that nurses were faced with activated alarms about 20% of the time. Response to saturation alarms occurred within a minute in only 20% of the cases. In fact a saturation alarm resulted in only a 50% increase in the chance that nurses would attend to an infant. The nurses were found to treat heart rate and saturation alarms with equal priority, about half that of respiration. Still, on average the nurses had an interaction with each infant every 6 minutes.

There appears to be little or information in the literature about implementation of different strategies for the adjusting FiO_2, based on SpO_2. We are aware of two reports of beside FiO_2 adjustment guidelines. Neither suggests that they reflect a proposed standard or are accompanied with any information

on compliance or effectiveness. Wilkinson suggested that adjustment to an out of target range event should occur within 20 seconds, with medical intervention when infant response is inappropriate, after two minutes.[18] DiFiore reported an approach of responding within 30 seconds to a severe desaturation, but within 1 minute to other out of target range situations.[19] Both of these are more attentive than the experience reported by Bitran.

There are two reports of the actions of a full time operator addressing just FiO_2. Both were conducted as a control group in comparison to investigational closed loop FiO_2 controllers. Urschitz and colleagues reported their experience with two groups of 12 preterm infants during NCPAP.[20] In both groups the frequency of adjustment (11.7 and 7 per hour) of the full time operator were comparable to the incidences outside the target range and much more frequent than during the period of routine care (1.7 and 3 per hour). This more frequent "optimal care" also resulted in more time in the target range. Claure and colleagues reported on the use of dedicated FiO_2 adjustment during IMV in 14 extremely preterm infants.[21] Dedicated care in this group received 29 adjustments per hour, which was consistent, as seen by Urschitz, with the frequency of SpO_2 outside the target range. Claure also found that the essentially continuous adjustment of the closed loop system resulted in more time in the target range than did dedicated care.

Measured adjustment of FiO_2 whenever SpO_2 is outside of the intended target range seems like an aggressive but appropriate approach to maximizing time in the desired SpO_2 range. Some have suggested less intervention; that is, adjustments prioritized to responding to hyperoxemia and severe hypoxemia, by setting alarm limits wider (eg, 80%-95%).[3,22] It seems likely that many of the SpO_2 alarms not addressed in Bitan's study, did not reflect extreme conditions. However the perceived severity of the SpO_2 alarm is tempered by both the nurse's education as to risk and the workload at the moment. Regardless, response to only severe conditions will certainly result in less time in the SpO_2 target range.

Unpublished data from another controlled targeting study, where routine care was electronically logged, provides some additional basis for consideration.[23] In this study 32 VLBW infants were each monitored for 24 hours during mechanical ventilation. The SpO_2 went out of the target range every 2 minutes on average. Severe desaturations occurred about once per hour. FiO_2 adjustments were made in only 13% of the episodes, on average 5 times per hour. These responses to alarms were typically made in less than 1 minute. Further the duration of episodes that did not receive intervention was much shorter. Nevertheless in 5% of the episodes intervention was delayed to 4 minutes or more. While this one-minute response would be considered prompt by most, the data reminds us that in routine care important alarms are occasionally ignored or missed.

It is not clear what the practical limit is to routine care. It depends to some degree to staffing levels, but even with 1:1 staffing it seems unlikely that adjustments could be made more frequently than every minute. It also seems unlikely to expect every severe hypoxemic and hyperoxemic episode to be addressed promptly over an 8 or 12-hour shift. It has been apparent to many that this problem could be addressed with automation. In fact commercial closed loop control systems are under development.[20,24-26] One of these systems is commercially available outside the US. Two evaluations of that system, the Avea CLiO (CareFusion, Yorba Linda, CA) have been reported.[23,26] As can be seen in the table below, the automated system shows promise of improving time in the prescribed target range, reducing severe hyperoxemia, reducing alarms and needed FiO_2 adjustments.

Table 1. Benefits of Automated Control of FiO2 as Compared to Routine Care

	Study 1[26]	Study 2[23]
Length of study period	4hrs each	24hrs each
Number of Infants	16	32
% increase in time in Target Range	38% *	25% *
% decrease in time SpO_2 > 98%	81% *	86% *
% decrease in time SpO_2< 75%	30%	13%
% decrease in manual FiO_2 adjustments	79% *	91% *

* $p<0.05$.

Conclusion

The first decade of the 21st century has brought focus to the need to target SpO_2 in extremely premature infants. The past thinking of reducing desaturations by tolerating hyperoxemia has been shown to be inappropriate. Studies are underway which will identify the tradeoffs and establish an appropriate SpO_2 target range. However, the therapeutic benefits and risks of oxygen come not from a target range, but rather from actual oxygen exposure. There are significant challenges to successfully implementing SpO_2 targeting. Careful selection of SpO_2 targets and alarm levels, effective education as to the risks of oxygenation extremes and automation all have a critical role to play.

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Economic Results of a Palivizumab Seasonal Prophylaxis Using a Cohorting Software and Vial Sharing

Elio Coletta, Salvatore Coppolino, Febronia Federico, Francesco Fulia

Abstract

Background: Respiratory syncytial virus is the most important pathogen in lower respiratory tract infection in infants and young children. In high-risk populations it may develop severe, sometimes fatal, lower respiratory tract infections. A proportion of these infants require admission to intensive care units due to the severity of the condition and the level of care needed. Furthermore, we must consider the possible increased risk of asthma following RSV infection in infancy.

Methods: The aim of this work is to show how we strictly coordinated, during the 2008-2009 RSV season, the delivery of prophylaxis while minimizing drug cost through vial sharing and cohorting infants with a software performed through Visual Basic programming system.

Results: By using this method we have been able to obtain a saving of the 29.2% compared to the theoretical amount. No infant requested hospitalization for a RSV infection.

Conclusions: Such a model ensures all patients to receive appropriate immunization and thus positively influencing the cost-benefit of palivizumab prophylaxis. We hope that our model of care delivery will be of use to other hospitals.

Introduction

Respiratory syncytial virus (RSV) is the most important pathogen in lower respiratory tract infection in infants and young children.[1] It causes coughs and colds in winter season. The virus belongs to the same family as the human parainfluenza viruses and mumps and measles viruses. By 2 years of age, approximately 80% to 90% of children experience at least one episode of RSV infection. Although the majority of RSV infections are mild, high-risk populations such as premature infants (gestational age <33 weeks) or children with hemodynamically significant heart disease or with lung abnormalities or with immunodeficiency may develop severe, and sometimes fatal, lower respiratory tract infections.[2] In Italy, about 4-5000 RSV infected high-risk infants are hospitalized every year. A proportion of these infants require admission to intensive care units due to the severity of the condition and the level of care needed[3] and have higher mortality rates than healthy infants.

Furthermore, as potential long-term sequelae, we must consider the possible increased risk of asthma and allergies following RSV infection in infancy and its impact on life quality.[4] Palivizumab, an intramuscular humanized mouse monoclonal antibody, is used to reduce the risk of hospitalization secondary to RSV infection.[5] Seasonal prophylaxis with this antibody demonstrated clinical efficacy and satisfactory tolerability and it doesn't interfere with the administration of other vaccines.[6,7] The aim of this work is to show how we strictly coordinated, during the 2008-2009 RSV season, the delivery of prophylaxis while minimising drug cost through vial sharing.

Materials and Methods

The 2008-2009 RSV prophylaxis started in November 2008 and ended in April 2009. The vaccination program was designed to ensure that every eligible infant received RSV prophylaxis and his or her parents received necessary education to prevent RSV-related hospitalisation. The 4 bed UTIN unit at "Barone I. Romeo" Hospital, Patti (Messina) accepts 249 admissions per year. During the RSV prophylaxis season to 24 high-risk eligible children was administred the prophylaxis with palivizumab. High-risk criteria indicating the prophylaxis are reported in Table 1. The current recommended palivizumab dosage is 15mg/kg intramuscular injections (once per month for a total of 5 -6 doses during the RSV season). The cost of 50mg and 100mg vials of Synagis (Abbott Laboratories Limited) were 490.37€ and 814.35€

Table 1. High-risk criteria

Evidence grade I	Infants born from 32 weeks of gestation or earlier to 12 months at the beginning of RSV season.
Evidence grade I	Infants and children younger than 24 months with CLD who required medical therapy (supplemental oxygen and/ or drugs).
Evidence grade I	24 months old or younger children receiving medication to control hemodybamically significant heart disease or diagnosed with moderate to severe pulmonary hypertension or diagnosed with cyanotic heart disease.
Evidence grade III	Infants, born at 32 to less 35 weeks of gestation, who are 12 months old, or younger, at the start of RSV season with at least two of the following risk factors: low weight at birth (<2.5Kg), exposure to environmental air pollutants or tobacco smoke, lack of breast-feed, twin birth, chest malformation, hematologic diseases, cystic fibrosis, school-aged siblings, congenital abnormalities of the airways, cancer, severe neuromuscular diseases, immunodefiency or living where the access to a hospital is difficult.

Autors Coletta and Fullia are with UOC Pediatria e UTIN; Coppolino is with the Dipartimento del Farmaco, Cittadella della Salute, Federico is with Servizio di Farmacia, Messina, Italy. Reprinted from BioMed Central, Italian Journal of Pediatrics,

Figure 1. Screen of the developed software – This figure shows the main screen of the software used to schedule young patients during treatment. It automatically evaluated the amount of drug to be administered and then it sorts infants by weight suggesting the best way to minimize waste.

respectively. Synagis requires storage in a refrigerator (2 to 8°C) and once reconstituted, the palivizumab shelf life is estimated at six hours[8] and multidose use of single-use vials is proven safe.[9]

We used a collaborative framework for the delivery of RSV prophylaxis. The multidisciplinary team (pharmacists, physicians, nurses) collaborated to create a RSV prophylaxis program logic model, ensuring that each discipline's perspective of the program process was considered. For each program component, the team identified process and program objectives and outcomes.

Before the beginning of the prophylaxis all infants were visited and weighted and the obtained data were recorded on a database. In order to start the administration infants were grouped in four cohorts of five and one of four with a software performed by Coppolino S. through Visual Basic programming system. Visual basic is used to write Windows-based computer programs; by doing so you are not bound by the limitations of a particular "off-the shell" computer program. What is more you are able to design applications to meet your own specific needs.[10] This software requests only to insert infants names and their weight. By the clicking of a button the software calculates the palivizumab dosage, in mg, to be administrated to each infant, and following to the vial selected (50mg or 100mg one) automatically divide infants in groups, evidenced by different colours, to use as few vials as possible to minimise waste (Fig 1). Children marked with the same colour were scheduled to be vaccinated within the same day.

All data were automatically collected in a ".txt" file created to generate reports to be analyzed afterwards with common softwares. For each dose, infants attended the Ambulatory Ward on five consecutive afternoons. The second dose was administred after 3 weeks and subsequent ones at 4 weekly intervals. In total 6800mg were bought and 6200mg were given to patients. During the season, adverse events following immunization did not occur.

Table 2. Use of palivizumab and resources saving during 2008-2009 campaign

	Theoretical single use	Real use with vial sharing	Saving
50mg vials	67	16	51
100mg vials	58	60	-2
mg wasted	3.176,88	777,08	2.399,80
Value	80.087,09€	56.706,92€	23.380,17€

Results

All infants successfully completed their full course of RSV prophylaxis and were followed for 150 days after the last scheduled injection. No one requested hospitalisation for RSV infection. We calculated theoretical vial usage if every infant had been individually dosed with one vial and compared this with our real use, obtained by using the cohorting software and vial sharing. The aggregate seasonal drug cost for the season was 56.706,92€ instead of 80.087.19€ with a saving of 23.380,17€ (29.2% of theoretical amount). At the individual partecipant level the average seasonal palivizumab prophylaxis cost was 2372,69€. All data are reported in Table 2.

Discussion

During all past seasonal prophylaxis with palivizumab we treated an almost constant number of high-risk eligible children for every year.

By using vial sharing and the above described software we obtained a drug cost saving of 25% compared to 2007-2008 season. Regarding the 2009-2010 campaign, in which we used vial sharing and software again, the cost saving was of about 2%, more or less the same of 2008-2009 season and linked to the children weight.

There are main other considerations besides costs in clinical decision making, but the careful use of resources must always be considered. In-hospital interdisciplinary communication and working relationships were a program strength point, particularly the relationship between pharmacy and " Pediatria e UTIN" staff. This strength was attributed to the ongoing opportunity for dialogue.

Like any expensive healthcare intervention, palivizumab immunization must be used judiciously. Our experience shows that it is possible to minimize the cost by an accurate cohorting and by multidose distribution with a maximising use of 100mg vials in preference to the more expensive 50mg vials for cost saving with no increased risk to patients. This does, however, required tight coordination between hospital pharmacist and ward and patient selection to discard ineligible children.

Conclusions

The use of palivizumab can be optimized through a model in which children are prospectively identified and vials are shared. Such a model ensures all patients to receive appropriate immunization and thus positively influencing the cost-benefit of palivizumab prophylaxis. We hope that our model of care delivery to high-risk infants will be of use to other hospitals who seek to optimise delivery of their RSV immunization programs.

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