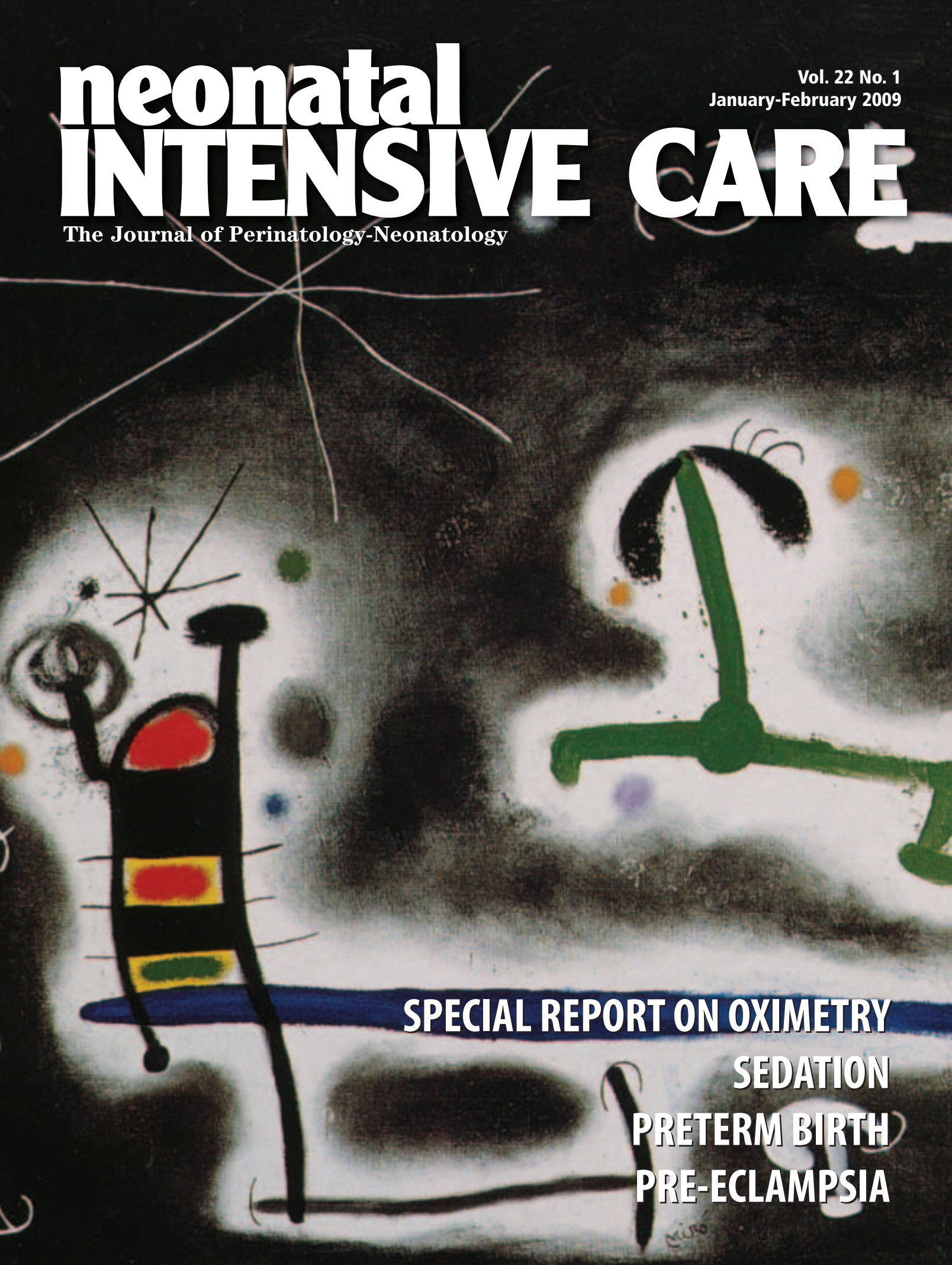
Vol. 22 No. 1
January-February 2009

neonatal INTENSIVE CARE

The Journal of Perinatology-Neonatology



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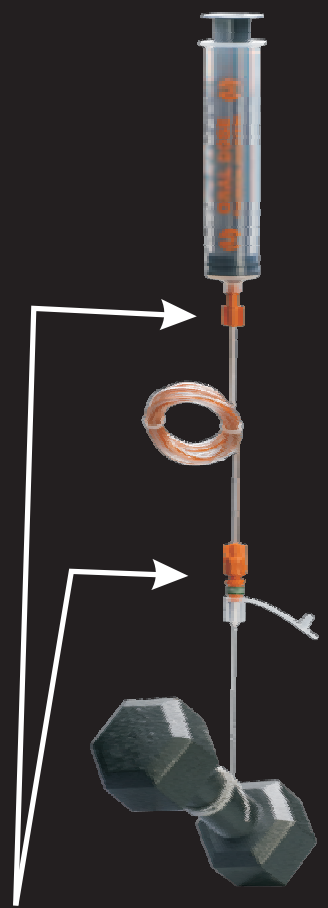

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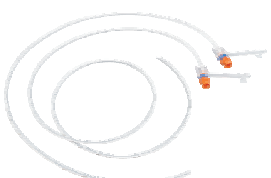

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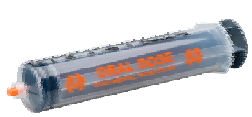

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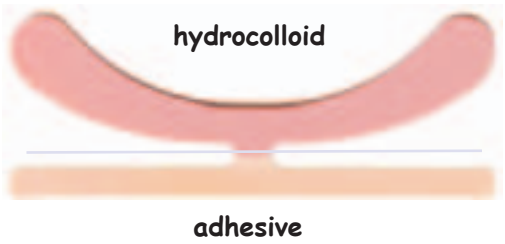

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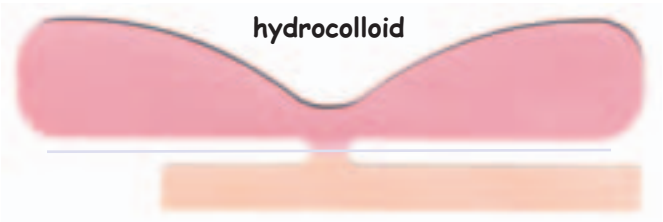

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Editorial

I Wanna Be Sedated

That's a line from the late great band, The Ramones. If preemies could talk, would they sing along? I think so. Here's a look at some comments from papers available on Medline.

Carbajal et al write in Seminars in Perinatology [2007 Oct:31(5):309-17, Elsevier] "Tracheal intubation is extremely distressing, painful, and has the potential for airway injury. Premedication with sedatives, analgesics, and muscle relaxants is standard practice for pediatric and adult intubation, yet the use of these drugs is not common for intubation in neonates. The risks and benefits of using premedications for intubating unstable newborns are hotly debated, although recent evidence shows that premedication for non-urgent or semi-urgent intubations is safer and more effective than awake intubations." The authors conclude, "The clinical benefits described in these studies and the need for pain control in neonates make the case for using appropriate premedication routinely for elective or semi-urgent intubations. Tracheal intubation without the use of analgesia or sedation should be performed only for urgent resuscitations in the delivery room or other life-threatening situations when intravenous access is unavailable."

A paper in Annals of Pharmacotherapy reports, "Preventing significant oxygen desaturation and hypotension through adequate analgesia and sedation during nonemergent intubation in neonates is desirable. However, in many neonatal intensive care units, elective intubations occur without adequate premedication. There is significant variation in the choice of premedication agent(s) and doses, and an ideal regimen for use during nonemergent intubation has not been developed." The authors studied algorithms for nonemergent intubation and concluded, "A systematic approach to premedication during nonemergent intubation successfully prevents acute physiological changes [Ann Pharmacother 2008 Jul;42(7):947-55. Epub 2008 Jul 1].

The Journal of Perinatology sought to determine the extent and types of premedication used for elective intubation in NICUs. The authors reported: Only 34 of the 78 respondents (43.6%) always use any premedication for elective intubation. Nineteen respondents (24.4%) reported to have a written policy regarding premedication. Morphine or fentanyl was used most commonly (57.1%), with a combination of opioids and midazolam or other benzodiazepines used less frequently. Fourteen respondents (25%) also used muscle relaxants with sedation for premedication, but only nine respondents combined paralysis with atropine and sedation. The authors concluded: Most neonatology fellowship program directors do not report always using premedication for newborns before elective endotracheal intubation despite strong evidence of physiologic and practical benefits. Only a minority of the NICUs has written guidelines for sedation, which may preclude effective auditing of this practice. Educational interventions may be necessary to ensure changes in clinical practice [J Perinatol. 2006 May;26(5):286-9.]

So let's get with the program. According to a British study published in the Archives of Disease in Childhood, "There is good evidence of physiological and practical benefit when neonates are sedated before intubation, and no evidence that it is harmful [Arch Dis Child Fetal Neonatal Ed 2000;82:F38-F41]."

As a coda, it might be useful to consider even the term "premedication" as prejudicial to the alleviation of pain in neonates. As a letter to the aforementioned journal pointed out, "In all other clinical areas where critical care is provided, such a structured clinical question would never have been asked. Even the term 'premedication' reflects our ignorance. The procedure we undertake everyday in our neonatal intensive care units is elsewhere termed rapid sequence induction of anesthesia, and has been described for many decades... The routine rotation of anesthetic trainees through neonatal intensive care units would be beneficial to all, and in the long run help to train more rounded neonatologists [Jonathan J. Walsh ADC Online, 4 Jan 2006]."

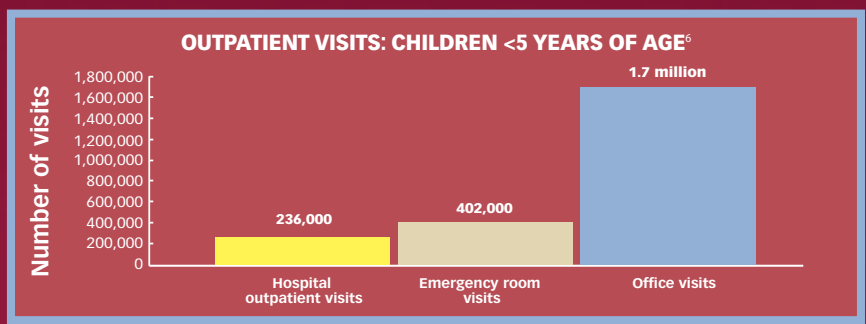
Les Plesko, Editor

The unrecognized impact of RSV-associated lower respiratory tract infection in the inpatient and outpatient settings

Respiratory syncytial virus (RSV) is a common infection that infects virtually all children by 2 years of age[1]

- Up to 125,000 infants are hospitalized annually in the US as a result of RSV disease[2,3]
- 6.52 million outpatient visits in children younger than 1 year of age were associated with bronchiolitis, the most common cause of which is RSV[4]
- 70% of infants and children <5 years of age who presented in outpatient settings with wheezing and signs of lower respiratory tract infection, who had a positive viral culture, had RSV[5]

RSV is extremely prevalent across all outpatient settings[6]

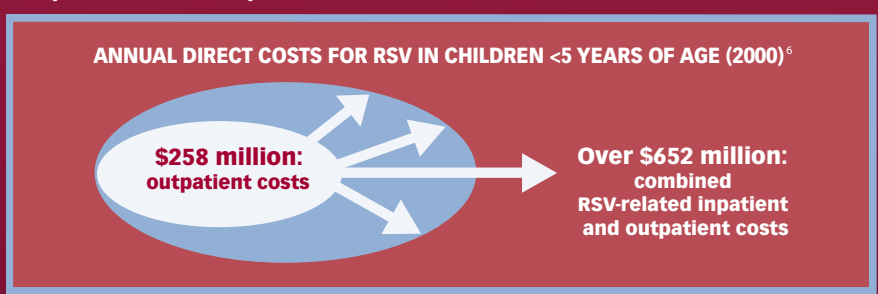


Adapted from Paramore LC et al. *Pharmacoeconomics*. 2004;22:275–284.

Estimated RSV-related visits (2000) in US children <5 years of age in several outpatient settings.

- RSV represents a substantial public health problem in outpatient settings, including hospital clinics[5]
- In fact, when infants and children present in the emergency department setting during RSV season with signs and symptoms suggesting lower respiratory tract infection, RSV is by far the most likely pathogen[7]
- In an 11-year study (1993–2004), emergency department visits for acute respiratory illnesses (ARI) in children <7 years old were estimated. Researchers found that the mean yearly rates of positive test results were 37.6% for RSV, 9.2% for influenza virus, 2.8% for parainfluenza virus, 4.6% for adenovirus, and 1.3% for enterovirus[7]

Outpatient costs represented 40% of all RSV-related costs in children <5 years of age in 2000[6]



"...[These] data underscore the enormity of the public health problem created by RSV."[5]

MedImmune: committed to ongoing research

MedImmune recognizes the need to help neonatologists continue to reduce the burden of RSV-related illness in hospital clinics and inpatient and outpatient settings and is dedicated to ongoing research in this field with the goal of helping infants live healthier lives.

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News

☐ January-February 2009

UNBELIEVERS

A national survey by the Florida Institute of Technology showed that one in four people still think vaccines may cause autism. Nineteen percent of the respondents said they weren't sure. Scientists continue to say there's no link between vaccinations and autism. Nonetheless, parents aren't vaccinating their kids as much as they used to, as evidenced by the increase in measles cases, the fastest in a decade in the US, and said to be soaring in Britain, Switzerland, Israel and Italy. All this stems from a 1998 study out of England linking autism and the MMR vaccine, a study that was retracted by some of its authors, and the purported harmful ingredient in the study, thimerosal, was removed from most vaccines in 2001. In the Florida survey, 19% of the respondents agreed with the statement, "Autism is caused by a preservative once found in childhood vaccines." An additional 43% weren't sure, meaning that fewer than half of the respondents believe no link exists between the vaccine and autism. The survey included responses from a thousand randomly selected men and women.

DO BLOW IT

As has been widely reported in the national press, using a fan in a room where a baby is sleeping can reduce the risk of SIDS. The incidence of SIDS has been decreasing because more parents are making sure their babies sleep on their backs (the baby's, not the parent's). Using a fan, and proper room ventilation, has been studied before. It has been proposed that carbon monoxide may remain around a baby's nose and mouth, leading to rebreathing, so moving the air around is the reason the risk is reduced. In the latest study, researchers at Kaiser in Oakland interviewed the moms of 185 infants who died of SIDS and the mothers of 312 random infants. The study identified several trends. For the babies who died, more slept on their stomachs or sides, didn't get a pacifier, slept on a soft surface, used bedding to cover the head, or shared a bed with someone not a parent. Using a fan during sleep was associated with a 72% decrease in SIDS deaths in comparison to sleeping in a room without a fan. This was especially true for the use of fans when the room temperature was higher. When the room was about 69° F, fan use decreased SIDS deaths by 94%. This was also true for infants who slept on their sides, shared a bed with someone other than their parents, or did not use a pacifier.

THEY BREATHE IT, TOO

The fetus suffers, too, when pregnant women breathe polluted air, according to a Swiss study. Researchers at the University of Bern obtained measurements of the day-to-day quality of the air that mothers breathed during their pregnancies and analyzed levels of three indicators of atmospheric pollution: ozone, nitrogen dioxide and airborne particulate matter. They also considered the distance between the mother's home and major roads. Finally, the team assessed the respiratory function during sleep of full-term babies when they reached five weeks of age. A mother's exposure to particulate matter during pregnancy appeared to cause changes in the newborn's respiratory parameters. The more polluted the air, the greater the increase in respiratory frequency, tidal flows and minute volume. For each 1µg/m3 increase of mean PM10 in the air breathed by the mother during pregnancy, the newborn's respiration increased by an average of 24.9 ml/min. The increase was even greater (39.2 ml/min) when the mother lived less than 150 meters from a major road. In comparison, babies whose moms had less exposure breathed an average of 48 times per minute instead of 42 times. Researchers also found that antenatal NO_2 exposure was associated with a significant rise in eNO: each 1µg/m3 rise in mean NO_2 during pregnancy was associated with a 0.98ppb increase in eNO in the newborns. These changes were most significant when mothers were exposed in the third trimester.

NO MOCHACCINOS

Pregnant women should cut their caffeine intake and drink no more than two cups of coffee or four cups of tea a day, a British government agency has advised, according to a report by the BBC. The Food Standards Agency has lowered its recommended levels of the stimulant from a maximum of 300mg a day to 200mg. The change comes after research by Leicester and Leeds universities linking caffeine to babies born with low birth weight. The study noted that women who've been drinking three cups shouldn't panic, in that "the risk is likely to be small." Women were also cautioned to watch their intake of cola, chocolate, and energy drinks. The study added that drinks brought in coffee shops may have a much higher caffeine level than a home-made cup.

THE RAIN IN SPAIN

Kids who live in counties with lots of rain tend to have higher rates of autism, according to a report posted on Medical News Today. Researchers at Cornell University studied autism rates for children born in California, Oregon, and Washington over a twelve-year period, and matched the prevalence of autism to annual rainfall. The authors concluded that autism was positively related to the amount of rain in these regions. How come? It was conjectured that rain may cause kids to stay indoors more, and thus be exposed to harmful chemicals such as cleaning supplies. Or, it could be due to a lack of exposure to sunshine. Or, the rain lets something harmful fall on the kids. The researchers cautioned that the correlation may, in fact, have nothing to do with rainfall at all, and said there was no cause for alarm. Information for the above is from Medical News Today; from an article by Anna Sophia McKenney.

WHAT HAPPENED?

Why weren't the harmful effects of thalidomide—which deformed kids fifty years ago—predicted in animal tests? German scientists say they have discovered that there was a biochemical basis for animal resistance to the drug's adverse effects. In mice cells, advanced antioxidant defenses compared to those in humans and other thalidomide-susceptible species. The biochemical basis for resistance involves a key difference between human embryonic cells and those of mice. Mice cells had advanced antioxidant defenses compared to those in humans and other thalidomide-susceptible species. Therefore, thalidomide was not able to induce the generation of large quantities of superoxides in mouse embryonic cells as it does in

human embryonic cells, where subsequent cell death is believed to be responsible for birth defects. The use of thalidomide caused the most extensive outbreak of drug-induced birth defects in medical history. It was never approved for use in the US, but is currently available elsewhere for treating myeloma and leprosy.

HEATED AND HAPPY

Babies who receive incubator care after birth are up to three times less likely to suffer depression as adults according to a study at the Université de Montréal and Sainte Justine Hospital Research Center. While logic would dictate that separation from the mother, when the baby was in the incubator, would increase later depression, the opposite turned out to be the case. Researchers studied a sample of 1,212 children, who received psychiatric assessments when they were 15 and 21 years old. Researchers found that of the 16.5% of babies placed in incubators only 5% suffered major depression by age 21. Among participants who were not placed in incubators, 9% developed depression, which is the average. Girls were three times less likely to experience depression by the age of 15 if they had received incubator care at birth, because more girls are depressed than boys during adolescence. The researchers found that direct stimuli, not just the incubator, could decrease depression. Children who received incubator care as babies typically received more emotional support from their mothers throughout childhood because they were perceived as more vulnerable.

NOT SO SWEET

Jane Brody reports in the New York Times that the incidence of gestational diabetes in the US has nearly doubled, a result of the rise in pre-pregnancy weight among American women. At the same time, it is known that even small blood-sugar abnormalities can cause problems. A seven-year study showed clear links between blood sugar levels and pregnancy outcomes, even when the mother's sugar levels were not high enough to be called diabetes. The study followed the pregnancies of more than 23,000 non-diabetic women, and revealed that as blood sugar levels increased during pregnancy, the risk of having a baby too large to be born vaginally rose as well, as did the baby's chances of being born with low blood sugar levels and high levels of insulin. The study found a continuous increase in risk as the mothers' blood sugar levels rose, with no cutoff point below which the risks were minimal. Women are at higher than average risk of gestational diabetes if they are overweight, older than 25, have a strong family history of diabetes, have had gestational diabetes during a prior pregnancy, have previously given birth to a baby weighing nine or more pounds, or have been told they are pre-diabetic. The risk is greater in African-American, Asian and Hispanic women than in Caucasians.

WORRYING AND WHEEZING

Babies of pregnant women who are stressed in late pregnancy have an increased risk of developing asthma, according to a study by the University of Bristol. By studying 5,800 families, the researchers found that very anxious pregnant women were 65% more likely to have a child who later developed asthma than calmer moms. Maternal anxiety was assessed by self-completion questionnaires that the mothers filled in at 18 and 32 weeks of pregnancy, and their children were assessed for asthma at 7.5 years of age. Bronchial hyperreactivity was also tested for when the children reached age eight, and skin prick tests were used to see whether a subject's asthma was of allergic origin. The researchers confirmed a strong connection between maternal anxiety at 18 and 32 weeks of pregnancy, and asthma in children aged 7.5 years. The asthma risk was found to be 17% higher for children born to mothers who were stressed at 32 weeks, and 14% higher where the mother was stressed at 18 weeks. In the most stressed moms group, the additional risk of asthma in the child reached 65% at 32 weeks and 53% for those severely stressed at 18 weeks. An analysis of a small sample of the cohort by other researchers found a correlation between maternal anxiety during pregnancy and disrupted cortisol secretion in children aged ten.

WAY TOO SOON

The BBC reports that there has been a dramatic rise in the number of babies being born prematurely in England. The charity Tommy's Baby's highlighted NHS figures showing 8.6% of babies were born early in 2006/7, after remaining around 7% for the previous 15 years. It said the increase equated to an extra 10,554 premature births. Experts said the rise was partly due to more older, and younger, mothers. But the NHS Information Centre, which published the latest statistics, said there had been changes to the way data had been collected which might have affected the rise. Tommy's pointed out that it's hard to tell from the figures whether the increase was due to spontaneous births or whether it was due to medically-induced premature delivery. As far as how the data was collected, possibly skewing results, there had been disparities in how different hospitals recorded premature births, and it was possible this had changed, according to the NHS. For example, if a baby was born at 36 weeks and six days, some hospitals may have round that up to 37 weeks, when they should round it down to 36.

OVERSTAYED WELCOME

Infants born more than a week past their due dates have a higher risk of impaired health and death, according to two new studies by the University of California. The studies compared more than 2.5 million normal-weight births from healthy pregnancies of 37 to 42 weeks gestation. The first study, which followed 1.8 million normal births, reported greater odds of infant death among those born at 41 and 42 weeks. The second study examined 2.5 million low-risk births and reported that the risk of cesarean deliveries and poor health outcomes for both mother and child increased at 40 weeks and beyond. Previous studies of infant mortality have reported that the rate of stillbirths is lowest at 37 to 38 weeks and increases six-fold to 2.12 stillbirths per 1,000 pregnancies at 43 weeks, but the UC studies confirm that the risk of cesarean deliveries and poor maternal or child outcomes starts to increase as early as 40 weeks. Compared with delivery at 39 weeks, women who delivered at 41 weeks had a 40% higher chance of having a cesarean delivery. Infants delivered at 41 weeks also had a higher risk of injury during birth, as well as nearly twice the rate of meconium in the amniotic fluid. The California study found that infants delivered at 41or 42 weeks had an increased chance of death within 28 days, and that the elevated mortality rates persisted across the entire range of normal birth weights.

TOO MUCH CUTTING

More than 31% of US births are now by cesarean section although a 5% to 10% rate is optimal, according to a report by three independent foundations. The studies, published in Evidence-Based Maternity Care, also point out that the cost of these c-sections is over $2.5 billion per year, and that the procedure doesn't necessarily result in a reduction of maternal or newborn deaths, and in fact causes exposure to adverse

affects. The report, by Childbirth Connection, The Reforming States Group, and the Milbank Memorial Foundation cites evidence that, as such, American women don't receive the best maternity care. It concludes that maternity care can be significantly improved using evidence-based care. According to the report, "We're paying too much and getting the worst results in the developed world because of unneeded care... The main causes are that providers earn more from unneeded care, while fear of malpractice litigation encourages the same unneeded care. C-section rates have risen by 50% since 1996. The report also showed that areas with higher rates of cesareans had more inappropriate care and more surgery in healthier women. It urged the use of effective practices such as the support of a doula, using upright and side-lying positions of giving birth, delayed cord clamping, and early skin-to-skin contact with the baby. But maternity care in US hospitals, the report said, was resource and technology-driven. Six of the 15 most commonly performed hospital procedures are associated with childbirth, and hospital charges for maternal and newborn care, $86 billion a year, are greater than for any other condition. For more see childbirthconnection.org/ebmc/.

BIG BUCKS

The American College of Medical Genetics has received a $13.5 million, 5-year contract from the Eunice Kennedy Shriver NICHD of the NIH for the development of a National Newborn Screening Translational Research Network. The NIH contract will fund the establishment of the Newborn Screening Translational Research Network Coordinating Center, whose activities will include the establishing of an organized network of state newborn screening programs and clinical centers, development of a national research informatics system for investigators and policy makers, establishment of a repository of residual dried bloodspots that is either virtual or physical, facilitation of research on screened and treated patients to define effectiveness of treatments and long-term outcomes, and facilitation of research on the development of new methods and technologies.

NO POKING

The New York Times reported on the development of techniques for noninvasive prenatal blood tests for Down syndrome that have yet to produce a false negative or a false positive result. The experimental noninvasive tests require only a blood sample. Sequenom, a biotechnology company in San Diego, CA, developed a test it plans to begin selling next year that has successfully diagnosed about 400 blood samples. It would be given to women at 12 to 14 weeks' gestation but the company hopes to be able to have the test work at 10 weeks' gestation. The Sequenom-developed test will initially be used to screen women who should subsequently undergo either amniocentesis or CVS. Researchers at Stanford University and the Howard Hughes Medical Institute developed a different noninvasive test that has been successful in testing 18 different blood samples. The new test could be administered as early as five weeks post-conception and the results could be back within days instead of weeks as with the amniocentesis and CVS. The Stanford test also has been shown to detect other chromosomal conditions such as Edward syndrome and Patau syndrome. It uses DNA technology. Information for the above is from nationalpartnership.org, © 2008 The Advisory Board Company.

THAT'S MR. POSTPARTUM TO YOU

Each day in the US, a thousand new dads become depressed, according to a report by Judy Fortin, CNN Medical correspondent. The report claims that a lot of men say they can't stand to be around their baby and/or can't stand the smell or the sound of their child screaming. Sleep deprivation and hormones are blamed for what's being diagnosed as male postpartum depression. Symptoms are sadness, a sense of worthlessness, and a loss of interest in sex and hobbies, and these everyday existential maladies are now being blamed not just on the economy but on the new baby's entry into dad's world. One reason for the onset of the "condition," in previous eras often pegged as the "human condition," is if mommy, too, is depressed. Among the symptoms noted in the CNN article are, "errands to the store that would maybe last 30 minutes, now taking an hour." There have been no reports of going to the store "for a pack of cigarettes" and not returning. A sufferer quoted in the article said he was cured by twice-weekly counseling sessions and a daily dose of antidepressants. There's even a website for these dads, saddaddy.com.

INFLAMMABLE

Treating babies with hydrocortisone may have no benefits, and low cortisol levels may not even be harmful, according to a study by Johns Hopkins Children's Center. In fact, high cortisol levels may increase bleeding in the brain. Contrary to popular belief, the study says, low blood concentrations of cortisol don't put ELBW babies at risk for ROP. Researchers found no difference in outcomes between babies with low cortisol levels and those given a placebo. Hydrocortisone didn't prevent RDS, infections or hemorrhages. The researchers compared cortisol levels of 311 low birth weight preemies immediately after birth and a week after. Bronchopulmonary dysplasia occurred in 58% of infants with low cortisol levels, in 58% of infants with midrange cortisol levels and in 62% of those with moderately elevated cortisol levels. Brain hemorrhages occurred in 24% with low cortisol levels, 36% with midrange cortisol levels and 49% with mildly elevated cortisol levels. Babies with moderate to severe cortisol levels had a higher risk of brain bleeds, gastrointestinal perforations and severe retinopathy. The researchers cautioned that a cause-effect relationship could not be established from this study because elevated cortisol concentration could have been a consequence of the hemorrhage but not necessarily a trigger of it.

SECOND OPINION

Get one, says Liesl Bradner, writing in the Los Angeles Times. Said Ms. Bradner, "My biggest concerns, on the day of my amniocentesis, were the huge needle that would be stabbed into my protruding belly and whether we wanted to find out the sex of the baby. What I was not prepared for was the vacant yet grim look on the sonogram doctor's face and the words he spoke: 'There's a problem with the baby's kidneys.' I can't remember what he uttered after that. It all sounded like mumbo jumbo: multicystic kidneys, dilations, cysts, renal pelvis and parenchyma. The diagnosis was not good. The baby would likely die in utero or, if he did make it to term, soon after delivery. Termination was recommended. I was 24 weeks along. We visited another doctor who gave us the same verdict. She threw out more medical jargon... She suggested we consult a specialist. Having seen two doctors who gave the same devastating recommendation of termination, and after reading horror story after horror story on the Internet, my husband and I were skeptical about seeing yet another physician. But we did meet with Dr Andrew Freedman, director of pediatric urology at the Endourology Institute at Cedars-Sinai Medical Center. He examined the sonogram pictures of our son's kidneys and

calmly said, 'This is hydronephrosis, not multicystic kidneys, and I believe I can fix it.' Because of a blockage, fluid was backing up into the kidneys, progressively damaging them. The worst-case scenario, Freedman said, was that the baby would need a transplant... We made it to the safe mark of 36 weeks when my water broke and a healthy 8-pound boy was born. When our baby was just four days old, Freedman successfully repaired the blockage, alleviating pressure on his right kidney. We were sent home with several medications to administer around the clock. A short time later, it was discovered that the left kidney, already badly damaged, was no longer functioning. It was removed laparoscopically when he was 4 months old. He was released after 24 hours—no medicine, no antibiotics. Just four tiny scars covered by cute, little animal-shaped bandages... My advice to any parent when given a similar diagnosis is to get as many opinions as you can—and stay away from the Internet." Liesl Bradner is the mother of two children, ages 6 and 5, and works in the L. A. Times Calendar section. This article appeared in the Los Angeles Times, in a slightly different version, on September 29, 2008.

FETAL FIGHTS

The preliminary schedule of sessions and speakers has been announced for the Controversies in Childbirth Conference, the first-ever open forum for voicing diverse opinions in timely discussion and debate, to be held March 27-29, at the Fort Worth Convention Center. The conference will focus on why providers and hospital should, or should not, continue to deliver babies. Topics will likely include: benefits of low c-section rates, hurdles facing birth practitioners, backup birth centers, homebirth in the hospital, natural birth advocates, in-hospital vaginal breeches, delivering tomorrow's babies, financial realities, malpractice, doula certification, c-sections and preemie births, abortion rights and birth rights, and more. Contact birthconference.org.

DON'T HELP

Infants conceived with assisted reproductive techniques are two to four times more likely to have certain birth defects than infants conceived naturally, based on a the results of a study published in the New York Times. The findings applied to single births only. The defects included heart problems, cleft lip and palate, and abnormalities in the esophagus or rectum. The study couldn't say if the procedures increased the risk for the defects, or whether the infertility itself was to blame. It included 281 women who had fertility procedures and more than 14,000 who didn't. Given the small comparison-sample size, the researchers said there wasn't necessarily a reason for concern. Information from the above is from an article in The New York Times by Denise Grady.

SCREEN SAVER

The BBC reports that scientists have shown a technique to screen IVF embryos which can double the chances of pregnancy for some women. Comparative genomic hybridization enables doctors to scrutinize an embryo's chromosomes for abnormalities more closely than ever before. Implantation rates using CGH were 62%, twice that achieved by other screening methods. CGH allows doctors to look at every chromosome in the developing embryo. Researchers from Oxford University and the Colorado Center for Reproductive Medicine enrolled 23 women who had tried IVF unsuccessfully. The women's eggs were fertilized, and the resulting embryos were allowed to grow for five days until they reached the blastocyst stage when they were analysed using CGH. All 23 women had at least one normal embryo to transfer to their womb, and 50 apparently healthy embryos were transferred in 23 cycles of treatment. This led to 21 pregnancies, of which 18 passed the crucial first three months. A 78% live birth rate was predicted. CGH works by labeling chromosomes taken from cells in the blastocyst with a green fluorescent tag. This DNA is mixed with the DNA of a chromosomally normal individual, which is tagged red. The red chromosomes act as a template to which the embryo's DNA attaches. You can then determine whether there are too many or too few of any chromosome from the color. For example, if there's an extra copy of chromosome 21, it'll look green, and if there is only one it will look redder.

NURSES GONE BAD

The LA Times reports that California regulators announced emergency measures to investigate the criminal backgrounds of all registered nurses in the state, after The Times reported that dozens of nurses had kept their licenses for years despite multiple convictions. The state nursing board is asking all nurses renewing their licenses whether they have been convicted of any crimes in recent years. This is the upshot of a report that some California nurses had criminal convictions for DUIs, drug and alcohol offenses, and burglary or theft. The Board of Registered Nursing also developed emergency regulations to obtain fingerprints from all nurses licensed before 1990. Until recently, about 40% of the active nurses in California had escaped scrutiny.

STAGE MOTHERS

AWHONN announced the release of Nursing Care and Management of the Second Stage of Labor: Evidence-Based Clinical Practice Guideline, 2nd Edition. The guideline, targeted toward perinatal registered nurses and certified nurse midwives, will help these nurses and other healthcare providers move away from traditional labor and birthing practices to a more contemporary, natural and research-based approach to patient care. The guideline includes updated literature sources that provide current and important evidence about the benefits of upright positioning, delayed and non-directed pushing during the second stage of labor. Use of these techniques during this critical time in labor has been shown to optimize outcomes for both the mother and her newborn. AWHONN also has expanded the original section on the evaluation of the physiologic process of the second stage of labor and created a new quick care guide that is meant to serve as an easy to use clinical reference. This guide also includes a suggested algorithm for second stage of labor management. The guideline includes 2.3 continuing nursing education contact hours and is available for purchase through the AWHONN online store at www.awhonn.org/store.

NEWS FEATURE

ENDORSEMENT

The National Quality Forum endorsed 17 perinatal standards to measure and thereby improve care received by mothers and babies during the third trimester of pregnancy through hospital discharge. Consensus standards improve quality of care by standardizing measurement in care settings and encouraging accountability and public reporting. NQF was guided in its endorsement of these perinatal care measures by nearly 300 comments from NQF members and the public.

Pregnancy, childbirth and care for newborns is the most common reason for hospital admission, and childbirth-related procedures account for the five most common procedures in patients

Title	Measure Description	Level of Analysis	IP Owner
Elective Delivery Prior to 39 Completed Weeks Gestation	All singletons delivered at ≥ 37 completed weeks gestation that are electively delivered prior to 39 completed weeks gestation.	Facility	HCA – St. Marks Perinatal Center
Incidence of Episiotomy	Number of vaginal deliveries with episiotomy procedures performed.	Facility	Christiana Care Health Services/NPIC
Cesarean Rate for Low-Risk First Birth Women	Proportion of livebirths born at or beyond 37.0 weeks gestation to women having their first delivery, that are singleton (no twins or beyond) and vertex presentation (no breech or transverse positions) that had a cesarean birth.	Facility, group, integrated system, or community	California Maternal Quality Care Collaborative
Prophylactic Antibiotic in C-Section	All women undergoing cesarean delivery without evidence of prior infection or already receiving prophylactic antibiotics for other reasons who received prophylactic antibiotics within one hour prior to surgical incision or at the time of delivery.	Facility	Massachusetts General Hospital
Appropriate DVT Prophylaxis in Women Undergoing Cesarean Delivery	Women undergoing cesarean delivery who receive either fractionated or unfractionated heparin or pneumatic compression devices prior to surgery.	Facility	HCA – St. Marks Perinatal Center
Birth Trauma Rate measures (harmonized)	Number of infants with specific birth traumas.	Facility	AHRQ/NPIC
Hepatitis B Vaccine Administration to All Newborns Prior to Discharge	Number of live newborns discharged from the hospital who were administered hepatitis B vaccine prior to discharge.	Facility, clinician, group, or plan	CDC
Appropriate Use of Antenatal Steroids	Total number of mothers who delivered preterm infants (24-32 weeks with preterm premature rupture of membranes or 24-34 weeks with intact membranes) who received antenatal steroids at any time prior to delivery.	Facility	Providence St. Vincent's Hospital/CWISH
Infants Under 1500g Delivered at Appropriate Site	The number per 1,000 livebirths over 24 weeks' gestation weighing less than 1500g delivered at hospitals not appropriate for that size infant.	Facility, integrated system, or community	California Maternal Quality Care Collaborative
Nosocomial Blood Stream Infections in Neonates	Selected bacterial blood stream infections per 1000 qualifying neonates.	Facility	AHRQ
Birth Dose of Hepatitis B Vaccine and Hepatitis Immune Globulin for Newborns of Mothers with Chronic Hepatitis B	Percentage of neonates born to hepatitis B surface antigen-positive mothers who receive a birth dose of hepatitis B vaccine and hepatitis B immune globulin within 12 hours of birth.	Facility	Asian Liver Center at Stanford University
Exclusive Breastfeeding at Hospital Discharge	Livebirths not discharged from the NICU who were fed by "breast only" since birth.	Facility, integrated system, or community	California Maternal Quality Care Collaborative
First Temperature Within One Hour of Admission to NICU	Proportion of infants with weights between 501-1500g whose first temperature was measured within one hour of admission to the NICU.	Facility	Vermont Oxford Network
First NICU Temperature < 36°C	Proportion of infants with weights between 501-1500g whose first temperature was taken within one hour of admission to NICU whose first temperature was < 36°C	Facility	Vermont Oxford Network
Retinopathy of Prematurity Screening	Number of infants born at 22 to 29 weeks gestation hospitalized at the postnatal age at which a retinal eye exam is recommended by the AAP who received a retinal exam for retinopathy of prematurity.	Facility	Vermont Oxford Network
Timely Surfactant Administration to Premature Neonates	Number of infants born at 22 to 29 weeks gestation who were treated with surfactant at any time who received the surfactant within 2 hours of birth.	Facility	Vermont Oxford Network
Neonatal Immunization	Neonates with a length of stay greater than 60 days who receive DTaP, Hepatitis B, IPV, Hib, and PCV vaccines according to current AAP guidelines.	Facility	Child Health Corporation of America

aged 18-44. Poor quality care during the third trimester, labor and delivery, and during the post-partum period can translate into unnecessary complications, prolonged hospital stays, and costly intensive care admissions. The newly NQF-endorsed measures are patient-focused and address care provided by individual clinicians such as nurses, doctors, and midwives, both in hospitals and in free-standing birth centers. The perinatal standards fill gaps in quality measurement and measure care at critical points for the mother and baby from the third trimester through hospital discharge and reflect aspects of care that can be substantially influenced by provider performance. Ultimately, through public reporting and accountability, the measures increase patient safety and decrease serious complications from childbirth. Visit qualityforum.org to see the full specifications for all new NQF-endorsed voluntary consensus standards and read NQF's research recommendations.

OXIMETRY ROUNDUP

OXIMETRY CASE STUDY

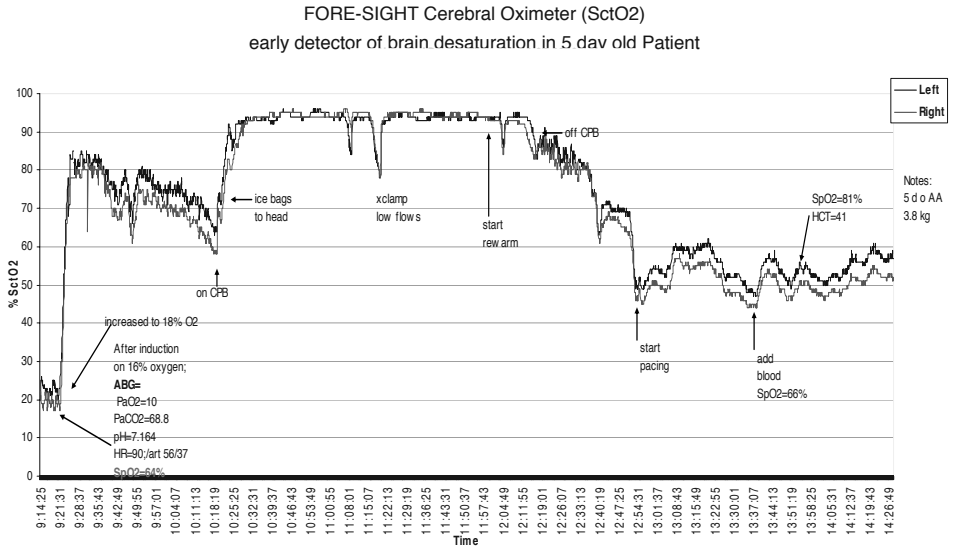
Introduction: Cerebral Oximetry is a non-invasive optically based technology that measures cerebral tissue oxygen saturation ($SctO_2$). The FORE-SIGHT (Casmed, Branford CT USA) cerebral oximeter measures absolute $SctO_2$ values without the need for a pre-induction baseline.

History: 5 day old African American patient with single Ventricle, open PDA, hypoplastic aorta undergoing a Norwood procedure.

Case Study: Initial FORE-SIGHT Cerebral Oximeter ($SctO_2$) readings on this dark pigmented 3.8 kg newborn were extremely low. (Normal values are typically in the 70% range). The forehead was smooth, and free from any hair and no external interference was observed. To keep PDA open prior to shunting, initial FiO_2% is 18% at this facility. After placing FORE-SIGHT sensors on the patient's forehead, it was noted that $SctO_2$ readings were very low (Left 21%, Right 22%). In addition to very low $SctO_2$ measurements, SpO_2 was decreasing, HR was dropping, BP(art) was dropping. Clinicians discovered that they were providing only 16% oxygen and quickly resolved the issue. After the change, the FORE-SIGHT responded quickly to improved saturation.

Discussion: After surgery, the chest was closed completely and the infant was shifted to an open crib, BP dropped and SpO_2 dropped to 50%. The patient was put on 60% FiO_2, and manual ventilation was increased. Patient was transferred to the CICU.

Conclusion: FORE-SIGHT Absolute Cerebral Oximeter measurements immediately alerted clinicians to the patient's compromised cerebral saturation, helping them to identify and correct the problem. This case study was provided by Casmed.



OXIMETRY GUEST COMMENTARY

Noninvasive transcutaneous monitoring of the newborn has developed slowly relative to developments in adult monitoring. However, recent dramatic advancements in monitoring technology make these instruments well suited for use in today's technology-reliant NICUs. The first transcutaneous monitors were expensive, cumbersome, cart-mounted devices with external gas canisters. Electrodes featured large heads and tended to drift. In short, they failed to inspire confidence in the clinicians who used them. Today's monitors and sensors are small, easy to use and so reliable that it is sometimes necessary to remind oneself to question the readings obtained from them. The importance of continuous monitoring is no longer merely focused on getting preterm newborns to survive, but on getting them to survive without major handicaps. Using transcutaneous monitoring, doctors now are able to save the lives of many premature or desperately ill newborns experiencing dramatic changes in O_2 or CO_2 that can occur with HFJV, HFOV or surfactant therapy. Thanks to advances in technology, transcutaneous monitoring has gained acceptance among neonatal specialists. The widespread use of continuous monitoring in the NICU can be regarded as one contributor to the steady decrease in the US infant mortality rate, as well as fewer adverse outcomes in the preterm infant. -- Phil Lazzara, Transcutaneous Product Manager, Radiometer America Inc.

OXIMETRY Q&A

This material was provided by Casmed, for its FORE-SIGHT product.

Why do I need to monitor brain tissue oxygen saturation?

Brain tissue oxygen saturation values are important to clinicians because cerebral hypoxia (lack of oxygen supply to the brain) is a leading cause of neurological injuries,[1,2] and occurs in many surgical and clinical situations.[18,19] If left unchecked, cerebral hypoxia may lead to adverse clinical outcomes such as short or long term brain damage, paralysis, disabilities or death.[1,19,20] In cardiac surgery, use of cerebral oximetry has been shown to significantly reduce adverse clinical outcomes, including permanent stroke, and to improve economic outcomes via decreased ventilation time, decreased ICU stays and decreased hospital stays.[3,4,5] The CAS Medical FORE-SIGHT Cerebral Oximeter was developed to provide information to guide the timely initiation of interventions and therapies to protect the brain from lack of oxygen.

How does the FORE-SIGHT cerebral oximeter work?

The FORE-SIGHT Cerebral Oximeter is a non-invasive device that incorporates CAS Medical System's exclusive Laser-Sight technology to project harmless near infrared light through the scalp and skull and into the brain via a disposable sensor on the patient's forehead. The FORE-SIGHT Cerebral Oximeter operates based on the principle that blood contains hemoglobin in two primary forms, oxygenated hemoglobin (HbO_2) and de-oxygenated hemoglobin (Hb). These two forms of hemoglobin absorb light in different, measurable ways. Cerebral tissue oxygen saturation ($SctO_2$) levels are found by determining the ratio of oxygenated hemoglobin to total hemoglobin at the microvascular level (arterioles, venules and capillaries) in the region of the brain that is interrogated. The FORE-SIGHT Cerebral Oximeter continuously monitors cerebral tissue oxygen saturation $SctO_2$ which is a mixed oxygen saturation parameter and reflects a proportional mix of arterial (~30%) and venous (~70%) blood in the outlying regions of the brain. This 70/30 determination is based on results from PET scan studies on the brain.[8] Laser light is projected into the brain in four precise (< 1nm) wavelengths to capture information needed for an absolute indication of cerebral tissue oxygen saturation levels. Four precise wavelengths are needed to maximize the measurement accuracy of oxy and de-oxy hemoglobin in determining cerebral tissue oxygen saturation ($SctO_2$), to compensate for wavelength dependent scattering losses, and to account for interference from other background light absorbers[6] (such as fluid, tissue and skin pigmentation). Reflected light is captured by detectors positioned on the sensor for optimal signal collection, and subtraction of interference from tissues outside the brain.[7] After analyzing the reflected light, the FORE-SIGHT Cerebral Oximeter displays the cerebral tissue oxygen saturation level on the monitor as an absolute number and provides a graphical representation of historical values.

How accurate is the FORE-SIGHT cerebral oximeter?

FORE-SIGHT Cerebral Oximeter readings have been confirmed in both animal and human studies. In a recent human validation study conducted at Duke University looking at 253 samples,

the FORE-SIGHT Cerebral Oximeter determined absolute cerebral tissue oxygen saturation values ($SctO_2$) showed a strong correlation with the reference $SctO_2$ over a wide range of pulse oxygen saturation values (SpO_2). The bias and precision (1 standard deviation) for the FORE-SIGHT Cerebral Oximeter $SctO_2$, compared to reference $SctO_2$, (derived from co-oximetry of arterial and jugular bulb blood samples) was 0.07 ± 3.699 (The absolute root mean are accurate to within 3.69 points). The high level of accuracy obtained by the FORE-SIGHT Cerebral Oximeter is achieved by compensating for the influence of background light absorbing and scattering elements in the blood and tissue not associated with hemoglobin. This is accomplished by a three-pronged technological approach: interrogation via a laser light source with four discrete wavelengths; a patented algorithm; and a novel sensor design.

Is the accuracy of the unit affected by the patient's temperature?
Temperature changes have been shown to have little or no effect on the absorption intensity of oxy and deoxy hemoglobin.[10,11] The validity of the saturation values should, therefore, not be affected by changes in patient temperature.

How often is the data updated on the screen?
The FORE-SIGHT Cerebral Oximeter absolute values are updated every 2 seconds.

How safe is Laser-Sight technology?
Laser-Sight technology, used in the FORE-SIGHT Cerebral Oximeter, incorporates a laser system that is designated as a Class 1 laser product by the FDA. Class 1 lasers are considered by the FDA to be "non-significant risk" devices. The Food and Drug Administration (FDA) §1040.10 states that "Class I levels of laser radiation are not considered to be hazardous."[12]

How does this technology differ from pulse oximetry?
Cerebral tissue oxygen saturation values are comprised of a mix of arterial (~30%) and venous (~70%) blood. Pulse oximeters monitor only arterial blood saturation values from peripheral tissue (oxygen supply).[14] The FORE-SIGHT Cerebral Oximeter measures the balance of cerebral tissue oxygen supply to cerebral tissue oxygen demand in the brain, giving the clinician a better indication of the patient's actual cerebral tissue oxygen saturation status. The FORE-SIGHT Cerebral Oximeter can also monitor cerebral tissue oxygen saturation values during low perfusion situations, and in cases in which there is no pulsatile flow—such as deep hypothermic circulatory arrest. Pulse oximetry requires pulsatile flow to operate.

At what depth into the brain is cerebral oxygen saturation measured?
Near-infrared light from the FORE-SIGHT Cerebral Oximeter penetrates the brain to measure mostly gray matter in the cerebral cortex.[13,14] The depth of penetration has been confirmed by comparing signals from cerebral oximetry to other established brain imagery modalities such as positron emission tomography (PET)[15] and magnetic resonance imaging (MRI).[16]

Furthermore, it is confirmed by brain function activation studies.[17]

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OXYMETRY PRODUCTS

IT'S A GEM
Instrumentation Laboratory's GEM Premier 4000 is the revolutionary critical care analyzer (BG, Electrolytes, Metabolites, Glu, Lac, Hct, tHb, O_2Hb, COHb, HHb, MetHb, sO_2, BUN, Creat, Total Bili, HCO_3^-) with a complete, onboard CO-Oximetry panel for point-of-care and centralized testing. Using the IL 682 as a reference standard, the GEM Premier

4000 with integrated CO-Oximetry, fully analyses the sample, providing lab-quality results anywhere a hemoglobin panel is required. Self-contained cartridges incorporate all components for patient testing and are maintenance-free. Enhanced Intelligent Quality Management (iQM) on the GEM Premier 4000 includes CO-Oximetry parameters and automates quality control, continuously detects, corrects and documents, to assure quality results and compliance, 24/7, regardless of operator or testing location. (the BUN, Creat, Total Bili and HCO_3- are in development). Contact ilww.com.

BRAINY

As the only simultaneous cerebral/somatic oximeter commercially available in the US, Somanetics' INVOS System enables noninvasive monitoring of site-specific brain and body blood oxygenation. Four OxyAlert NIRSensors can be placed to reveal continuous, real-time perfusion data on tissues beneath the sensor. When regional oxygen saturation (rSO_2) values drop, clinicians can intervene to lessen or prevent ischemic complications including those associated with neurologic damage, low cardiac output, shock and renal failure. OxyAlert NIRSensors for infants/neonates feature a gentle, medical-grade hydrocolloid adhesive commonly used in NICU products and a thin, flexible sensor that conforms to tight curvatures. Visit somanetics.com, (800) 359-7662.

FLEXING ITS MUSCLE

The ABL80 FLEX CO-OX matches the CO-oximetry performance of Radiometer's benchtop analyzers, representing Radiometer's commitment to providing quality solutions for both laboratory and point-of-care testing. The ABL80 FLEX CO-OX also accurately measures pH, blood gases, electrolytes and glucose. In addition, the ABL80 FLEX CO-OX provides: • Small sample size of 105 µL; • Fast turnaround, with only 140 seconds between results; • Easy, cartridge-based testing; • Portability, with full operation on battery power; • Minimal maintenance, with a self-cleaning sample inlet; • Fast start-up after installation of new consumables; • Auto-correcting automatic QC; • Full connectivity to the HIS/LIS. Contact radiometeramerica.com/abl80.

PRODUCTS AND COMPANIES

APPROVED

Discovery Laboratories, Inc announced that the FDA has accepted for review Discovery Labs' Complete Response for Surfaxin (lucinactant) for the prevention of RDS in premature infants. The FDA has designated the Complete Response as a Class 2 resubmission and has established April 17, 2009 as its target action date under the Prescription Drug User Fee Act (PDUFA) to complete its review and potentially grant marketing approval for Surfaxin. The Complete Response addressed all of the remaining requirements contained in the May 2008 Approvable Letter that had to be satisfied to gain US marketing approval for Surfaxin. Discovery Labs provided the FDA specific data, information and minor clarifying analyses and believes that its Complete Response supports the approval of Surfaxin. The Approvable Letter did not require any additional clinical trials. Prior to receiving the letter, Discovery Labs made notable progress towards gaining FDA approval, including agreeing with the FDA on the content of the Surfaxin package insert and successfully concluding a pre-approval inspection of Discovery Labs' manufacturing operations. Contact discoverylabs.com.

IT AIN'T WE, BABE

Inovo, Inc, which purchased the oxygen conserving assets and the right to market under the name "CHAD Therapeutics," is issuing a statement to clarify that the company is in no way affiliated with CHAD Therapeutics, Inc, Chatsworth, CA, which recently announced the suspension of its operations. Inovo Inc moved the production of CHAD's oxygen conserving devices to its facility in Naples, FL in June of this year. Inovo closed on the sale of Chad Therapeutics' oxygen conserving assets in February of 2008. Inovo retains the right to market and sell under the name of Chad Therapeutics. Chad Therapeutics is now located at 2975 Horseshoe Drive South, Suite 600, Naples, FL 34104. You can reach the company by calling (800) 423-8870, or visiting chadtherapeutics.com.

SEALED AND DELIVERED

B&B Medical Technologies has released The Hybrid Tape Collection for use in all neonatal and pediatric care environments. Hybrid Baby Tape and Hybrid Pediatric Tape are a unique combination of tapes that combine the gentle qualities of hydrocolloid to safely adhere to tender skin with a specially formulated acrylic adhesive strip to tightly secure endotracheal tubes, NG/OG tubes, cannulas and small catheters. Latex-free and hypoallergenic, the Hybrid tapes dramatically improve the functionality, comfort and reliability of securing devices for infants and pediatric patients while improving quality of patient care, "Providing the Right Tape for the Right Hold." Hybrid Baby Tape and Hybrid Pediatric Tape are for use in the NICU, PICU, Labor & Delivery, OR, Emergency Department and transport environments to secure artificial airways and other vital tubes and catheters. Very low birth weight and preterm infants, babies and pediatric patients often present with difficult endotracheal securing issues because of their delicate skin integrity, potential for copious secretions, frequent changes in position and sedation vacations. These factors often adversely affect adhesive securing ability. The Hybrid Tape collection delivers the best solution to secure endotracheal tubes and catheters while protecting tender skin. These tapes are precut, saving the clinician time and enabling one-person application. Hybrid Tapes are flexible yet provide firm adhesion while also absorbing exudates. The skin-friendly hydrocolloid tape can easily be removed with water without damaging the skin; folding a small tab after wrapping the specialty acrylic adhesive around the endotracheal tube allows for its easy removal. The tape may be trimmed to fit individual facial contours. These tapes (11700 and 11800), are packaged as a complete kit with two Hybrid Tapes each, two each skin preps and additional hydrocolloid strips for securing NG/OG tubes, small catheters and cannulas. Contact bandb-medical.com.

KEEPING WARM(ER)

A uniquely designed warming system that specifically addresses the clinical issues of cold stress and hypothermia in newborn babies has been introduced by NovaMed USA. The Koala Infant Warmer is a patented reusable conductive thermal mattress that provides continuous even warmth to an infant, effectively simulating a mother's natural body warmth. Unlike the traditional radiant warmer, the Koala conducts heat from beneath the infant rather than from above, thus optimizing heat transfer directly to the infant. Since radiant warmers transfer heat from above the infant, the system is subject to air currents within the room, making it less efficient. The radiant warmer design does not provide easy access to the infant and the infrared rays generated by the warmer can be extremely uncomfortable for medical personnel. The Koala can address

those infants prone to hypothermia outside the NICU and eliminate the need for intensive intervention and the complexity of an incubator or radiant warmer. The Koala Infant Warmer Controller offers temperature settings from 82°F to 102°F / 28°C-39°C. Engineered with patented carbon polymer thermal technology, Koala Infant Warmer Mattress provides continuous warmth to reduce infant cold stress and minimize risk of hypothermia. This FDA-approved product can be utilized in the Delivery Suite, Newborn Nursery, Neonatal ICU, ER, OR and can be configured for Intra-Hospital Transport. Contact novamed-usa.com.

WINNER

GE Healthcare Maternal-Infant Care is at the top for the third consecutive quarter and is increasing its lead over its competitors in this equipment category, according to the MD Buyline survey for the 2nd quarter of 2008. Not only did GE Healthcare earn the top composite score for the third straight quarter, it also posted increases in five of six customer satisfaction categories and nearly eclipsed competitor scores in all categories, reflecting the market's approval of continuous improvements in GE Healthcare's Maternal-Infant Care services based on listening to customers and developing programs to meet their needs. The six categories evaluated by the survey are system performance, system reliability, installation and implementation, applications training, service response time and service repair quality. There have been several changes within the Maternal-Infant Care Services Team that contributed to the third straight top ranking, including a new emphasis on GE's Customer Champion program, which offer BMET support; leveraging LEAN principles at GE's call center; use of segmental Global Parts Teams; and more training in more places, including a webinar format. Contact gehealthcare.com.

EXCELLENT

CAS Medical Systems, Inc announced that the Children's National Medical Center in Washington, DC will participate in CASMED's Center of Excellence Program. The hospital has also purchased Fore-Sight Cerebral Oximeters for use in its Neonatal Intensive Care Unit (NICU). Children's National is ranked among the top ten pediatric hospitals for neonatal care in America by US News & World Report. It's the only exclusive provider of pediatric care in the Washington metropolitan area, and is the only freestanding children's hospital between Philadelphia, Pittsburgh, Norfolk, and Atlanta. Children's National has 283 beds, 48 of which are Level IIIC NICU basinets, a Cardiac Intensive Care Unit, and a Neuro Intensive Care Unit. As a participant in the Center of Excellence Program, the hospital will work with CASMED to develop protocols and conduct research regarding the use of cerebral oximetry. In addition, Children's National will act as a reference site, and as a beta testing center, for the Fore-Sight monitor and sensor products.

QUIET!

In an NICU, excessive noise and bright lights are proven detrimental variables. These factors compromise a newborn's well-being and negatively impact growth and developmental outcomes. SONICU was created not only to resolve these issues but also to provide tools for research and study. SONICU provides empirical data and visual cues to facilitate unbiased and intuitive control of noisy activities. SONICU makes it easy to maintain an optimal sound level environment. SONICU facilitates compliance with developing NICU noise control standards, and can be reconfigured easily as those standards evolve. SONICU's flexibility can meet any client's current needs and makes future system expansion easy and cost-effective. Key features of the SONICU system include: • Simplicity – aesthetically pleasing design blends with surroundings; • Reliability – proven integrated circuitry and standard open-source software; • Flexibility – wall, ceiling, or crib mount; • Configuration – easy install with user-friendly, designed to meet individual needs; • Usability – simple web based, intuitive interface; • Documentation – clear and accurate; • Support – 24 hours a day, 7 days a week; • Warranty – full one-year replacement warranty on all components; • Lighting integration – each controller ships standard ready to control diurnal lighting. The SONICU system includes the following components: crib-mounted microphone, wall-mount microphone and sound-level meter, sound-level indicator, rack-mounted switch (PoE), and rack-mounted server. Contact sonicu.net.

DON'T CRY FOR ME, EVITA

Draeger Medical, Inc announced release of Version 7.0 of Software for its Evita XL ventilator. The new Evita XL 7.0 Software can help to address some everyday challenges faced by respiratory therapists. Clinicians can find the appropriate expiration time and easily apply a constant I:E ratio as well as realize better recruitment maneuvers via standard QuickSet and PressureLink features. A new measured value called "f trigg" indicates the frequency of all triggered breaths to help with the patient weaning process. The more breaths triggered by the patient, the more active the patient is. The software offers easier ventilator screen information access and visibility, with stronger more contrasting colors and larger numbers, a big yellow standby indicator, as well as an options overview page to quickly determine what options a particular ventilator has installed. Users can apply standard O_2 therapy with an ICU ventilator, using one device, a ventilator, for both O_2 therapy and ventilation (no O_2 flowmeter needed). Evita offers online help text (Cause/Remedy) in case of alarm messages, and easier recognition when a ventilator is not ventilating a patient and is in standby mode. With Evita XL 7.0 software, clinicians can provide a direct backup for O_2 therapy for quicker reaction time and therefore enhanced patient safety for patients when ventilation is needed again. Contact draeger.com.

Y NOT?

Siemens Healthcare has received FDA 510(k) market clearance for the Ysio, a new generation digital radiography system with a wireless detector (wi-D) for maximum positioning flexibility. Offering one digital radiography (DR) solution for virtually all clinical demands of the growing digital radiography market, the Ysio can be customized to suit the patient's needs—such as one or two detectors, with or without a patient table, and with fully automated or synchronized movements. Due to its versatility, the Ysio serves radiography needs no matter what the imaging volume, protocols, or patient profiles, and its performance features geared toward short examination times make it an ideal system for increasing daily patient throughput. Ysio is available in a variety of configurations based on customers imaging needs: as a wall stand with an integrated detector, a wall stand and table system with a wireless detector, or even as a mixed detector solution for high throughput and flexibility. Ysio serves as an integrated command center where users can control their workflow from registration to image data management with features like more than 500 automated system positions, power-assisted movements, a unique table design, together with the wi-D, and a color touch screen panel for convenient system

utilization. With more than 500 different preset examination positions, Ysio can save preparation time and effort. Simply pressing a button on the wireless remote will automatically move the X-ray tube into position. The system can be configured to bypass room fixtures during its automated travel to the imaging position. Thus, Ysio is also a tailored solution in terms of space planning. Power-assisted servo movements help to further reduce the strain of heavy workloads while the collimation can be adjusted from anywhere in the room via remote control. Contact siemenshealthcare.com.

GOING HOME

Vapotherm has announced that industry veteran Nick Macmillan has joined the company as Manager of its Home Care Segment. Macmillan will be responsible for developing and managing the company's expansion of respiratory therapy products that address chronic and sleep disorders. Macmillan has been in the healthcare management and respiratory industry for more than 25 years, having most recently served as National Clinical Director at Rotech Healthcare Inc. Macmillan was the Global Sleep Product Director of Sunrise/DeVilbiss where he oversaw sleep product strategies and successfully executed several product launches. He has held several state and national appointments and elected positions including the President of the Indiana Society for Respiratory Care and Chairperson for the Home Care Section of the American Association for Respiratory Care. In 2003, Nick was inducted as a Fellow of the American Association for Respiratory Care. Contact vtherm.com.

BE A WINNER

Instrumentation Laboratory (IL) announced its "Passion & Results" award, and is now accepting nominations. Award recipients will be selected from top laboratorians, physicians and nurses who have demonstrated true passion for their profession and gone "above and beyond" to enhance the quality of patient care. Three winners whose stories reflect uncommon effort and energy will each receive an award plus a $2,000 educational grant for their institution. Their compelling stories will be told and posted on the IL website, ilus.com, in brochures and featured in industry publications. From now through March 31, 2009, individuals worldwide can nominate themselves and/or others for this award. Judging and selection of the three winners will be conducted by the ILeader Panel, a group of select IL employees with substantial experience in the diagnostics industry. Winners will be honored in July, 2009. Applications can be downloaded or completed online at ilus.com/50forward.

PORTAL-ABLE

Siemens Healthcare introduces LifeNet 2.0 at usa.siemens.com/lifenet, a secure, online Web portal to help oversee and manage the productivity of Siemens imaging equipment. Providing a direct online connection between Siemens and its customers, this enhanced portal allows customers instant access to real-time service information, 24 hours a day, seven days a week. Using best practices in Web design and information sharing, LifeNet 2.0 allows users to view crucial information directly from the home page, but also provides access to tools for in-depth analysis. Users can review a list of open service requests and see the details and latest updates for those requests. Or, by browsing through the equipment page, users can review a list of their equipment, service status, service agreements, and planned maintenance events. The LifeNet 2.0 reports page includes a variety of service management reports, including asset management, service activity, equipment maintenance and compliance; as well as equipment performance reports regarding uptime, utilization management, and The Guardian Program (remote monitoring) events. Customers can program LifeNet 2.0 to automatically deliver those reports to a designated e-mail address every week, month, and quarter. Another important feature of LifeNet 2.0 is that it accommodates different user preferences within each facility. The user can select the systems they are responsible for, then track and query only information pertaining to those systems. In addition, users have access to a compliance resource page, with valuable details about how Siemens is helping to ensure regulatory compliance on all of their Siemens equipment, regardless of service level. It also contains links to relevant industry Websites to make it easier to find up-to-date information. The service history and billing page provides a list of service activity and includes service reports and invoices for each service event. The service and support page displays all open service calls in real-time. Contact usa.siemens.com/lifenet, or /healthcare.

SIMULATING

Laerdal Medical in alliance with the American Academy of Pediatrics (AAP) has released the SimNewB neonatal patient simulator. Designed to meet the training requirements of the Neonatal Resuscitation Program (NRP) course, SimNewB provides the ideal clinical training for the specific needs of neonates. Laerdal's youngest simulator accurately represents a full-term, 50th percentile newborn. Measuring 21 inches and weighing 7 lbs, SimNewB can simulate a wide range of conditions from a healthy, vigorous, crying infant to a limp, cyanotic newborn with no vital signs. From the delivery room to the NICU, the SimNewB simulator allows for hands-on training in realistic settings. Participants can practice all aspects of neonatal care from positive pressure ventilation and ET tube insertion to umbilical catheterization and IO access. Designed to be easily integrated into all neonatal clinical training curriculums, SimNewB comes complete with scenarios that are directly mapped to the NRP course. With lifelike clinical feedback and customizable scenarios, the SimNewB simulator offers the simple solution for critical neonate education. SimNewB is now available through Laerdal Medical's website, laerdal.com, or its local sales representatives.

Every high-risk newborn deserves a head start towards a healthy life.

At Children's Medical Ventures, we create quality care, process improvement and consulting programs to promote the healthy development of infants at risk. Drawing on evidence-based research and utilizing adult teaching principles presented by clinically active neonatal professionals, we challenge your clinicians and NICU staff to meet the highest standards of developmental care in support of these special babies. Call us today to learn more about our Wee Care process improvement program or for a free catalog detailing our comprehensive education and e-Learning offerings.

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Car Seat Safety: The Challenge

Paula D. Cowan, RRT-NPS; Mary E. Coughlin, RN, MS, NNP

Introduction

The National Transportation Safety Board (NTSB), established in 1967, performed a landmark investigation in 1996 regarding the use of child restraint systems. Their examination of 120 accidents involving children revealed that in 62% of the cases, there was improper use of the safety system (NTSB 2007). This data brought national attention to the use of infant car restraint systems compelling lawmakers, industry leaders and healthcare professionals to advocate and ensure passenger safety for infants and children.

As public awareness mounted, pediatric and NICU professionals began to consider the safety implications for the NICU graduate in anticipation of discharge to home and car seat safety. In 1996, the American Academy of Pediatrics (AAP) published its recommendations and guidelines to ensure safe transport of premature and low birth weight infants. These recommendations remain in place today. The AAP's publication highlights the unique needs of this population in proper product selection and use of the car safety seat and other occupant restraint devices for hospital discharge culminating in the Car Seat Challenge Guidelines (AAP 1996). Prematurity is defined as infants with a gestational age less than 37 weeks and low birth weight is categorized as less than 2500 grams.

The Dilemma

No one disputes the benefits of car seat safety. The NTSB and the AAP recommendations for the universal use of car seats for all infants have collectively contributed to a dramatic reduction in infant death from motor vehicle accidents. However, in the wake of this practice initiative, preterm infants have been identified at risk for positional challenges in the standard car safety seat (Lincoln 2005). Ensuring a safe transport to home for this vulnerable patient population has challenged prudent neonatal clinicians for decades. The paucity of evidence-based research regarding the validity of the Car Seat Challenge and the questionable implications of transient episodes of oxygen desaturation during car travel leaves healthcare professionals searching for "best practice." The Cochrane Review (Pilley and McGuire 2006) was unable to identify any randomized controlled studies demonstrating the efficacy of a pre-discharge Car Seat Challenge, adding to the ambiguity in "best practice."

This article was provided by Children's Medical Ventures.

The Literature Review

Williams and Martin (2003) performed a nationwide telephone survey of 72 NICUs and newborn nurseries from 37 states regarding their Car Seat Challenge program. The survey consisted of 14 questions with four key themes:

- Who is performing the Car Seat Challenge in their facility?
- How are the challenges being performed?
- Are there written policies in place?
- What are the recommendations for infants who do not pass the challenge?

The objective of the survey was to obtain a baseline of existing practice regarding the implementation of the AAP's recommendations (Williams and Martin 2003). At the time of the survey, 19% of Level III units, 9% of Level II units and 78% of Level I units did not have an infant car seat testing program as recommended by the AAP. This inconsistency in implementation poses a safety risk to an already fragile patient population. Lagging technological advances, research and development in car seat/car bed design add to the current dilemma.

Monitoring studies of some infants less than 37 weeks gestation have demonstrated episodes of apnea, bradycardia and oxygen desaturation when seated in a standard car safety seat (Pilley and McGuire 2005, Merchant et al 2001). Merchant et al (2001) showed that 12% of infants with a gestational age between 35 and 36 weeks experienced apnea and/or bradycardia in their car seat. A subset of the study group (7%) experienced oxygen saturations between 85% and 90%. Although this degree of hypoxia is thought not to be harmful, it is clearly not normal for healthy infants and may be an early indicator of sleep disordered breathing (Gaultier 2000, Rosen et al 2003). In the Merchant study group, there was a correlation between oxygen desaturation and the length of time the infant was positioned upright in the car seat.

During a cross-sectional study of 42 preterm infants with gestational age range between 24 and 35 weeks, subjects were monitored for cardiorespiratory stability for 45 minutes during and after placement in a car seat (Ojadi et al 2005). Ojadi et al (2005) discovered that the preterm infant with and without pre-existing cardiorespiratory abnormalities had a near equal probability (80% and 83.3%) for the development of cardiorespiratory symptoms during the Car Seat Challenge.

The authors concluded that pre-discharge testing is important for safe transportation. However, they point out that when symptoms manifest in the upright position, alternative modes of safe transportation must be considered (Ojadi et al 2005).

One recent study reveals that the events may be independent of the transportation device. Salhab et al (2007) tested 151 infants in both a car seat and car bed and found that 43 (2%) of the infants had at least one event in either or both transportation devices; 23 (15%) had an event in the car seat; and 29 (19%) had an event in the car bed. Their study has three major findings:

1. Apnea, bradycardia and desaturation episodes may still occur at discharge when very low birth weight infants are placed in a transportation device, particularly among infants who were born most prematurely or who are recovering from bronchopulmonary dysplasia (BPD);
2. No evidence was found that indicated that these episodes are less likely in a car bed than a car seat;
3. A brief observation period in a transportation device is not sufficient to identify infants at risk, but the longer these infants remain in such devices, the more likely oxygen saturation is to fall.

Further, Salhab et al (2007) showed a mixture of the types of adverse events while in transportation devices. These are shown in the table below.

Type of Adverse Events

	Number of Infants	
	Car Seat	Car Bed
Central Apnea	7	5
Obstructive Apnea	3	5
Mixed Apnea	2	7
Bradycardia	5	8
Oxygen Desaturation	20	27

Some infants are included in more than one category.

The Car Seat Challenge

In examining the literature available, there is a lack of specific guidelines for car safety seat screening, but there are a few key findings described above. In line with the AAP recommendations, some general practices included as part of the Car Seat Challenge are summarized as follows:

1. Prior to hospital discharge, every infant born at less than 37 weeks gestation should undergo a car safety seat screening to monitor for possible apnea, bradycardia or oxygen desaturation for a specified period of time (generally between 60 and 90 minutes or the anticipated duration of the car ride from hospital to home).
2. "Failure" of the Car Safety Seat Screening is commonly defined as infants who experience apnea that lasts longer than 20 seconds, bradycardia less than 80 beats per minute or oxygen desaturation less than 90% (Ojadi et al 2005). Infants who fail the screening are generally managed in the following ways:
   - Delaying hospital discharge and retesting the infant at a later date
   - Using blankets or rolls to provide sufficient postural support
   - Repositioning the car safety seat at 30 degrees (rather than 45 degrees) in order to reduce slouching and respiratory compromise
   - Using an alternative recumbent car bed for infant transport
   - Prescribing a respiratory stimulant such as caffeine or theophylline (Williams and Martin 2003) Note: The choice of method for weaning treatment remains one of individual physician preference. Discharge from hospital after apnea requires close monitoring and some infants will require home apnea monitors. The decision to provide a home apnea monitor should be individualized for each patient depending on the effectiveness of treatment and clinical response (Bhatt-Mehta 2003).
3. Families are instructed to minimize travel for infants at risk for respiratory compromise and are instructed to never leave an infant unattended in a car safety seat (AAP 2006).

Prudent Practices to Consider

In evaluating the stability of the former premature infant in an infant car safety seat, appropriate physiologic parameters must be evaluated to ensure safe transport to home. In addition, sleep and the infant's capacity to auto-resuscitate while in a seated position in the car safety seat add a dimension of concern that warrants consideration for evaluation. Presentations at the 2008 Annual Conference on Sleep Disorders in Infancy and Childhood addressed topics including cerebellar injury and autonomic outflow (R.M. Harper), auto resuscitation from upper airway obstruction (H. Wulbrand) and former preterm infants are three times more likely to develop sleep disorder breathing than their full-term counterparts (C.L.Rosen). Given that total sleep time in infants ranges between 16 to 20 hours per day, it is conceivable that cardiorespiratory events in this population may be a manifestation of alterations in sleep mechanics (Givan 2003, Halasz et al 2004, Iglowstein et al 2003). Institutions that utilize multi-channel monitoring (heart rate, respiratory effort, pulse oximetry and airflow) as part of their discharge planning process should consider the incorporation of the Car Seat Challenge during such evaluations or in the instance where an infant demonstrates respiratory compromise during routine car seat testing procedures.

The additional information gathered during a multi-channel study could provide the discharge team and family with a comprehensive picture of the infant's cardiopulmonary stability while seated upright in a car safety seat during sleep and wakefulness. This information is valuable not only for the immediate purpose of a safe transport but also vital information for the family in understanding the autonomic vulnerabilities of their infant at time of discharge.

Summary

Understanding the physical vulnerabilities of the preterm infant, the learning needs of the family and emerging science pertaining to sleep-wake maturation enables neonatal clinicians to provide for a safe discharge to home (Howard-Salsman 2006, Givan 2003). While not every infant warrants a multi-channel physiologic assessment to evaluate their cardiopulmonary stability prior to discharge, the use of such tools provides the clinician with a more complete assessment of the infant's physiologic stability during the Car Sear Challenge. Several studies have been performed to assess the importance of the Car Seat Challenge and the most critical physiologic channels to observe. This document provides insight into these studies as well as proposed practices to consider when performing the Car Seat Challenge.
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The Use of Absolute Cerebral Oximetry in Cardiovascular Surgery

Gregory W. Fischer, MD; Konstadinos A. Plestis, MD

Introduction

Cerebral oximetry, based on near infrared spectroscopy (NIRS) technology, provides information on the availability of oxygen in brain tissue at risk during numerous pathological conditions.[1] Cerebral oximetry measures local concentrations of hemoglobin (oxy- and deoxy-), and regional cerebral tissue oxygen saturation ($SctO_2$) at the microvascular level (arterioles, venules, and capillaries only).[2,34] As a result, cerebral oximetry $SctO_2$ is a mixed oxygen saturation parameter which has a value between arterial (SaO_2) and jugular venous oxygen saturation ($SjvO_2$) under normal physiological conditions, therefore $SaO_2 > SctO_2 > SjvO_2$. Complementary to the arterial oxygen saturation (SaO_2) measured by pulse oximetry, $SctO_2$ reflects regional cerebral metabolism and the balance of local cerebral oxygen supply/demand. The advantages of cerebral oximetry are: 1) It provides $SctO_2$ values continuously and non-invasively at the bedside;[5] 2) $SctO_2$ is a sensitive index of cerebral hypoxia and/or cerebral ischemia[6,7] which is one of the main causes of brain injury in clinical settings.[8,9]

The FORE-SIGHT Cerebral Oximeter (CAS Medical Systems) is significantly different from cerebral oximeters currently on the market. The FORE-SIGHT monitor was developed with the support of a series of Small Business Innovation Research Grants from the National Institute of Neurological Disorders and Stroke (NINDS) of the National Institute of Health (NIH).[10] It is the only absolute cerebral oximeter cleared by the FDA[11] based on accuracy. The FORE-SIGHT Cerebral Oximeter, with its ability to provide absolute measurement makes it possible to establish threshold values for $SctO_2$ that can be used to guide clinical interventions.

FORE-SIGHT Cerebral Oximeter determined cerebral tissue oxygen saturation, $SctO_2$, is defined as the ratio of concentrations of HbO_2 and $Hb + HbO_2$ in the brain tissue, thus $SctO_2 = 100\% \times HbO2 / (Hb + HbO_2)$. The value of $SctO_2$ reflects a proportional mix of arterial and venous blood that can be calibrated from arterial and internal jugular venous blood.[12] It is estimated that the NIRS cerebral oximeter interrogated brain tissue microvasculature is about 70% venous and 30% arterial during most physiological conditions in humans based on Positron Emission Tomography (PET) studies.[13] In validation studies, FORE-SIGHT cerebral oximeter determined $SctO_2$ showed a strong correlation with the reference $SctO_2$ over the spectrum of pulse oximeter determined arterial oxygen saturation SpO_2 values between 70 and 100% from 18 subjects.[14,15] The bias and precision (1 standard deviation) for the FORE-SIGHT Cerebral Oximeter $SctO_2$ compared to reference $SctO_2$ derived from co-oximetry of arterial and jugular bulb blood was 0.18±3.7 (1SD). The FORE-SIGHT Cerebral Oximeter, with its ability to provide absolute measurement of cerebral tissue oxygen saturation $SctO_2$, overcomes the limitations of previous cerebral oximeters.[16] Particularly, clinically relevant $SctO_2$ threshold values can be established with the FORE-SIGHT Cerebral Oximeter for physicians to provide tailored patient management.[17] It is known that $SjvO_2$ has a normal lower limit at ~45% and the upper limit at 70%.[18,19] The FORE-SIGHT $SctO_2$ is about 10% higher than $SjvO_2$ consistently over a wide range of oxygen saturation values. Therefore, the absolute FORE-SIGHT Cerebral Oximeter lower safe $SctO_2$ threshold is about 55%.

The Need for Bedside Cerebral Oximetry

Monitoring brain oxygenation is critical in providing information used to guide patient management in many clinical situations.[20,21] Currently, brain oxygenation can be measured invasively by jugular bulb oximetry $SjvO_2$ or brain tissue pO_2 sensor.[22,23] Benefits of $SjvO_2$ monitoring include: a) improved outcome in physiologic management of head injury patients (370,000 cases/year, in the US);[24,25,26] b) detection of critical events when brain oxygenation could be compromised during cardiac surgery (800,000 cases/year worldwide),[27] and neurosurgery.[28] In some institutions, $SjvO_2$ monitoring is routinely applied in surgery of the aorta,[29] and in neuro intensive care units.[30] Therefore, a bedside cerebral oximeter that can provide non-invasive measurement of cerebral oxygenation is highly desirable.

Despite decline in overall mortality after coronary artery bypass grafting (CABG) and valvular surgery with cardiopulmonary bypass (CPB), the rates of cognitive dysfunction have not improved.[31] In some reports, most patients had subtle signs of impaired cognitive performance, with incidences ranging from

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60 to 80%.[32] There are two different forms of brain injury that may occur after CABG or thoracic aorta surgery: neurological dysfunction (ND) and neurocognitive dysfunction (NCD). ND is defined as clinically evident focal or global neurological injury resulting in stroke, hypoxic encephalopathy, transient ischemic attack, or stupor. NCD is defined as postoperative confusion, agitation, delirium, prolonged obtundation, or transient Parkinsonism. NCD occurs more frequently, affecting 40% to 80% of CABG/aortic surgery patients, depending on the method of detection.[33] While it is easy to diagnose post-operative ND, NCD is more subtle, and needs to be evaluated with a full battery of neurocognitive testing administered by trained professionals. Recent reports based on accurate neurocognitive testing before and after surgery have suggested that NCD can no longer be considered a benign self-limiting condition, but rather a long-lasting neurocognitive insult capable of reducing quality of life by impairing memory and fine motor function.[34]

The etiology of brain injury following cardiac surgery is still not completely understood and somewhat controversial. Some of the possible mechanisms include diffuse microembolization, cerebral hypoperfusion, and metabolic factors; the incidence of injury seems to be higher when CPB duration exceeds 70 minutes, and when there is rapid rewarming, particularly in the older surgical population.[35] Regardless of the immediate cause, such persistent cognitive dysfunction likely results from brain ischemia during surgery, which may be a result of focal arterial embolism,[36] global hypo-perfusion of the brain,[37] or an interaction of the two.[38]

Strategies for preventing arterial embolism and brain hypo-perfusion differ. To avoid arterial embolism during CPB, arterial line filters, intraoperative imaging, and careful manipulation by the surgeon are essential. On the other hand, diffuse hypo-perfusion of the brain can be avoided only by very careful planning: if something goes wrong, the only hope is early detection and immediate restoration of adequate perfusion before irreversible brain damage develops. For this purpose, sensitive, real-time monitoring of brain ischemia during such surgical procedures is needed.[39] At the present time cerebral oximetry is the only feasible technology that monitors cerebral hypoxia and/or cerebral ischemia noninvasively and continuously.

Cerebral oximeters provide information that other bedside brain monitors, such as electroencephalography (EEG) and transcranial Doppler (TCD), cannot offer. Other modalities, such as positron emission tomography (PET), perfusion CT, and magnetic resonance imaging (MRI) can provide detailed "snapshot" information about cerebral oxygenation, but cannot be used at the bedside. Since cerebral oximetry can provide an immediate indication of cerebral blood flow changes, oxygenation changes, it could find a wide range of applications in operating rooms (OR), in recovery rooms, as well as in intensive care units (ICU). In all of these situations, cerebral oximetry can be used to monitor the safety and efficacy of treatment interventions.

Why Absolute Cerebral Oximetry

Current trend-only cerebral oximetry may be inadequate: Previous cerebral oximeters on the market measure cerebral oxygenation as a trend only.[40] Some studies suggest that operative technique can be modified based on application of trend-only cerebral oximetry. Since these monitors measure trends only, a baseline first has to be established and cerebral oximetry values need to be maintained at or near preoperative baseline.[41,42] Another approach is to keep the cerebral oxygen saturation at levels within 20-25% of the anesthesia pre-induction value.[43,44] However, studies have shown that seventy five percent of patients undergoing coronary bypass have a significant impairment in baseline regional cerebral perfusion (rCP).[45] Other studies also demonstrated that patients undergoing cardiovascular surgery have a high prevalence of cerebral vascular disease in varying degrees.[46] In addition, abnormal preoperative rCP was found to be a strong indicator for post surgical decline in neuropsychologic testing.[47] These findings suggest that it is difficult to define a "normal" pre-induction baseline value for the trend only cerebral oximetry. A percentage drop based on the unreliable baseline value is more questionable to serve as a threshold for clinical intervention. In fact, studies have confirmed that while a trend only cerebral oximeter can detect adverse brain oxygenation by measuring the change in $SctO_2$ from a baseline value, it cannot provide accurate and reliable normal and threshold values of cerebral tissue oxygen saturation.[48,49,50,51,52,53,54]

Absolute cerebral oximetry is essential for tailored patient management: There is an increasing amount of evidence that has demonstrated the need for a tailored patient management protocol as current approaches for managing flow, arterial blood pressure, and pH during cardiac surgery are based on studies that included few elderly or high-risk patients and predated many other contemporary practices.[55] For example, watershed-distribution stroke happens more frequently in patients undergoing cardiac surgery than in general stroke population (over 40% versus 2-5%, respectively).[56,57,58] Gottesman et al, reported that mechanism of watershed stroke after cardiac surgery may include an intraoperative drop in blood pressure from a patient's baseline.[59] This suggests that following the standard protocol to maintain an optimal range for blood pressure during cardiac surgery is insufficient for some patients. We believe that what is needed, is an online monitor to evaluate the effect of blood pressure level as well as blood pressure change on the brain. Our own studies suggest that the FORE-SIGHT Absolute Cerebral Oximeter could be used for this tailored patient management approach. Readings of cerebral tissue oxygen saturation $SctO_2$ indicated that maintaining mean arterial blood pressure at 50-60 mmHg during hypothermic CPB is tolerated by most patients, but this level seems to be inadequate for certain patients.

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Performance Observations of the Rainbow "Pulse CO-Oximeter"

D.E. Bebout, PhD; P.D. Mannheimer, PhD

Background

While providing the normal functionality of a pulse oximeter for non-invasively monitoring functional oxygen saturation (SpO_2), Masimo's recently introduced multi-wavelength "Pulse CO-Oximeter" device is advertised to additionally provide accurate monitoring of carboxyhemoglobin (COHb) and methemoglobin (MetHb) levels in the blood.

Based in part on a published letter to the editor reporting inaccuracy of the non-invasive Pulse CO-Oximeter's COHb measurements, and the fact that the manufacturer's accuracy claims for COHb and MetHb did not clearly indicate whether those accuracy levels applied during conditions of reduced arterial oxygen saturation,[†] we wished to further explore the performance of this system in individuals who had mild to moderately reduced oxygen saturation levels (ie elevated levels of deoxyhemoglobin in the arterial blood). Furthermore, we wanted to investigate if there are differences in the system's SpO_2 accuracy provided by the sensor's extra wavelengths. Covidien commissioned a study (as summarized below) to independently evaluate performance of the Masimo Rainbow SET system—specifically, to assess SpO_2, SpCO (fractional COHb) and SpMet (fractional MetHb) accuracy over the 70%-100% oxygen saturation range.

The evaluation was conducted by Clinimark in Louisville, Colorado, an independent testing facility experienced in conducting in vivo pulse oximetry desaturation studies for research purposes and regulatory submissions. Study protocols, Institutional Review Board (IRB) approval, laboratory procedures, and data collection were managed by the test facility. This report summarizes the procedures used in the study, presents data collected in the study, and provides observations regarding the data.

Methods

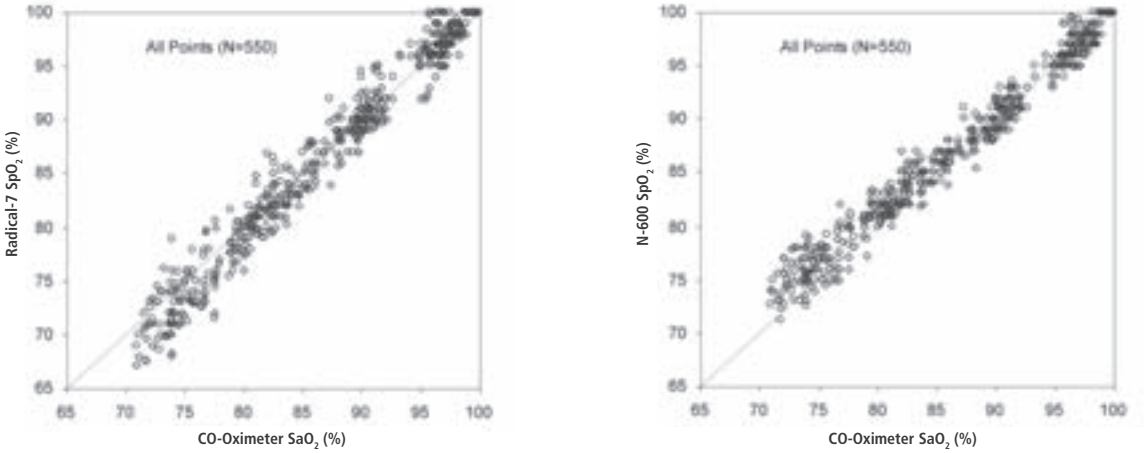
Following IRB approval and subject informed consent, 13 volunteers were studied (ages 20-44 years, 130-195 lbs, with light to dark pigmentation and a mix of smokers and non-smokers). The subjects were healthy with normal blood constituent levels and perfusion as indicated by the CO-Oximetry data and pulse oximetry strength at the sensor site. Each subject was cannulated in the left arm with an indwelling radial artery catheter for blood sampling. Two Masimo Radical-7 (Rainbow R25 adhesive sensors) and two Nellcor N-600 (Max-A adhesive sensors) systems were placed on each subject. New sensors were used on each subject. All sensors were placed and connected to their respective monitors according to the manufacturers' labeled Instructions-For-Use and Prior In-Service Training.

Hypoxemia was induced in each subject by varying the fraction of inspired oxygen (FIO_2), creating stable oxygen saturation levels between 100% and 70% SaO_2 (stability was assessed using SpO_2 readings from a fifth pulse oximeter). The COHb and MetHb levels within each subject were not actively altered; their individual values remained stable over the data collection period. Both hands remained stationary throughout the arterial blood draws. SpO_2, SpCO and SpMet values as available from the pulse oximeters were collected via computer simultaneous with blood drawn from the indwelling catheter. For each stable oxygen saturation level, approximately five arterial blood samples were collected approximately 20 seconds apart, targeting up to 25 blood draws per subject. Samples were immediately analyzed with a bench-top CO-Oximeter* to measure the arterial oxygen saturation (SaO_2), fractional carboxyhemoglobin (FCOHb) and fractional methemoglobin (FMetHb) levels for comparison with SpO_2, SpCO and SpMet readings, respectively. Accuracy was computed as the root-mean-square of the pooled reading differences (A_{rms}). All procedures followed the methods outlined in ISO9919:2005.

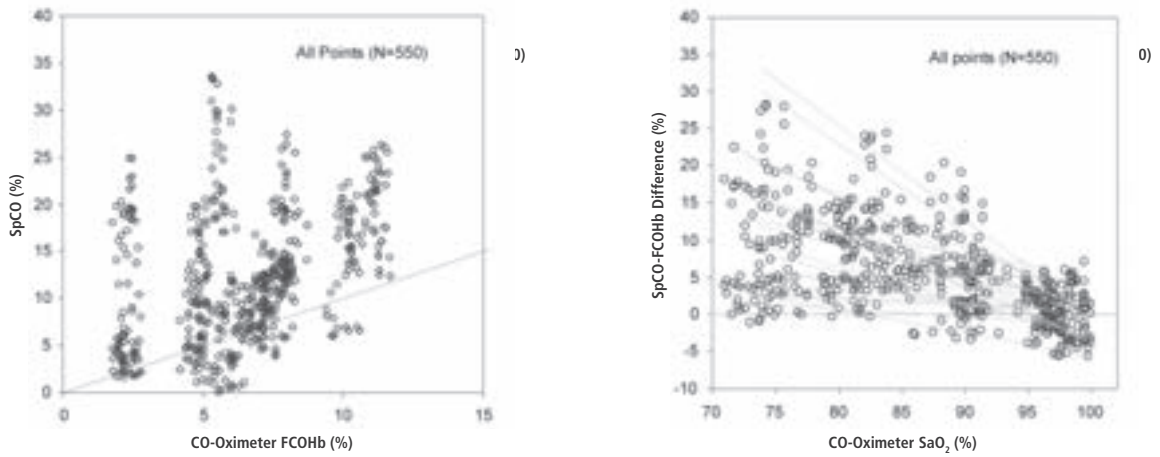
Results & Observations

The 13 volunteers enrolled in the study included a mix of non-smokers and smokers, providing an FCOHb range of 1.8% to 11.7% per laboratory CO-Oximeter. Subject FMetHb ranged between 0.1% and 0.9%. There were 275 blood samples drawn during stable reading periods, spanning a 71.0% - 99.9% SaO_2 range and yielding 550 data pairs for analysis of each system. The Radical-7 displayed "low SpCO confidence" messages during some of the monitoring periods while continuing to post SpCO values; Observation 4 below offers analysis that excludes these data pairs.

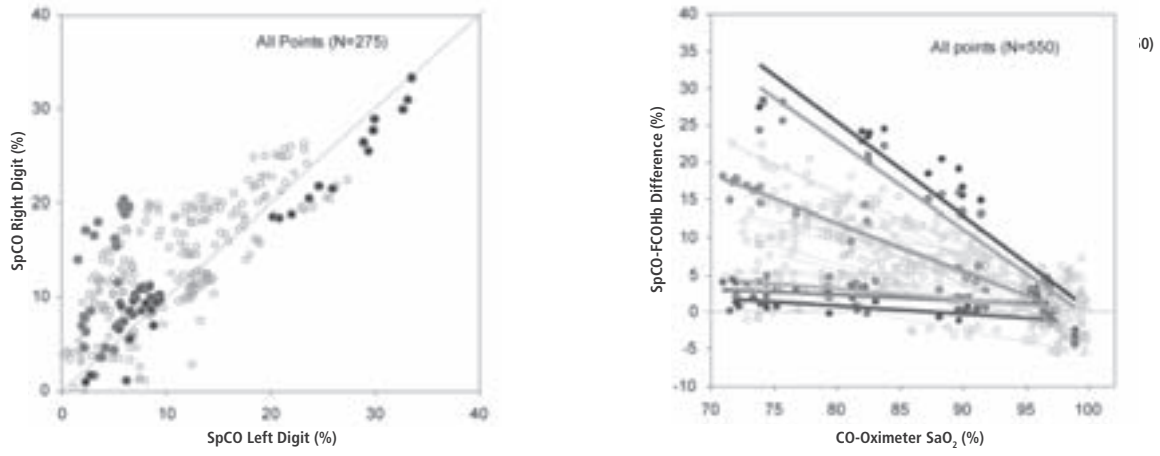
This article was provided by Covidien, which makes the Nellcor product mentioned in the article.



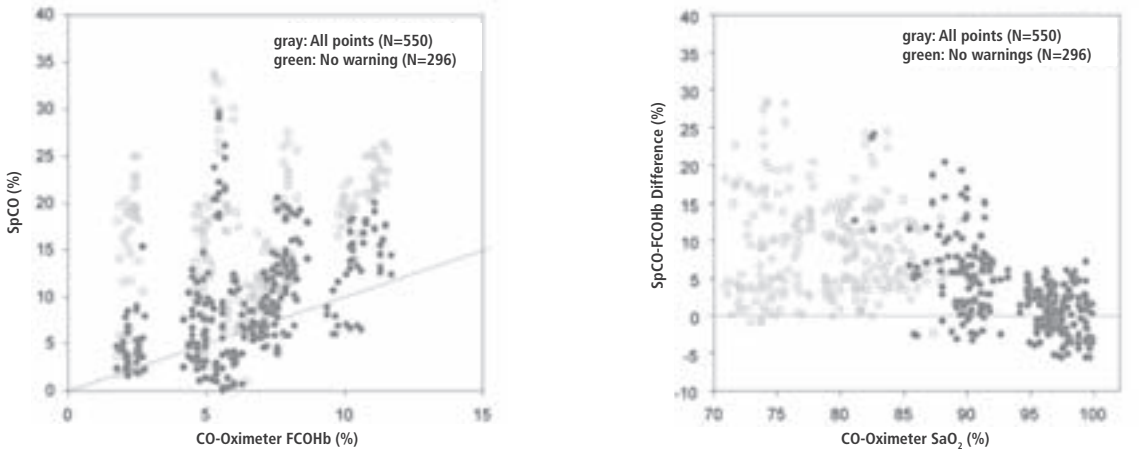
Observation 1: SpO_2 accuracy for the Radical-7/R25 (A_{rms}=1.8%) and N-600/Max-A (A_{rms}=1.6%) were both consistent with their labeled accuracy claims of $A_{rms} \leq 2\%$ SpO_2, even when including subjects with elevated FCOHb levels. In these observations, the COHb did not meaningfully influence the SpO_2 correlation to SaO_2 (Note: Neither SaO_2 or SpO_2 are direct measures of fractional oxyhemoglobin, FO_2Hb.)



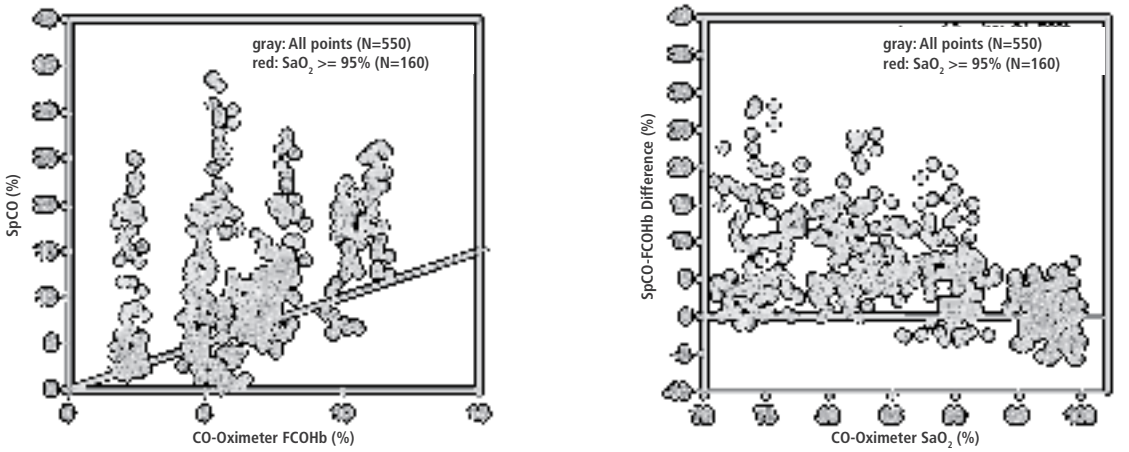
Observation 2: Radical-7 SpCO readings were significantly affected by the subjects' SaO_2 levels. The left graph below plots SpCO versus CO-Oximeter FCOHb for all data. A_{rms} accuracy for all points was 8.6%. The right hand graph plots the SpCO error versus blood SaO_2, indicating the 26 individual regression lines.



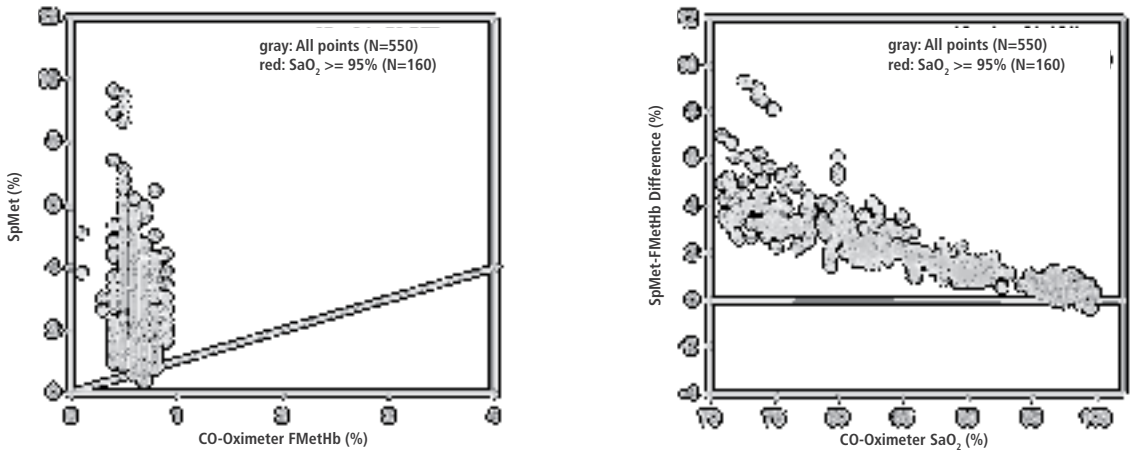
Observation 3: SpCO consistency between two simultaneously-placed Radical-7 systems varied among subjects. The graph on the left plots all observations, highlighting similar or disparate readings in three subjects (blue, black and red points). The graph on the right compares these subjects' SpCO readings to CO-Oximeter SaO_2, along with their individual regression lines (blue/aqua, black/grey, red/orange pairs).



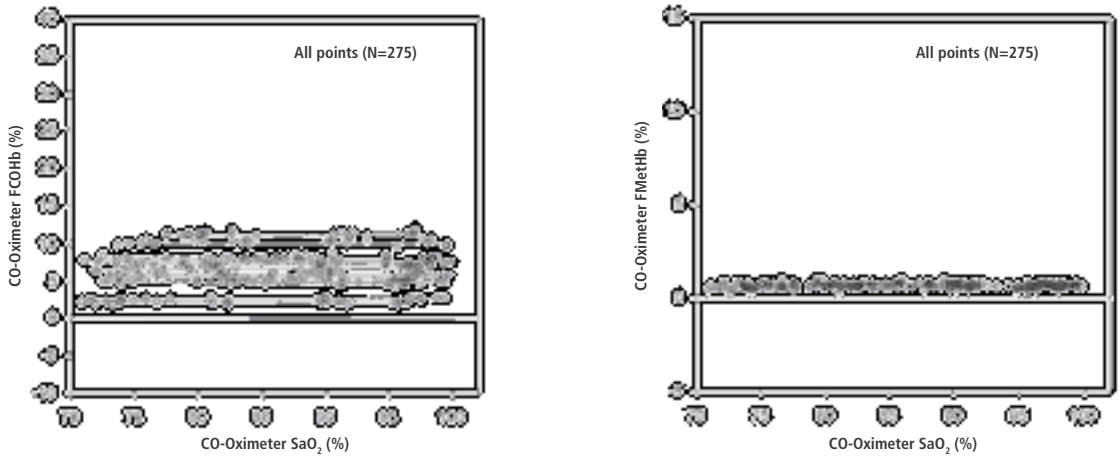
Observation 4: Excluding observations made during display of "low SpCO confidence" messages (typically at the lower SaO_2 levels) improves accuracy. Green points in the graphs below indicate observations made while no messages were displayed. A_{rms} improves to 5.7%, though remains outside the manufacturer's specified accuracy. (Open gray circles indicate the excluded data.)



Observation 5: Best performance in tracking FCOHb occurred at the highest SaO_2 levels. The solid red points in the graphs below indicate the observations made with blood $SaO_2 \geq 95\%$. A_{rms} for this set of observations was 3.0%, more in line with the manufacturer's specified performance.



Observation 6: Similar behaviors were seen with the SpMet readings (though available data is limited to FMetHb < 1%). A_{rms} for all readings was 2.5%; including only $SaO_2 \geq 95\%$ data improves A_{rms} to 0.5%.



Observation 7: The bench-top CO-Oximeter did not show SaO_2-dependence in FCOHb and FMetHb readings – each individual's readings were stable across the SaO_2 span. (FCOHb vs. SaO_2 regression lines are shown for each of the 13 subjects in the left hand graph below.)

Conclusion

The Masimo Radical-7 Rainbow SET system reported SpO_2 values similar to the Nellcor N-600 two-wavelength pulse oximeter in comparison to blood SaO_2. Although not statistically significant, the N-600 was more accurate.

Both the SpCO and SpMet measurements of the Radical-7 were most accurate and consistent with the manufacturer's specifications when the subject's SaO_2 levels were 95% or higher. However, there was a clear correlation of each of these parameters becoming increasingly less accurate with a higher bias as the subjects became more hypoxemic.

[†]According to the user manual, the Radical-7's accuracy claims for COHb and MetHb are ±3% and ±1% respectively; however, the claims do not indicate whether or not the COHb or MetHb accuracy levels are the same regardless of the concurrently occurring oxygen saturation levels.

*IL-682, Instrumentation Laboratories, Lexington, MA. Data analyses using values simultaneously measured with an OSM-3 Hemoximeter (Radiometer, Westlake, OH) were not meaningfully different than the results presented here.

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Noninvasive Sensors Designed for Unprecedented Neonatal Care and Safety

Michael O'Reilly, MD

Caring for the tiniest and most vulnerable of newborn patients is a delicate balancing act. A premature neonate's organs and systems are often under-developed and their survival dependent on a host of interventional medical care. Their delicate skin and unique physiology can make attaching and removing lifesaving medical equipment and monitoring devices a traumatic and, in some cases, an impossible feat. Improving outcomes for critically-ill preterm infants in today's NICU environment requires that clinicians minimize the deleterious effects of the intensive care experience on the developing neonate. What's more, clinical protocols calling for 90-second neonatal resuscitation, detection of congenital heart disease (CHD) before discharge, the reduction of retinopathy of prematurely (ROP), and methemoglobinemia from inhaled nitric oxide (iNO) therapy are giving rise to the increasing need for more advanced and more intelligent neonatal pulse oximetry solutions and sensors.

Masimo, a global medical technology company, understands the heroic efforts NICU clinicians undertake to guide at-risk newborns through the critical recovery process. The company translates this understanding into practice—combining the unique characteristics of neonatal physiology with advanced physics and innovative engineering breakthroughs—to develop monitoring solutions specifically-designed to overcome the clinical challenges, alleviate care concerns and meet the unique protocols and clinical requirements of these special patients. With more than 100 different pulse oximetry sensor and cable combinations, Masimo leads the way in sensor innovation, performance and selection—providing clinicians with vital monitoring capabilities to optimize care and ease the transition from illness to health for the baby and their families.

Sensor Selection For Greater Clinical Flexibility

Masimo offers the widest selection of pulse oximetry sensors available. Low Noise Optical Probe (LNOP) and Low Noise Cabled Sensors (LNCS) provide accurate arterial oxygen saturation (SpO_2), pulse rate (PR), and perfusion index (PI) measurements under the most challenging of patient conditions—including motion and low perfusion—while Masimo Rainbow sensors offer five additional noninvasive measurement capabilities, including: total hemoglobin (SpHb), arterial oxygen content (SpOC), methemoglobin (SpMet), carboxyhemoglobin (SpCO), and pleth variability index (PVI).

These sensor solutions provide a variety of reusable, adhesive, non-adhesive and multi-site options that deliver the best in patient monitoring performance and flexibility based on clinical preference. Today, when life hangs in the balance and neonatal clinicians need to obtain immediate measurements wherever they can, adhesive sensors are preferred. Whether the monitoring site is a finger, toe, hand, or foot, Masimo has the broadest range of clinically-proven sensor solutions available. Although time-tested single-patient-use adhesive sensors are favored for improved safety and sensor adhesion, non-adhesive sensors provide a new alternative for very fragile and sensitive skin types.

Moreover, the unique clinical challenges and concerns of neonatal patients require extra special care. That's why Masimo offers 15 neonatal sensors to address a wide range of clinical uses—from extremely low birth weight (ELBW) preemies requiring resuscitation to newborns with congenital cyanotic cardiac lesions (CCHD) and critically low oxygen saturation values. And, because size really does matter when it comes to neonates, Masimo has recently introduced the LNCS NeoPt-500 SofTouch sensor designed specifically for smaller neonates. At just 20 mm in size, this sensor has much smaller dimensions than most neonatal sensors, making it a perfect fit for even the tiniest preterm baby hand or foot. Additionally, NeoPt-500 contains no adhesive materials that can damage or compromise the integrity of an ELBW baby's paper-thin skin.

Gentler Sensors

For any patient, comfort is paramount. This is especially true of neonates with extremely delicate epidermal tissue. By using softer attachment materials and adhesive tapes that are gentle to the skin, Masimo neonatal sensors can provide both maximum comfort and protection.

Masimo SofTouch sensors are designed for single-patient use whenever skin sensitivity issues are a concern. SofTouch sensors incorporate a VelAid hook and loop wrap, allowing the sensor to be quickly and securely applied even on wet and slippery sites and easily repositioned if necessary. Thin neonatal skin

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is further protected by soft foam material that surrounds the sensor attachment for maximum comfort. This unique soft foam also gives SofTouch sensors added "stick-sion," allowing them to remain secure even when the skin is wet.

In addition, Masimo adhesive sensors use a special tape material that is not only soft and pliable, but also more durable and longer lasting. In fact, longevity studies show a nearly two-fold increase in durability with Masimo sensors compared to conventional disposable sensors.[1] The result is a sensor that is both comfortable and easy to remove and re-apply multiple times during a patient's stay.

Advanced Technology and Sensor Design

Accurate and reliable SpO_2 measurements are of critical importance for preemies with under-developed respiratory and circulatory systems who struggle to make every breath count. This is especially true for the relative risk reduction of ROP, a potentially blinding eye disorder often caused by hyperoxia and wide fluctuations in oxygenation. Of the 28,000 babies born in the U.S. weighing 2.75 pounds (1,247 grams) or less, more than half are affected by some degree of ROP.[2] ROP is preventable, yet it is one of the most common causes of visual loss in childhood and can lead to lifelong vision impairment or blindness. However, ongoing research continues to support the significant importance of high-fidelity pulse oximetry monitoring to help avoid and reduce ROP in critically-ill infants. In fact, Masimo Measure-Through-Motion-and Low Perfusion pulse oximetry technology has been shown to dramatically reduce the incidence of ROP by 40%.[3]

The key to Masimo's line of award-winning noninvasive patient monitoring solutions is the company's dedication to staying on the cutting-edge of technology. It all starts with Masimo's advanced signal acquisition technologies, which are truly unique. While conventional sensors use only 2 wavelengths of light, Masimo Rainbow sensors incorporate up to 12 wavelengths to acquire a richer physiological data stream capable of noninvasively measuring multiple blood constituents that typically require an invasive blood draw and laboratory analysis.

Masimo sensors are designed with added protection from ambient light and electro-surgical interference resulting in better signal quality. And, to further filter out non-physiological noise, Masimo has invested years in creating Low Noise Cabled (LNC™) technology. This ultra-modern cable technology helps Masimo LNCS sensors achieve the highest performance of any integrated pulse oximetry sensor cable, making it the best solution for neonatal applications where the connector needs to be away from the sensor site. These proprietary sensor designs and technology advances provide increased shielding and protection from noise and other environmental interferences, which can compromise the incoming signal, physiological data stream and the resulting measurements.

Sensor Intelligence for Specialized Care

When special clinical conditions call for advanced care, neonatal clinicians look to Masimo for breakthrough technologies that provide the clinical intelligence they require to deliver the most appropriate intervention, care and treatment. These breakthroughs include sensors with built-in artificial intelligence.

Masimo LNOP Newborn Neonatal SofTouch and LNOP Newborn Infant/Pediatric SofTouch sensors are specifically designed with newborn resuscitation in mind. When neonatal resuscitation is required, there's no time for slow measurements. Appropriate resuscitation protocol for neonates, according to American Academy of Pediatric (AAP) guidelines, suggests the use of pulse oximetry in the periodic evaluation of neonates at 30-second intervals. These specialty sensors, when connected to Masimo-equipped technology version 4.1 or higher, automatically enable the fastest SpO_2 and pulse rate readings at maximum sensitivity. This built-in sensor intelligence eliminates the need for clinicians to waste valuable seconds configuring the monitor to deliver the fastest performance required.

In addition, newborns with cyanotic cardiac lesions, who frequently measure low saturation values below 70%, present a special challenge in obtaining reliable pulse oximetry readings. After extensive research and development, Masimo introduced LNOP Blue, the first-and-only neonatal sensor specifically-designed and tested on cyanotic pediatric patients with arterial oxygen saturations as low as 60%.[4] Other pulse oximetry sensors are developed and tested on normal newborn babies with normal oxygen saturation values and are neither accurate nor reliable for measuring oxygen saturation in CHD newborns. In contrast, LNOP Blue is clinically-proven accurate and reliable for continuous pulse oximetry monitoring in cyanotic newborns—making it the ideal sensor for clinicians looking to better manage cardiac medications and ventilation therapy for neonatal, infant, and pediatric patients with this condition.

Earlier Detection of Critical Disease States

Only Masimo can offer eight noninvasive measurements to help clinicians identify and detect life-threatening conditions, such as anemia, methemoglobinemia and CHD, sooner and initiate life-saving intervention earlier. Conventional two-wavelength pulse oximeters typically only measure three core parameters (SpO_2, PR, PI)—providing values that may mask underlying problems and provide clinicians with a false sense of security.

The ability to immediately detect and continuously monitor methemoglobinemia in neonates undergoing inhaled nitric oxide (iNO) therapy has important clinical implications. Because high levels of iNO cause toxic risks and low levels result in suboptimal therapeutic doses, it is critical to administer optimal doses of both iNO and oxygen, and to monitor methemoglobin levels for safety. Even the prescribing and safety information for INOmax warns that "methemoglobinemia is a dose-dependent side effect of inhaled nitric oxide therapy. Therefore, methemoglobin levels should be monitored during INOmax administration."[5]

However, when using conventional two-wavelength pulse oximetry technology to monitor oxygen saturation, methemoglobinemia "pushes" the SpO_2 value to 85%—clearly misrepresenting the patient's oxygenation status. Illustrating this danger of methemoglobinemia and the advantages of using 12-wavelength Masimo Rainbow technology, one Patient Safety Alert warned that methemoglobinemia "renders routine 2-wavelength pulse oximetry unreliable, thus reducing your ability to detect a critical level of hypoxia" and instructed them to "not rely on routine 2-wavelength pulse oximetry to detect hypoxemia in the presence of MetHb."[6]

Furthermore, a Johns Hopkins study on the prevalence of methemoglobinemia concluded "if CO-oximetry tests had been

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The Cues and Care Trial: A Randomized Controlled Trial of an Intervention to Reduce Maternal Anxiety and Improve Developmental Outcomes in Very Low Birthweight Infants

Phyllis Zelkowitz, Nancy Feeley, Ian Shrier, Robyn Stremler, Ruta Westreich, David Dunkley, Russell Steele, Zeev Rosberger, Francine Lefebvre, Apostolos Papageorgiou

Abstract

Background: Very low birthweight infants are at risk for deficits in cognitive and language development, as well as attention and behavior problems. Maternal sensitive behavior (i.e. awareness of infant cues and appropriate responsiveness to those cues) in interaction with her very low birthweight infant is associated with better outcomes in these domains; however, maternal anxiety interferes with the mother's ability to interact sensitively with her very low birthweight infant. There is a need for brief, cost-effective and timely interventions that address both maternal psychological distress and interactive behavior. The Cues and Care trial is a randomized controlled trial of an intervention designed to reduce maternal anxiety and promote sensitive interaction in mothers of very low birthweight infants.

Methods and design: Mothers of singleton infants born at weights below 1500 g are recruited in the neonatal intensive care units of 2 tertiary care hospitals, and are randomly assigned to the experimental (Cues) intervention or to an attention control (Care) condition. The Cues intervention teaches mothers to attend to their own physiological, cognitive, and emotional cues that signal anxiety and worry, and to use cognitive-behavioral strategies to reduce distress. Mothers are also taught to understand infant cues and to respond sensitively to those cues. Mothers in the Care group receive general information about infant care. Both groups have 6 contacts with a trained intervener; 5 of the 6 sessions take place during the infant's hospitalization, and the sixth contact occurs after discharge, in the participant mother's home. The primary outcome is maternal symptoms of anxiety, assessed via self-report questionnaire immediately post-intervention. Secondary outcomes include maternal sensitive behavior, maternal symptoms of posttraumatic stress, and infant development at 6 months corrected age.

Discussion: The Cues and Care trial will provide important information on the efficacy of a brief, skills-based intervention to reduce anxiety and increase sensitivity in mothers of very low birthweight infants. A brief intervention of this nature may be more readily implemented as part of standard neonatal intensive care than broad-based, multi-component interventions. By intervening early, we aim to optimize developmental outcomes in these high risk infants. The trial registration code is ISRCTN00918472.

Background

Advances in neonatal intensive care have ensured the survival of 85% of very low birthweight infants (VLBW, i.e., infants born at weights under 1500 g), but these medically fragile infants remain at high risk for developmental delays, learning difficulties, and emotional and behavioral problems. VLBW children are at twice the risk of behavior problems compared to children in the general population, and are 2.5 times more likely to develop attention deficit hyperactivity disorder (ADHD). VLBW children are also at greater risk than their normal birthweight (NBW) peers for more subtle deficits including learning disabilities, anxiety disorders, social withdrawal, and social problems, and are almost 50% more likely than NBW children to require special education services, even in the absence of major neurocognitive disability. These functional deficits persist in adolescence and early adulthood, with continued lower IQ scores and poorer academic achievement, as well as more behavioral and emotional difficulties than their NBW peers. VLBW young adults are more likely to exhibit chronic health problems, lower levels of academic attainment, and higher rates of unemployment. This high-risk group of children is disproportionately represented among users of health, special education, and social services,

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and tax the physical, emotional, and financial resources of their families. In addition to direct medical costs associated with premature birth, indirect costs related to short- and long-term morbidity have been estimated at approximately $3 billion per year.

Given the significant risk associated with low birthweight, interventions have been designed to improve developmental outcomes in these children. These interventions have ranged from those targeting specific aspects of infant care, such as the need for supplementary sensory stimulation, and those which adapt the physical environment to the individual needs of the VLBW infant, to those offering a comprehensive package of services including medical follow-up, parent support, and educational daycare for the infants. One significant limitation of broad, comprehensive intervention programs, such as the Infant Health and Development Program, is that they are of long duration, costly and time-consuming for both service providers and families. This raises questions about the economic feasibility and practical utility of transferring broad-based, multi-component interventions into clinical practice. Moreover, these programs do not always target the infants and families at greatest risk, but instead offer services to families of infants born at weights under 2500 g. Saigal and Doyle have noted that one of the current challenges in the care of VLBW children is to provide support to parents to help maximize each child's potential. There is a need for brief, cost-effective and timely interventions that address specific processes that may affect infant development.

The current empirical evidence points to parental sensitivity and maternal psychological distress as two important factors influencing the development of VLBW children. Parental sensitivity includes awareness of and responsiveness to the infant's interactive cues. VLBW infants are difficult interaction partners who are less responsive to social stimulation, and produce less clear behavioral signals; as a result, their caregivers may have greater difficulty in behaving sensitively with them. Not only do mothers look, smile, vocalize and touch their VLBW infants less often than mothers of NBW infants, but they are also less well able to coordinate their behavior with their infants' brief periods of alertness. Parental sensitivity supports the infant's ability to maintain attentional focus and helps to organize the infant's behavior. This promotes cognitive and social development in VLBW infants, who continue to show benefits even into early adolescence in terms of social and cognitive competence. In contrast, controlling, restrictive parental behavior is associated with poorer cognitive, language, and social skills in VLBW children at 3 years of age. Maternal warmth and sensitivity have been found to moderate the effects of low birth weight (LBW) on attentional deficits, hyperactivity and internalizing problems in children aged 5 to 8 years.

Psychological distress, such as feelings of anxiety, depression and posttraumatic stress, is common in mothers of VLBW infants, and can affect both parental sensitivity and infant developmental outcomes. Such distress can persist for more than a year after the birth of the VLBW infant. Moreover, VLBW infants have been found to be more reactive to maternal depression than are NBW infants. The work of our research group has shown that maternal self-reported feelings of anxiety are related to less sensitive and more intrusive parenting behavior in infancy and early childhood, and to more internalizing behavior problems and poorer cognitive development in the infants at 24 months of age.

To summarize, VLBW infants are at risk for poorer cognitive and language development, as well as attention and behavior problems. Maternal sensitive interaction with her VLBW infant is associated with better outcomes in these domains; however, maternal psychological distress interferes with the mother's ability to interact sensitively with her VLBW infant. A consensus is now emerging that early intervention programs must address both mother-child interaction patterns and maternal distress in order to have a positive impact on the mother-child relationship and child developmental outcomes. A meta-analysis of diverse interventions aimed at improving maternal sensitivity found that interventions are significantly and moderately effective in improving sensitivity in mothers of children less than 4.5 years of age (effect size Cohen's $d=0.33$, $p < .001$). Interventions that focused only on improving sensitivity were more effective (d=.45) than all other types of interventions (d=.27) (e.g., support, or examination of mother's mental representations of the infant). Interventions using video feedback were more effective (d=.44) than those that did not use this method (d=.31). Interventions with less than 5 sessions (d=.42) were as effective as those with 5-16 sessions (d=.38), but interventions with more than 16 sessions were less effective (d=.21).

The Cues and Care trial tests a brief intervention designed to reduce anxiety and develop sensitive interaction skills among mothers of VLBW infants. By intervening at the level of maternal distress and maternal interactive behavior, it may be possible to promote a better parenting environment and optimize child developmental outcomes. This trial addresses several gaps in the literature on interventions with low birthweight infants: 1) it targets mothers of VLBW infants, who are at greater biological risk than heavier LBW (low birthweight) infants, 2) it begins shortly after birth, before dysfunctional patterns of parent-infant interaction have been established and when brain development is most rapid, and 3) it compares the intervention to an attention control condition, thus controlling for the effects of the extra support received by mothers in the experimental condition. Moreover, the experimental intervention 1) is relatively brief compared to many previous broad-based, multi-component interventions, and so has the potential to be applied in clinical practice, 2) employs empirically-based techniques from the domains of cognitive-behavior therapy (CBT) and parent sensitivity training, and 3) is a unique combination of 2 components—training in anxiety reduction strategies and sensitivity.

Methods and Design

The Cues and Care Trial is a randomized controlled trial with stratification by study site and centrally controlled randomization. The principal research question addressed by the Cues and Care Trial is as follows: What is the effect of a brief skills-based intervention (Cues program) on anxiety, defined as a subjective emotional state characterized by feelings of tension, apprehension, nervousness and worry, in mothers of VLBW infants? Anxiety is measured using the State-Trait Anxiety Inventory (STAI). The Cues intervention teaches mothers to attend to their own physiological, cognitive, and emotional cues that signal anxiety and worry, and to use cognitive-behavioral strategies to reduce distress. Mothers are also taught to understand infant cues and to respond sensitively to those cues. The primary hypothesis of the study is that immediately post-intervention, mothers in the intervention group will be less anxious than those in the attention control group. Secondary hypotheses examine differences between the two groups on

other measures of maternal distress, including symptoms of posttraumatic stress, stress associated with the Neonatal Intensive Care Unit (NICU) experience, and maternal sensitivity in interaction with her infant. We also collect exploratory data on postpartum depression and on infant development at 6 months corrected age.

Ethical considerations: The study protocol has been approved by the institutional review boards of the two hospitals where the trial is being conducted. Written informed consent is obtained from all participants prior to enrolment in the trial.

Participants: Mothers are recruited from the NICUs at 2 Montreal hospitals, with eligible admissions totalling approximately 250 per year. Inclusion criteria are: 1) singleton infant born weighing less than 1,500 grams, and mother 2) is able to speak and read either English or French, 3) is able to sign informed consent, and 4) resides within a 90-minute drive of the hospital. Mothers are excluded if: 1) they will not be caring for the infant after discharge from hospital (ie, foster placement, adoption), 2) their infant is in a highly unstable medical condition that is likely to result in death, has a major congenital anomaly or is known to have a major sensory handicap (ie, blind or deaf), 3) their infant is likely to be transferred or discharged in less than 4 weeks, or 4) they have given birth to multiples (twins or triplets). Mothers of multiples are excluded because pilot data showed that time constraints resulting from differing discharge dates for their infants made it difficult for them to complete the planned intervention. At one site, the practice of room assignments necessitated the exclusion of mothers who shared a room with women who had already been recruited as study participants, in order to avoid contamination.

Recruitment is undertaken by a trained member of the research staff. Birth records at each site are examined several times per week for eligible new admissions. Eligible mothers are informed about the study soon after birth as most require several weeks to decide whether to participate. At the initial contact, the recruiter gives the mother written information about the study and a copy of the consent form. Mothers are encouraged to make a decision by the 4th week after birth, in order to allow sufficient time to participate in the sessions prior to discharge.

Randomization is centrally controlled, concealed, in random blocks of 4 or 6, and stratified by hospital (stratification is required because one hospital serves a primarily francophone population while the other has a more diverse, multi-ethnic patient group). Randomization takes place using randomize.net, a centrally controlled, secure, online service.

Power analysis was based on the work of Mohide, which indicated that a change of 7 points on the STAI scale (the primary outcome) is considered clinically meaningful. Setting alpha=0.05 and power=0.8, we would need 40 subjects per group. To account for attrition, a sample of 46 mothers per group will be recruited.

Trial interventions: The experimental Cues intervention consists of 6 sessions to teach mothers to: 1) read their own cues and recognize signs of anxiety/distress, 2) utilize various strategies to reduce their distress, including muscle relaxation, imagery, and cognitive reframing, 3) read their infant's communication cues, and 4) respond sensitively to infant cues and distress. In the first two sessions, the intervener explains the relationship between thoughts, feelings, and behavior, and teaches mothers how to identify negative automatic thoughts. Participants acquire skills that help them to relax and to counteract maladaptive thought patterns. The next two sessions focus on understanding the behavior of VLBW infants, identifying infant states cues and learning how to interact sensitively with the infant. The fifth session is devoted to mother-infant interaction during feeding. Each teaching session lasts 60-90 minutes. There is also a telephone follow-up call, to review the techniques that have been taught and to maintain contact with participant mothers. The first 5 sessions take place in the NICU at a frequency of 1-2 sessions per week. The last session takes place in the mother's home 2-4 weeks after discharge. Total dose is 9-10 hours.

The program is delivered in one-on-one sessions between the mother and an intervener. Group sessions are not feasible because mothers differ greatly in the timing and frequency of their NICU visits; moreover, other studies with postpartum women report a high level of non-compliance with group interventions. Prior to each session, the mother is given a booklet describing the main ideas to be discussed at that session, and is asked to read the booklet before meeting with the intervener. Learning exercises are also included to assist mothers to apply the content to their own experience.

The final session takes place 2-4 weeks after discharge in the mother's home, as this is a time of heightened anxiety when the mother first assumes full responsibility for infant care. The convenience of a home visit facilitates mothers' compliance. We videotape the mother playing with her infant for 10 minutes. The intervener and mother then review the tape to help the mother to apply the skills acquired in previous sessions. Anxiety reduction techniques are also reviewed. This modality was incorporated in the Cues intervention because a meta-analysis of interventions designed to enhance maternal sensitivity in mothers of both preterm and full-term infants has shown that interventions that used video feedback were more effective than those that did not use this method.

The trial includes an attention control or Care group, in order to: 1) control for effects of the additional support and contact that experimental mothers receive, 2) promote participation by providing something beyond usual care for all participants, and 3) minimize drop-out from the control group. Control group mothers also have 6 contacts with an intervener at regular intervals coinciding with the timing of the experimental group contacts. The format for these contacts parallels that of the intervention group. Prior to each contact, the mother is given a brochure. Mothers are given information on common health problems of preterm infants as well as general information about infant care and feeding readily available to all mothers of infants. At each contact, the control group intervener meets with the mother in a private setting, discusses the content with the mother and answers any questions. Both groups receive usual medical, nursing and other care provided at the two study sites. We collect data on other services that mothers in both groups receive, such as consultations with mental health professionals or participation in support groups, at enrolment, prior to NICU discharge and post-intervention.

The interveners are nurses or clinical psychology graduate students, who are skilled in developing therapeutic relationships and teaching. To avoid contamination, some interveners are

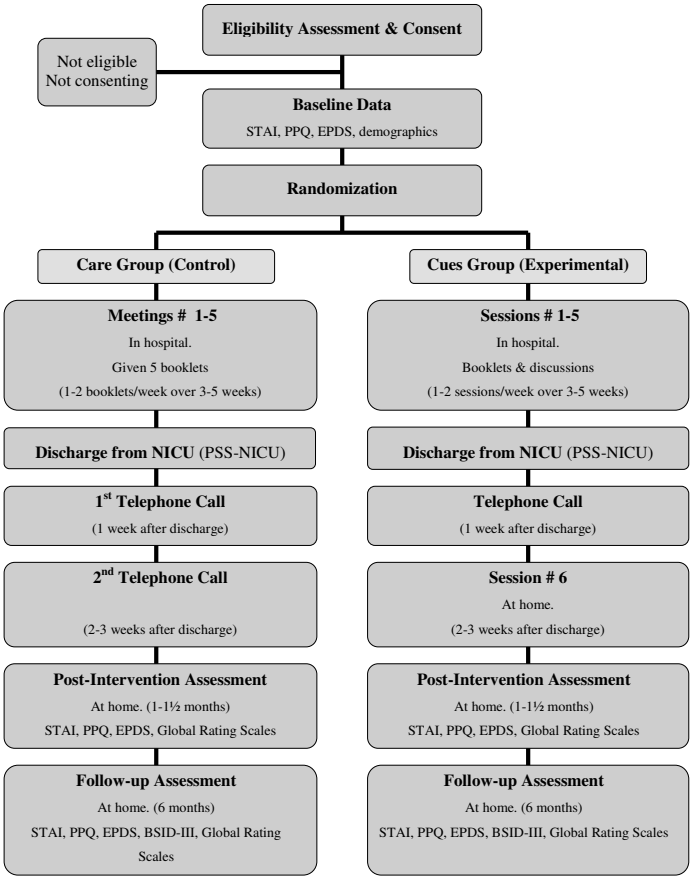

Figure 1: Cues and Care Trial timeline

STAI = State Trait Anxiety Inventory
EPDS = Edinburgh Postnatal Depression Scale
PPQ = Perinatal PTSD Questionnaire
PSS-NICU = Parent Stressor Scale: Neonatal Intensive Care Unit
BSDI-III = Bayley Scales of Infant Development-third edition

trained to deliver the Cues intervention, and other interveners are trained to deliver the Care intervention. Each participant mother is assigned to one intervener, who delivers all intervention sessions to that mother.

Manuals have been developed for both the Cues and the Care interventions; these manuals explicitly describe the teaching content and methods for each session. During their training, interveners read the manual and review the purpose, content and methods of each session with the principal investigators. In addition, interveners delivering the Cues program are trained with the Keys to Caregiving program developed to train professionals how to teach parents about sensitive interaction. This training program consists of a 5 1/2 hour videotape with an accompanying 70-page manual. Interveners view the tapes, read the accompanying manual and discuss the content. After completing the Keys Program, the interveners also view videotapes of mother-infant interactions to verify their understanding of the content. Training for the anxiety-reduction components of the Cues intervention is done by experienced cognitive-behavior therapists on the research team. First, interveners read and discuss articles on cognitive-behavioral interventions in treating anxiety symptoms. Second, role play is used to practice specific intervention techniques. Third, under supervision each intervener practices intervention skills with a hospitalized postpartum mother (not a study participant).

Training of the control group interveners delivering the Care program is done by a nurse/collaborator. The control group interveners do not have prior knowledge, nor are they taught the cognitive-behavioral interventions or the sensitivity content. They are instructed to refer mothers with any concerns beyond the scope of the topics addressed in the booklets to the appropriate NICU staff member (i.e., physician, social worker).

To ensure consistency of delivery across interveners, the interveners refer to their respective manuals and follow the procedures outlined in them. Interveners also record the relevant details of each session with each mother on a standardized record sheet. There is ongoing supervision during the course of the study, with separate meetings for the experimental and control group interveners. Furthermore, every 7th session (15% of total) is audio-taped and reviewed by the supervisors and feedback given to the intervener involved to ensure fidelity to the intervention design.

Primary and secondary outcomes: The primary outcome of the trial is maternal anxiety, measured by the state portion of the State-Trait Anxiety Inventory (STAI). This self-report measure consists of 20 items that ask about the intensity of the respondent's feelings of anxiety, tension, apprehension, nervousness and worry at the time of completion of the questionnaire. The STAI has been translated into more than 60 languages and has been used in thousands of studies designed to assess stress-related psychiatric and medical disorders, and in treatment outcome studies. Respondents rate each item on a 4-point scale, indicating whether they experience the particular feeling: 1 (not at all), 2 (somewhat), 3 (moderately so), or 4 (very much so). Standardized on more than 5000 subjects, the STAI has high internal consistency, with a median Cronbach's alpha of .93 (in VLBW mothers, Cronbach's alpha=0.91). In terms of construct validity, STAI scores increase significantly in stressful situations, and decrease after relaxation training.

The following are secondary outcome measures:

1. Maternal perinatal posttraumatic stress is assessed with the Perinatal PTSD Questionnaire(PPQ). This self-report questionnaire assesses symptoms of posttraumatic stress specifically related to the childbirth experience. Fourteen items tap intrusive thoughts, avoidance and increased arousal. Internal consistency of the measure is high (alpha=.83) and test-retest reliability very good (r=.92). PPQ scores have been significantly correlated with other well-validated measures of posttraumatic stress, and with use of psychotherapy.
2. The revised Parental Stress Scale: Neonatal Intensive Care Unit (PSS: NICU) is used to assess two dimensions of stress particularly salient to the experience of mothers of hospitalized VLBW infants: a) stress related to the infant's behavior and appearance, and b) stress related to feeling restricted in their maternal or caregiver role. The internal consistency of this self-report questionnaire is excellent (Cronbach alpha's .89-.94). Evidence of construct validity has been demonstrated, in that the PSS: NICU has been significantly correlated with state anxiety scores (r=.45).
3. Sensitivity of mother-infant interaction is assessed immediately post-intervention and at the 6-month follow-up with the Global Rating Scales of Mother-Infant Interaction. A five-minute videotape of mother-infant interaction is made in the home; mothers are instructed to play with their infants without the use of toys. Maternal and infant behaviors are then rated, by a coder who is blind to the mother's group

assignment, on several dimensions, including maternal sensitivity, intrusiveness, remoteness, and depression, as well as infant engagement, liveliness and fretfulness. The overall quality of the interaction between mother and infant is also rated. We evaluate inter-rater reliability by having two coders rate the videotapes, and then comparing their scores using intraclass correlations. The measure has been found to discriminate between mothers with and without postpartum depression, and has also been used with other clinical groups such as schizophrenic mothers and mothers with borderline personality disorder.

Additional variables: For the purposes of sample description, we collect data on demographic variables such as maternal age, education, occupation, parity, and current use of psychosocial services (e.g., social worker, support groups). Infant illness severity is assessed with the Revised Nursery Neurobiologic Risk Score (NBRS). It includes 7 items that assess the presence, severity and duration of medical events associated with the risk of later abnormal neurodevelopment for the infant. The NBRS is scored following a review of the infant's medical record. NBRS scores correlate with later child neurological examination scores, as well as with poorer subsequent social, cognitive and psychomotor development of children born VLBW. At the time of discharge, the NBRS is scored by a rater blind to the mother's group assignment.

We are also collecting data for exploratory analyses of two important outcome variables: 1. Maternal depression is assessed using the Edinburgh Postnatal Depression Scale (EPDS). This 10-item scale is designed to screen for postpartum depression in community samples. The items are rated on a scale from 0 to 3, and refer to symptoms experienced in the past 7 days. Respondents who score above the cut point of 12 are classified as at risk for a depressive disorder. The split-half reliability of the scale is 0.88, and the standardized alpha coefficient is 0.87. In validation studies, using a cut score of 12, the EPDS was found to have a sensitivity of 68% to 95%, and a specificity of 78% to 96%, when compared to a diagnosis of major depression made by psychiatric interview. 2. Bayley Scales of Infant Development, 3rd edition (BSID-III, 2005) are used to gather pilot data on infant cognitive development. This is the most recent revision of a widely used measure of infant development, and consists of 5 scales: cognitive, language, motor, social-emotional, and adaptive. This instrument has excellent psychometric properties, and has been validated on over 1700 children.

Given that maternal depression is a dichotomous outcome, the sample size required to adequately test any related hypotheses would be prohibitive. Similarly, the trial is not adequately powered to test differences between the experimental and control groups in terms of infant developmental outcome on the BSID-III. Although we cannot test hypotheses related to these variables, the pilot data that we are collecting on these variables will help with future projects in this area.

Procedures

The study timeline can be found in Figure 1. Following recruitment, informed consent is obtained, and baseline measures (STAI, PPQ, and EPDS) are administered. Participants are then randomized to either the Cues or the Care condition. Within a day of randomization, an intervener contacts the participant and arranges for the first session of the intervention. Post-intervention measures are administered at the participant's home 2-3 weeks after the intervention ends (when infants are 1-1.5 months corrected age). This assessment includes observation of mother-infant interaction, and completion of the self-report measures of anxiety, depression, and posttraumatic stress. In addition, participant mothers are asked to report on their satisfaction with the intervention that they received. A follow-up assessment of mothers and infants takes place at home when the infants are 6 months old (corrected age). At this time, the BSID-III is administered, in conjunction with observation of mother-infant interaction, and the completion of the same set of self-report measures used at baseline and at the immediate post-intervention assessment.

Blinding: It is not possible to blind participant mothers because the experimental treatment condition teaches mothers specific skills to reduce distress and interact sensitively with their infants, while mothers in the control group receive non-specific attention. However, we tell both groups that their intervention may reduce anxiety and distress, in order to minimize any differences in participants' expectations. Careful attention is paid to the blinding of assessors and data collectors. All pre-intervention data are obtained blinded because they are collected prior to randomization. The research assistants who collect the post-intervention data (1 and 6 months of age) are not involved in the pre-intervention data collection. Research assistants are instructed not to ask participants about their group assignment, and participants are asked not to reveal their group assignment to research or medical staff. Mothers read and respond to self-report questionnaires independently. The research assistants who videotape interactions in the home are not involved in the coding of the videotapes. All interaction videotapes are coded at a later date by a research assistant hired just for this task, and who has no contact with the NICU or with participants and thus is blind to group assignment. Other staff, also blind to group assignment, are trained to score the NBRS via chart review. Finally, post-intervention research assistants and interveners are housed in separate buildings to minimize the chance of information transfer, and there are separate meetings for interveners and other research staff.

Contamination: Contamination is a potential concern when delivering an intervention to mothers in NICUs, which are large open units, with infant incubators located in close proximity to one another. Inevitably, there is interaction between mothers. In order to address this issue, we have adopted inclusion/exclusion criteria that preclude the recruitment of mothers who are sharing a room. Once participants are enrolled in the study, we employ several strategies to deal with contamination. First, we explain to participants that we can only test the effectiveness of the intervention if they do not share information. Second, interveners are instructed not to discuss the program content with non-participants or with NICU staff. Third, whenever possible, interveners deliver the intervention sessions at a private location where their discussion cannot be overheard by other mothers or NICU staff. Fourth, when sessions take place at the infant's bedside, the interveners place a screen around the bedside to maximize privacy. Fifth, when the intervention is completed we ask mothers if they have shared any of the program information with other NICU mothers, and if so with whom. Finally, we measure contamination post-intervention by asking mothers in both the experimental and control groups to respond to a questionnaire testing their knowledge of the content of both programs and to indicate the source of this knowledge.

Planned analyses: No interim analyses are planned. Upon completion of the study, we will compare baseline values for demographic variables to assess the adequacy of randomization. These include maternal age, education, parity, psychosocial services used by the mother, and infant illness severity. The primary outcome is the difference in STAI scores between the intervention group and the control group, evaluated immediately post-intervention. This is a continuous measure and will be analyzed using an unpaired t-test (i.e. comparison of scores between two independent samples) and an intent-to-treat strategy. The overall significance level will be considered at a two-sided 0.05 level. As a secondary analysis, we will use a multiple regression model to account for other predictors of outcome, including baseline STAI, and the demographic variables noted immediately above. Finally, as an exploratory analysis, we will compare groups based on actual treatment received in addition to our primary intention-to-treat analysis. The analysis of secondary measures will proceed in a likewise fashion. We will also report on contamination and describe other services used during and after the intervention. Because we only have 46 subjects per group, we cannot use sophisticated multiple imputation techniques to estimate expected results in subjects who withdraw from the study. Therefore, we will document and describe the reasons for attrition within each group, but exclude these subjects from the multiple regression analyses.

Safety: The Cues and Care programs are psychosocial interventions, so there are no medical risks to either mother or infant. Mothers may find that the completion of questionnaires asking about anxiety and stress may arouse feelings of distress, though this has not been a problem in pilot work; those who experience such distress will be offered a consultation with one of the clinical psychologists affiliated with the trial, who may then refer them to appropriate services as needed. In addition, all mothers who score above the cut point for depression on the EPDS are offered a referral for evaluation by a mental health professional.

Discussion

Conducting a randomized controlled trial of a psychosocial intervention in a critical care unit of a hospital poses significant challenges. Timing of recruitment is an important factor: potential participants must be approached early enough after the infant's birth to allow sufficient time to complete the intervention prior to the infant's discharge. However, mothers are unlikely to agree to participate until their infant's condition is relatively stable. Moreover, depending on the number of admissions to the NICU, stable infants are sometimes transferred to other hospitals so that their growth can be monitored before being discharged home. Such transfers may interfere with completion of the intervention program. Recruiters and interveners have developed procedures to address these issues, by delaying the recruitment of mothers of extremely small or ill neonates, and by working closely with the transfer coordinators of the NICUs.

The Cues and Care trial will provide important information on the efficacy of a brief, skills-based intervention to reduce anxiety and increase sensitivity in mothers of VLBW infants. A brief intervention of this nature may be more readily implemented as part of standard NICU care than broad-based, multi-component interventions. By intervening early, we aim to optimize developmental outcomes in this high risk group of infants.

Noninvasive Sensors…continued from page 30
performed on every blood aliquot sent for arterial blood gas analysis during the 28-month study period, the incurred cost at $25 per test would have totaled approximately $9 million."[7]

Undetected CHD is a growing concern among neonatal clinicians who currently rely on physical examination assessments to diagnose CHD in neonates. Clinical evidence suggests that up to 30% of all deaths from CHD occurring within the first year of life are due to unrecognized cases being discharged from the hospital—prompting clinicians to look to new diagnostic and monitoring tools for more accurate CHD detection.

Masimo perfusion index (PI) is an automated noninvasive measure of the changes in peripheral perfusion and circulatory status, which has been shown to greatly improve a clinician's ability to detect critical CHD in newborns before discharge. A clinical study of over 10,000 newborns showed that when Masimo PI was added to routine neonatal examination and saturation screening, all babies with critical CHD were identified, improving the detection rate from 78% to 100%.[8]

Masimo believes that every patient, regardless of size, age or demographics, deserves the best chance at survival that modern science and technology can provide. Pulse oximetry sensors play a vital role in patient monitoring and choosing the right sensor for the right application can make a lifesaving difference. That's why for nearly twenty years, Masimo's mission has remained focused on "improving patient outcomes and reducing the cost of care…by taking noninvasive monitoring to new sites and applications."

For copies of the case studies referred to in this article, and for more information about Masimo advanced patient monitoring solutions, please visit masimo.com.

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Area-Level Poverty and Preterm Birth Risk: A Population-Based Multilevel Analysis

Emily A. DeFranco, Min Lian, Louis A. Muglia, Mario Schootman

Abstract

Background: Preterm birth is a complex disease with etiologic influences from a variety of social, environmental, hormonal, genetic, and other factors. The purpose of this study was to utilize a large population-based birth registry to estimate the independent effect of county-level poverty on preterm birth risk. To accomplish this, we used a multilevel logistic regression approach to account for multiple co-existent individual-level variables and county-level poverty rate.

Methods: Population-based study utilizing Missouri's birth certificate database (1989–1997). We conducted a multilevel logistic regression analysis to estimate the effect of county-level poverty on PTB risk. Of 634,994 births nested within 115 counties in Missouri, two levels were considered. Individual-level variables included demographics factors, prenatal care, health-related behavioral risk factors, and medical risk factors. The area-level variable included the percentage of the population within each county living below the poverty line (US census data, 1990). Counties were divided into quartiles of poverty; the first quartile (lowest rate of poverty) was the reference group.

Results: PTB < 35 weeks occurred in 24,490 pregnancies (3.9%). The rate of PTB < 35 weeks was 2.8% in counties within the lowest quartile of poverty and increased through the 4th quartile (4.9%), $p < 0.0001$. High county-level poverty was significantly associated with PTB risk. PTB risk (< 35 weeks) was increased for women who resided in counties within the highest quartile of poverty, adjusted odds ratio (adjOR) 1.18 (95% CI 1.03, 1.35), with a similar effect at earlier gestational ages (< 32 weeks), adjOR 1.27 (95% CI 1.06, 1.52).

Conclusion: Women residing in socioeconomically deprived areas are at increased risk of preterm birth, above other underlying risk factors. Although the risk increase is modest, it affects a large number of pregnancies.

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Background

Preterm birth is a major public health burden whose prevalence continues to rise. The rate of preterm birth in the US is 12.7%, the highest rate reported to date. The financial burden of caring for infant survivors of preterm birth is substantial, with a lower-end estimate of approximately 26.2 billion dollars annually in the US. Preterm birth is a complex disease with etiologic influences from a variety of social, environmental, hormonal, genetic, and other factors. Our limited understanding of the complex interactions among these factors contributes the lack of effective intervention strategies available to reduce the rate of preterm birth.

It has been hypothesized that the association between preterm parturition and individual-level socioeconomic deprivation is primarily accounted for by the co-existence of other significant risk factors such as medical comorbidities, lack of prenatal care, and adverse behaviors (smoking and alcohol use) which occur more commonly in women of lower socioeconomic status. However, many prior studies have been limited by design constraints and the inability to thoroughly account for potential confounding factors.

Implementation of appropriate statistical methodologies, rigorous adherence to study design, and consideration of as many clinically important covariates as possible optimizes the capability to accurately quantify the independent association between area-level poverty and preterm birth risk. When taking into consideration that people who reside within the same area share common area-level neighborhood conditions, individual-based statistical models such as traditional logistic regression analyses are not optimal to determine the true strength of the association. Using multilevel logistic regression analysis has the advantage of allowing one to estimate not only the fixed effects of individual-level and area-level factors, but also the random effect of geographic variation of preterm birth between areas.

The purpose of this study was to utilize a large population-based birth registry to estimate the independent effect of county-level poverty on preterm birth risk. To accomplish this, we used a

Table 1: Baseline characteristics of the study population according to county poverty rate

County Poverty Rate	Reference 1st quartile	2nd quartile	3rd quartile	Highest Poverty 4th quartile	p-value
Total	92,072	196,672	170,701	175,549	
Demographic factors					
Maternal age (mean ± SD)	27.0 ± 5.4	27.33 ± 5.8	25.4 ± 5.7	24.9 ± 5.8	< 0.0001
Reside inside city limits (n,%)	64,198 (69.1%)	121,346 (61.7%)	143,357 (84.0%)	124,625 (71.0%)	< 0.0001
Black race (n,%)	1,823 (2.0%)	29,384 (14.9%)	26,551 (15.5%)	47,140 (26.8%)	< 0.0001
Mother's education level < high school (n,%)	12,180 (13.2%)	26,930 (13.7%)	37,232 (21.8%)	51,609 (29.4%)	< 0.0001
Father's education level < high school (n,%)	7,697 (8.4%)	13,794 (7.0%)	19,384 (11.4%)	22,270 (12.7%)	< 0.0001
Married (n,%)	73,198 (79.5%)	147,841 (75.2%)	111,350 (65.2%)	102,479 (58.4%)	< 0.0001
Indicators of low SES * (n,%)	25,066 (27.2%)	64,428 (32.8%)	87,947 (51.5%)	111,913 (63.7%)	< 0.0001
Prenatal Care					
Inadequate prenatal care ** (n,%)	8,246 (9.0%)	21,285 (10.8%)	26,455 (15.5%)	38,045 (21.7%)	< 0.0001
Behaviors					
Maternal tobacco use (n,%)	21,084 (22.9%)	36,417 (18.5%)	40,774 (23.9%)	43,416 (24.7%)	< 0.0001
Maternal alcohol use (n,%)	1,703 (1.8%)	4,755 (2.4%)	4,003 (2.3%)	3,671 (2.1%)	< 0.0001
Medical Risk Factors					
Medical risk factors (n,%)	19,792 (21.5%)	37,235 (18.9%)	36,802 (21.6%)	40,055 (22.8%)	< 0.0001

* composite variable including recipient of state-funded Medicaid, foodstamps or WIC assistance
** prenatal care initiated after 20 weeks of pregnancy

multilevel logistic regression approach to account for multiple co-existent individual-level variables and county-level poverty rate.

Methods

A data set which included Missouri birth records from 1978–1998 was provided in a de-identified fashion for this analysis by the Missouri Department of Health and Senior Services. The study was considered exempt from review by the Missouri Department of Health and Senior Services IRB and the Human Subjects Committee of Washington University in St. Louis. This data set has been a rich source for the analysis of factors associated with birth timing.

A total of 1,577,082 births occurred in Missouri between 1978 and 1998. To optimize our capability to examine the influence of important individual factors, we limited our study to those births which occurred between 1989 and 1998, due to an unacceptable amount of missing demographic data for births that occurred before 1989 because of revisions in the birth certificate format in 1989 and improvements in edit and query systems after that date. Because deliveries which occur prior to 20 completed weeks of pregnancy are considered miscarriages rather than births, we limited our analysis to births recorded as having occurred at 20 weeks or greater. We excluded births resulting from a multifetal gestation, intrauterine fetal demise, or involving a major congenital malformation due to their know propensity to deliver preterm, potentially for mechanisms unrelated to the exposure we wished to evaluate. After these exclusions, the study population consisted of 675,044 births. We further limited our analysis to births occuring to mothers whose reported residence at the time of delivery was in the state of Missouri. There were 40,050 births in Missouri to mothers who resided in other states during the study period, yeilding a final population of 634,994 births available for analysis. We performed our primary analysis with preterm birth defined as less than 35 completed weeks in order to enrich for a population of deliveries which were truly preterm by avoiding births occurring at borderline gestational ages between 35 and 37 weeks, in an effort to minimize misclassification bias. We defined early preterm birth as birth occurring prior to 32 completed weeks of gestation, because the risk of neonatal morbidity is higher for births of shorter gestations.

We included the following individual-level measures: maternal age, maternal race (self-reported), maternal and paternal highest educational attainment, residence within city limits, birth sequence, marital status, presence of medical risk factors, marital status, indicators of low income (recipient of food stamps, Medicaid, or WIC state-funded assistance), adequacy of prenatal care received, health-related behaviors (maternal tobacco or alcohol use), and presence of medical risk factors. Individual-level risk factors were selected from the data set based on clinical relevance and association with preterm birth.

Maternal and paternal education levels are recorded in the database in years of education completed, which we dichotomized as educational levels of < 12 years versus 12 years or more in order to identify those with less than a high school education. The variable of maternal education had minimal missing data, and paternal education was less complete with 22.6% missing data. A composite dichotomous variable of low socioeconomic status was created from the individual dichotomous variables of recipient of any of three state funded support programs. A dichotomous variable of inadequate prenatal care was created from a continuous variable which indicated the month of pregnancy when prenatal care was initiated. Inadequate prenatal care was defined as having initiated prenatal care after 20 weeks of pregnancy. A composite variable of heterogeneous medical risk factors indicated pregnancies complicated by anemia, maternal cardiac disease, acute or chronic lung disease, diabetes, genital herpes, hydramnios/oligohydramnios, hemoglobinopathy,

Table 2: Prevalence of preterm birth at less than 35 weeks and less than 32 weeks of gestation according to quartile of county-level poverty

County Poverty Rate	Reference 1st quartile	2nd quartile	3rd quartile	Highest Poverty 4th quartile	p value
Total	92,072	196,672	170,701	175,549	
PTB (< 35 wk)	2,551 (2.77%)	6,684 (3.40%)	6,671 (3.91%)	8,584 (4.89%)	< 0.0001
PTB (< 32 wk)	893 (0.97%)	2,521 (1.28%)	2,646 (1.55%)	3,402 (1.94%)	< 0.0001

Table 3: Multilevel logistic regression analysis results of preterm birth risk by quartile of county-level poverty, entire study population

	PTB (< 35 wk)			PTB (< 32 wk)		
	OR (95% CI)	IOR-80 *	MOR†	OR (95% CI)	IOR-80 *	MOR†
Model I: Poverty Only			1.21			1.22
2nd Quartile	1.14 (0.94, 1.38)	0.79, 1.63		1.15 (0.92, 1.43)	0.79, 1.68	
3rd Quartile	1.28(1.06, 1.55)	0.89, 1.83		1.33 (1.07, 1.65)	0.91, 1.94	
4th Quartile	1.30(1.09, 1.56)	0.91, 1.87		1.40 (1.14, 1.72)	0.96, 2.05	
Model II: Model I + Demographic factors			1.10			1.07
2nd Quartile	1.09 (0.97, 1.22)	0.91, 1.31		1.09 (0.97, 1.23)	0.96, 1.24	
3rd Quartile	1.18 (1.06, 1.32)	0.99, 1.42		1.24 (1.10, 1.39)	1.09, 1.41	
4th Quartile	1.15 (1.04, 1.28)	0.96, 1.39		1.25 (1.12, 1.41)	1.10, 1.43	
Model III: Model II + Prenatal Care			1.11			1.09
2nd Quartile	1.09 (0.97, 1.22)	0.90, 1.32		1.09 (0.96, 1.25)	0.92, 1.30	
3rd Quartile	1.19 (1.06, 1.33)	0.98, 1.44		1.23 (1.08, 1.40)	1.04, 1.46	
4th Quartile	1.15 (1.03, 1.28)	0.95, 1.39		1.23 (1.08, 1.39)	1.03, 1.46	
Model IV: Model III + Behaviors			1.11			1.10
2nd Quartile	1.09 (0.97, 1.23)	0.90, 1.33		1.10 (0.96, 1.25)	0.92, 1.31	
3rd Quartile	1.19 (1.06, 1.34)	0.99, 1.45		1.24 (1.08, 1.41)	1.04, 1.47	
4th Quartile	1.16 (1.04, 1.30)	0.96, 1.41		1.24 (1.09, 1.41)	1.04, 1.48	
Model V: Model III + Medical Risk Factors			1.14			1.18
2nd Quartile	1.12 (0.97, 1.29)	0.87, 1.44		1.13 (0.94, 1.37)	0.83, 1.55	
3rd Quartile	1.23 (1.07, 1.42)	0.95, 1.59		1.28 (1.06, 1.55)	0.94, 1.75	
4th Quartile	1.18 (1.03, 1.35)	0.91, 1.52		1.27 (1.06, 1.52)	0.93, 1.73	

Refer to table 1 for a complete list of co-variates included in each model
*IOR-80 = 80% interval odds ratio
†MOR = median odds ratio

chronic hypertension, pre-eclampsia, eclampsia, incompetent cervix, previous infant weighing > 4000 gm, previous preterm or small-for-gestational-age infant, maternal renal disease, Rh sensitization, or uterine bleeding.

Poverty rate was obtained from US census data (1990) and was defined as the percentage of the population falling below the US federal poverty line at the county level of the mother's reported residence as a measure of area socioeconomic position. Results

The study population was comprised of 634,994 live births to mothers who resided in 115 counties in Missouri from 1989–1998 for an average of 5,522 births per county. The racial distribution of the study cohort was 82.4% White, 16.1% Black, 0.3% Indian, 0.5% Asian/Pacific Islander, 0.6% other/unknown.

Women who resided in counties with higher rates of poverty were significantly younger, and more likely to be black, less likely to graduate from high school, to be unmarried, and be of low income. Likewise, parturiants residing in areas with higher county-level poverty were more likely to have inadequate prenatal care, smoke cigarettes, drink alcohol during pregnancy, and have at least one medical risk factor.

The overall rate of preterm birth < 35 weeks for the entire study population was 3.9%. The rate of preterm birth < 35 weeks was 2.8% for mothers who resided in counties within the lowest quartile of poverty. The rate of preterm birth increased with increasing county poverty rate (2nd quartile: 3.4%, 3rd quartile: 3.9%, 4th quartile: 4.9%), $p < 0.0001$. Similarly, early preterm births (< 32 weeks) occurred more commonly in mothers who resided in counties with higher poverty rates. The rate of early preterm birth nearly doubled from 1.0% in the 1st quartile to 1.9% in the quartile with the highest poverty rate.

Compared to births to mothers residing in counties with the lowest poverty rate (1st quartile), the risk of preterm birth < 35 weeks increased with increasing rates of county-level poverty in univariate analysis. This risk increase resulted in women in counties with the highest poverty rate being 1.30 times more likely to deliver preterm. The risk of early preterm birth was also significantly increased in mothers living in areas with the highest county-level poverty rate. This effect was similar when the study population was stratified by race. Both black and white mothers residing in counties with the highest poverty rate had an increased risk of preterm birth.

When demographic factors are added to county-level poverty, the odds ratio for preterm birth < 35 weeks of women residing in counties with the highest poverty rate was reduced from 1.30 to 1.15. When considering preterm births that occurred at earlier gestational ages (< 32 weeks of gestation), the risk increase associated with high county-level poverty was similarly influenced by individual-level factors. The unadjusted risk of early preterm birth with high county-level poverty was reduced to 1.0 when individual-level demographic factors were added to the model. The addition of other individual-level covariates such as prenatal care, behavioral risk factors, and medical risk factors only minimally influence the adjusted odds ratio. Stratified analysis by race (black, white) demonstrated similar effect sizes when individual-level factors were added to the models. Many more of the confidence intervals of risk in the analysis stratified by black race cross one than in the analysis by white race, but the effect sizes are very similar regardless of race.

Discussion

In this study we found that women who gave birth in counties with the highest poverty rates were at increased risk of preterm birth at < 35 and < 32 weeks of gestation. Although these

Table 4: Multilevel logistic regression analysis results of preterm birth risk by quartile of county-level poverty, stratified by maternal race

White	PTB (< 35 wk)			PTB (< 32 wk)		
	OR (95% CI)	IOR-80 *	MOR†	OR (95% CI)	IOR-80 *	MOR†
Model I: Poverty Only			1.12			1.07
2nd Quartile	1.10 (0.97, 1.26)	0.88, 1.38		1.08 (0.96, 1.21)	0.95, 1.23	
3rd Quartile	1.25 (1.10 1.43)	1.00, 1.57		1.30 (1.16, 1.46)	1.14, 1.48	
4th Quartile	1.24 (1.10, 1.41)	0.99, 1.55		1.33 (1.19, 1.49)	1.17, 1.52	
Model II: Model I + Demographic factors			1.1			1.04
2nd Quartile	1.09 (0.97, 1.21)	0.91, 1.30		1.06 (0.96, 1.17)	0.99, 1.14	
3rd Quartile	1.16 (1.04, 1.30)	0.97, 1.39		1.19 (1.08, 1.31)	1.11, 1.27	
4th Quartile	1.13 (1.02, 1.26)	0.95, 1.36		1.20 (1.09, 1.32)	1.12, 1.29	
Model III: Model II + Prenatal Care			1.1			1.07
2nd Quartile	1.09 (0.97, 1.23)	0.90, 1.32		1.07 (0.95, 1.21)	0.94, 1.23	
3rd Quartile	1.17 (1.04, 1.31)	0.97, 1.41		1.18 (1.05, 1.33)	1.03, 1.34	
4th Quartile	1.13 (1.02, 1.26)	0.94, 1.37		1.18 (1.05, 1.32)	1.03, 1.35	
Model IV: Model III + Behaviors			1.11			1.07
2nd Quartile	1.10 (0.98, 1.24)	0.91, 1.33		1.08 (0.96, 1.22)	0.95, 1.24	
3rd Quartile	1.18 (1.05, 1.33)	0.98, 1.43		1.19 (1.06, 1.34)	1.04, 1.36	
4th Quartile	1.15 (1.03, 1.28)	0.95, 1.39		1.20 (1.07, 1.34)	1.05, 1.37	
Model V: Model III + Medical Risk Factors			1.14			1.16
2nd Quartile	1.12 (0.97, 1.30)	0.87, 1.45		1.12 (0.93, 1.34)	0.84, 1.49	
3rd Quartile	1.22 (1.05, 1.41)	0.94, 1.57		1.24 (1.03, 1.49)	0.93, 1.65	
4th Quartile	1.17 (1.02, 1.34)	0.91, 1.51		1.23 (1.04, 1.46)	0.92, 1.65	
Black	PTB (< 35 wk)			PTB (< 32 wk)		
	OR (95% CI)	IOR-80 *	MOR†	OR (95% CI)	IOR-80 *	MOR†
Model I: Poverty Only			1.2			1.22
2nd Quartile	1.21 (0.88, 1.68)	0.86, 1.70		1.25 (0.82, 1.90)	0.85, 1.83	
3rd Quartile	1.26 (0.91, 1.76)	0.90, 1.77		1.39 (0.91, 2.14)	0.95, 2.04	
4th Quartile	1.46 (1.08, 1.98)	1.04, 2.05		1.33 (0.89, 1.97)	0.91, 1.94	
Model II: Model I + Demographic factors			1.11			1.19
2nd Quartile	1.18 (0.90, 1.54)	0.96, 1.45		1.24 (0.83, 1.85)	0.90, 1.71	
3rd Quartile	1.18 (0.89, 1.55)	0.96, 1.45		1.34 (0.89, 2.02)	0.97, 1.86	
4th Quartile	1.33 (1.04, 1.72)	1.09, 1.64		0.87 (0.87, 1.85)	0.92, 1.76	
Model III: Model II + Prenatal Care			1.11			1.18
2nd Quartile	1.18 (0.90, 1.54)	0.96, 1.44		1.23 (0.82, 1.82)	0.89, 1.68	
3rd Quartile	1.16 (0.88, 1.53)	0.95, 1.42		1.30 (1.87, 1.96)	0.95, 1.79	
4th Quartile	1.30 (1.01, 1.68)	1.06, 1.60		1.22 (0.83, 1.77)	0.89, 1.67	
Model IV: Model III + Behaviors			1.12			1.19
2nd Quartile	1.16 (0.88, 1.52)	0.93, 1.44		1.21 (0.81, 1.81)	0.87, 1.68	
3rd Quartile	1.14 (0.86, 1.51)	0.92, 1.42		1.28 (0.85, 1.94)	0.93, 1.78	
4th Quartile	1.31 (1.01, 1.69)	1.05, 1.62		1.21 (0.83, 1.78)	0.88, 1.68	
Model V: Model III + Medical Risk Factors			1.16			1.29
2nd Quartile	1.20 (0.89, 1.63)	0.91, 1.60		1.29 (0.80, 2.07)	0.79, 2.10	
3rd Quartile	1.16 (0.85 1.58)	0.87, 1.54		1.36 (0.84, 2.21)	0.84, 2.21	
4th Quartile	1.24 (0.93, 1.65)	0.93, 1.65		1.16 (0.74, 1.82)	0.71, 1.88	

Refer to table 1 for a complete list of co-variates included in each model
*IOR-80 = 80% interval odds ratio
†MOR = median odds ratio

risks are modest, with odds ratio estimates of 1.18 and 1.27 respectively, the confidence intervals consistently excluded the value of one even after accounting for numerous individual demographic, obstetric, behavioral, and medical risk factors. These effects were similar regardless of maternal race. Modest increases in MOR and IOR values suggest that county-level poverty was an important area-level characteristic for geographic heterogeneity of PTB. But, other unmeasured area-level characteristics may also partly contribute to the geographic heterogeneity of preterm birth.

Other investigators have reported an association of individual and area-level socioeconomic deprivation with adverse perinatal outcomes, such as low birth weight and preterm birth. Although numerous, these studies vary significantly with respect to sample size, study design, and methodologic strategies. Although women who are economically disadvantaged are disproportionately likely have co-existent risk factors for preterm birth, attempts to adjust for these factors in prior studies have not completely eliminated the modest association between poverty and prematurity. Our goal was to use optimal statistical techniques

on a large-population based sample to describe the effect of regional poverty on prematurity. Due to the variety of information available, we were able to evaluate the effect of several partitions of clinically relevent social and medical factors on preterm birth while accounting for the random variation of prematurity across counties. Despite accounting for many sociodemographic, obstetric, medical, and other factors our results suggest that county environments may in fact independently influence birth outcomes.

The advantage of multilevel analytic approaches to health outcome research is that they enable us to evaluate and quantify the heterogeneity of the outcome across geographic areas. When minimal geographic heterogeneity exists, this implies high area-level correlation. When individuals within the population are similar and vary little with respect to health, this provides optimal conditions for regional prevention strategies. Likewise, health outcomes such as preterm birth, which can be significantly influenced by behavior-related factors (smoking, alcohol use, receipt of prenatal care) may be less influenced by area-level factors than diseases with a long natural history such as atherosclerotic disorders. Also, considering that area-level effects are minimized as individuals move geographically, it is unlikely that population mobility significantly accounted for our findings given the finite time of the gestational period. In the case of preterm birth, a serious complex disease process whose incidence continues to rise, refining our ability to identify at-risk populations in which to target preventative health care strategies has particular appeal.

The datasource used for this study has many advantages such as its large size and population-based nature. It includes a breadth of demographic information regarding the parents, detailed medical and obstetrical characteristics of the mother's antepartum and intrapartum course, as well as specific information regarding the status of the neonate at birth. Despite the extensive data available for analysis regarding each birth, there are some limitations to consider as well. One of the most commonly cited limitations of birth outcome research from vital statistics data is validity of the recorded gestational age. In an effort to minimize the effect of gestational age estimation inaccuracies and potential misclassification bias, we chose our primary outcome as birth prior to 35 weeks of gestation rather than the traditional definition of preterm birth, less than 37 weeks. The data set also had no information which could be used to reliably delineate spontaneous from medically indicated preterm births. Other limitations inherent to the datasource are more difficult to adjust such as the potential for undercoding or underreporting of obstetric and medical risk factors and errors in birth certificate data extraction and entry. A large amount of underreporting of important risk factors, if non-random, could have resulted in an increased effect size estimation of poverty on preterm birth risk due to the inability to adjust for the unreported risks in multivariable analyses. It is unlikely, though, that significant underreporting of the most important obstetric and medical risk factors occurred within the database period we evaluated as the relative prevalence of those included in our analyses are consistent with known rates elsewhere in the US. On the other hand, many social and demographic variables are likely to be accurate, such as race, level of education, receipt of state-funded assistance programs, and county of residence.

Another limitation of the study is the lack of ability to account for other county-level factors which could have possibly influenced the association between poverty and preterm birth risk, such as regional crime rates, adverse environmental exposures, etc. We incorporated as many clinically importanty concomitant factors into our analysis as were available through the data source, but we acknowledge that other unmeasured and unknown potential co-existant risk factors could potentially exist.

In this study we chose counties as the geographic units of analysis. There are several reasons for this approach. US counties are the smallest geographical entity within a state with the social, political and legal responsibility for providing a broad range of social services and health care. Counties may qualify as communities to the extent that individuals and groups within them participate in community development by identifying county-wide problems, collecting health, social and environmental data, and by formulating and implementing specific public policy measures. Counties are also the smallest geographical entity for which health, socioeconomic, and population statistics are consistently available over time. They are stable sociopolitical and geographic entities, but also provide an apppropriate socioeconomic, political, and community context within which many social and public health policies are formulated. From a governmental perspective, using a county-based approach, rather than examining outcomes by zip code or census tracts, allows for organized implementation of healthcare policies and interventions.

In conclusion, county-level poverty was associated with an increased risk of preterm birth. Although the association is modest, even a modest increase in preterm birth risk as demonstrated in this study has the potential to have a robust effect given the large number of women residing in areas with relatively high poverty levels.

Conclusion

Individual-level and area-level poverty have been associated in the past with an increased risk of preterm birth, but prior studies have been limited by design constraints and the inability to thoroughly account for potential confounding risks. We utilized a large population-based birth registry from the state of Missouri to perform a multi-level analysis of the association between poverty and preterm birth while accounting for many potential co-existent risks via optimal methodologic strategies. The findings from our study provide obstetrical care providers and health-care policy makers with important information regarding the prevalence of preterm birth in counties with high poverty and an accurate estimate of the effect of high area-level poverty on preterm birth risk.

Tests for Predicting Complications of Pre-Eclampsia: A Protocol for Systematic Reviews

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Abstract

Background: Pre-eclampsia is associated with several complications. Early prediction of complications and timely management is needed for clinical care of these patients to avert fetal and maternal mortality and morbidity. There is a need to identify best testing strategies in pre eclampsia to identify the women at increased risk of complications. We aim to determine the accuracy of various tests to predict complications of pre-eclampsia by systematic quantitative reviews.

Method: We performed extensive search in MEDLINE (1951–2004), EMBASE (1974–2004) and also will also include manual searches of bibliographies of primary and review articles. An initial search has revealed 19500 citations. Two reviewers will independently select studies and extract data on study characteristics, quality and accuracy. Accuracy data will be used to construct 2 × 2 tables. Data synthesis will involve assessment for heterogeneity and appropriately pooling of results to produce summary Receiver Operating Characteristics (ROC) curve and summary likelihood ratios.

Discussion: This review will generate predictive information and integrate that with therapeutic effectiveness to determine the absolute benefit and harm of available therapy in reducing complications in women with pre-eclampsia.

Background

Hypertension is a common medical complication of pregnancy, affecting about 6–8% of all pregnancies.1 Hypertensive disorders in pregnancy consist of a group of disorders that include pre-eclampsia, latent or chronic essential hypertension, a variety of renal diseases, and transient (gestational) hypertension. The definitions used to distinguish these disorders differ, leading to uncertainty about their prevalence, natural history and response to treatment. Pre eclampsia is associated with several complications[2] and remains one of the largest single cause of maternal and fetal mortality and morbidity.[3,4] They have been reported to account for 14% of direct maternal deaths and 18% of fetal or infant deaths.[3,4]

Once the diagnosis of pre-eclampsia is established, timely management is of the essence to avoid or minimise mortality and morbidity. Clinical prediction of disease complications using a combination of patients' characteristics, symptoms, physical signs and investigations all of which we consider tests, forms the basis of clinical care in these situations.[5] Therefore, there is a need for guidance regarding the best testing strategies with which to predict the development of complications in pre-eclampsia. As well as allowing clinicians to avoid unnecessary interventions in low risk groups, this would allow high-risk groups to benefit from monitoring of disease severity, use of antihypertensive therapy, administration of anticonvulsants, and antenatal corticosteroids.[6,7]

Methods

A systematic quantitative overview of studies of complications of pre-eclampsia will be conducted to obtain summary estimates of accuracy of all available tests. The proposed methodology is in line with the guidance of the NHS Centre for Reviews and Dissemination[8] and that of the Cochrane Methods Working Group on Screening and Diagnostic tests.[9] The investigation will be carried out in the following recommended steps: (i) Question formulation, (ii) Study selection and identification, (iii) Study quality assessment, (iv) Data extraction and (v) Data synthesis.

The tests to be considered by the review are specified in the form of structured questions in Table 1. We have generated a priority list based on importance to clinical practice using a modified Delphi survey.[10] An exhaustive list of the tests and outcomes in the prediction of pre eclampsia were sent to experts in the field. Each one of the issues were rated according to their importance to clinical practice and ranked accordingly. The review will focus on the prioritised tests obtained from the survey.

We have a thorough search protocol by which literature is identified via general bibliographic databases including

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Table 1: Structured questions for systematic review of test accuracy studies

Question Components	Tests for predicting complications of pre eclampsia
Population	Pregnant women with pre eclampsia
Tests	
History	Parity; Race; Maternal age; Previous severe pre eclampsia/Eclampsia; Family history of pre eclampsia/ eclampsia; Obesity; Weight gain; Pre existing hypertension, renal disease, diabetes, lupus, thrombophilia, other auto immune diseases; Multiple pregnancy; Symptoms-headache, epigastric pain, nausea, visual disturbance or combination of symptoms
Examination	Blood pressure; Peripheral oedema; Exaggerated tendon reflexes; Clonus; Papilloedema; Retinal changes; Oliguria; Symphysio fundal height; Oxygen saturation
Investigations	**Biochemical**: Serum uric acid, urine dipstick (Bedside Urinalyses) 24 hour urine protein, urinary calcium excretion, hypoalbuminaemia, microalbuminuria, fibronectin, protinuria, renal and liver function tests; **Ultrasound**: Growth, liquor volume, Doppler (uterine, umbilical artery, Middle cerebral artery, venous, uteroplacental) Bio Physical Profile; **Haematological**: Anti thrombin III, platelet count, haemoglobin, fibrinogen, thrombophilia screen, Maternal serum Alpha feto protein(MSAFP), Serum Human Chorionic Gonadotropin (HCG); Computerised Tomography; Magnetic Resonance Imaging
Outcome	***Maternal*** Eclampsia; Pulmonary oedema; Cerebral Haemorrhage; Hepatic, renal, haematological complications; Cardiac arrest; Abruption; Thromboembolism; stroke; psychiatric problems; Complications of labour and delivery; Maternal death; Need for hospitalisation, Day care unit visits, Use of intensive care, ventilation and dialysis ***Fetal*** Intra uterine growth restriction; Pre maturity; Abnormal p H at birth or antenatal; Abnormal Apgar; Hypoxic Ischemic Encephalopathy; Perinatal death; Long term effect, learning disabilities, Developmental and special needs after discharge; Need for neonatal intensive care admission, mechanical ventilation and duration of hospital stay
Study design	**Systematic review of test accuracy studies**

MEDLINE and EMBASE. Specialist computer databases like DARE (Database Of Abstracts of Reviews of Effectiveness), MEDION (a database of diagnostic test reviews set up by Dutch and Belgian researchers), the Cochrane Library and relevant specialist registers of the Cochrane Collaboration, particularly the Pregnancy and Child Birth group are searched. Individual experts and those with an interest in this field will be contacted to uncover grey literature. SciSearch will be used to identify frequently cited articles. Hand-searching of selected specialist journals and conference proceedings will be done to identify reports of studies for the review. Reference lists of articles obtained by iterative search will be checked as an adjunct to other methods.[11] Language restrictions will not be applied. A comprehensive database of relevant articles will be constructed. The search will be updated every year to enable inclusion of current evidence in the reviews and including other databases like SCOPUS where needed. A search term combination was constructed after exhaustive planning and piloting of possible search concepts capturing the relevant population, tests and outcomes. Our search terms and flow chart of search strategy are shown in Table 2 and in Fig 1. An initial search in Medline yielded 11,711 citations. The search strategy was adapted for searching in Embase to obtain a total of 19,500 citations. From this citation set, studies will be selected for inclusion in the review in a two-stage process.

In the first stage the electronic searches will be scrutinised by two independent reviewers and full manuscripts of all citations that are likely to meet the predefined selection criteria will be obtained. All available reports, irrespective of language will be included to reduce bias.[12] Subsequent final inclusion or exclusion decisions will be made on examination of these manuscripts. In cases of duplicate publication, the most recent and complete versions will be selected. Two reviewers will then independently select the studies, which meet predefined and explicit criteria regarding population, tests, outcomes and study design (Table 1). These criteria will be piloted using a sample of papers and agreement between reviewers will be measured. When disagreements occur, the two reviewers will meet and if necessary the issue will be resolved by consensus involving a third reviewer.

A review of papers meeting the eligibility criteria will be conducted by the same reviewers who judged eligibility, but this time rating the methodological quality of the primary research. Methodological quality is a reflection of the degree to which the study design, conduct and analysis has minimised bias in addressing the research question. This ensures a high level of internal validity (i.e. the degree to which the results of an observation are correct for the patients being studied). The potential sources of bias and variability arising from spectrum composition and other variations in test protocol or the use of reference standard in individual studies will be considered when interpreting the results.[13] In addition to using study quality as possible explanation for differences in results, the extent to which primary research met methodological standards is important per se for assessing the strength of any conclusions that are reached.[8] We will evaluate elements of study design which are likely to have a direct relationship to bias and variability in a test accuracy study.[13-19] The criteria for study validation are shown in Fig 2.

The extraction of study findings will be conducted in duplicate using a pre-designed and piloted data extraction form to avoid any errors. Two authors will independently extract information from each article in order to construct 2×2 tables of the diagnostic test result and outcomes. Any disagreement will be resolved by consensus. Given the extent of insufficient reporting in the medical literature, we propose to obtain missing information from investigators whenever possible. It is otherwise impossible to distinguish between what was done but not reported and what was not done. To avoid introducing bias, unpublished information will be obtained in writing, and will be coded in the same fashion as published information with equal

Table 2: Search term combinations for identification of studies predicting complications of pre eclampsia

Population	Test			Outcome	
	History	Examination	Investigation		Final Refinement
1. pre adj eclampsia 2. preeclampsia 3. hypertens $ 4. pregnan $ 5. pre-eclampsia #.DE. 6. hypertension #.DE. 7. pregnancy #.DE. 8. 3 or 6 (hypertension) 9. 4 OR 7 (pregnancy) 10. 8 and 9 (pregnancy and hypertension)	12. history 13. parity 14. multiparity or nulliparity 15. matern$ near age 16. (previous or prior) near eclampsia 17. (previous or prior) near preeclampsia 18. (previous or prior) near pre adj eclampsia 19. multiple near pregnan$* 20. twin$ or triplet$ or quadruplet$ 21. symptom$ 22. headache 23. epigastric near pain 24. naus$ or vomit$ 25. race 26. diabet$ 27. stress 28. lupus 29. thrombophilia 30. medical-history-taking#.DE. 31. maternal-age#.DE. 32. pregnancy-multiple#.DE. 33. headache#.DE. 34. signs-and-symptoms-digestive#.DE. 35. vision-disorders#.DE. 36. weight gain#.DE. 37. population-groups#.DE. 38. diabetes-mellitus#.DE. 39. stress-psychological#.DE. 40. autoimmune-diseases#.DE. 41. thrombophilia#.DE.	43. blood adj pressure 44. oedema or edema 45. tendon$ near reflex$ 46. hyperreflexia 47. clonus 48. papilledema or papilloedema 49. retina$ near change$ 50. oliguria 51. symphys$ near fundal 52. symphys$ near height 53. cardiotocogra$ 54. oxygen near saturat$ 55. blood-pressure-determination#.DE. 56. edema#.DE. 57. reflex-abnormal#.DE. 58. retinal-diseases#.DE. 59.oliguria#.DE. 60. cardiotocography#.DE. 61.oximetry#.DE.	63. serum near uric adj acid 64. urin near analys $ 65. urin$ 66. maternal near (feto adj protein$ or fetoprotein$ or alphafetoprotein$) 67. urin$ near calcium 68. hypoalbuminemia or hypoalbuminaemia 69. microalbuminuria 70. fibronectin$ 71. proteinuria 72. renal adj function near test$ 73. liver adj function near test$ 74. liquor near volume 75. biophysical near profile 76. ultraso$ 77. antithrombin$ 78. platelet adj count 79. anti adj thrombin$ 80. fibrinogen 81. antiphospholipid $ 82. haemoglobin 83. uric-acid-QN.DE 84. alpha-fetoproteins #.DE 85. calcium-ur. DE 86. hypoalbuminemi a#.DE. 87. fibronectins .DE. 88. proteinuria #.DE. 89. kidney-function-test s#.DE. 90. liver-function-tests #.DE. 91. ultrasonography #.DE. 92. haematologic-test s#.DE. 93. antithrombin-III. DE. 94. fibrinogen #.DE. 95. antibodies-antiphospholipid #.DE. 96. diagnostic-imaging #.DE.	99. complicat$ 100. (renal or kidney$) near (disease$ or complicat$) 101. (hepatic or liver$) near (disease$ or complicat$) 102. death or mortality 103. morbidity 104. eclampsia 105. (pulmonary or lung) near (complicat$ or disease$) 106. thromboembolism 107. pulmonary near (oedema or edema) 108. ventilat$ 109. stroke 110. uter$5 near haemorrhage 111. abruption 112. (heart or cardiac) near arrest$ 113. (psychiatric or mental) near (illness$ or complication$1 or disorder) 114. hospitali$ 115. hypox$ near isch$ 116. (development$ or learning) near (disorder$ or difficult$) 117. pregnancy-complications#.DE. 118. kidney-diseases#.DE. 119. renal-dialysis# 120. liver-diseases#.DE. 121. death# 122. eclampsia# 123. pulmonary-embolism.DE. 124. respiration-artificial# 125. cerebrovascular-disorders#.DE. 126. brain-edema.DE. 127. intracranial-hypertension#.DE. 128. uterine-haemorrhage.DE. 129. abruption-placentae#.DE. 130. heart-diseases# 131. mood-disorders#.DE. 132. hospitalization# 133. infant-newborn-diseases# 134. respiratory-distress-syndrome-newborn.DE. 135. mental-disorders-diagnosed-in-childhood#.DE.	137. 11 and 98 and 136 (Captures *Population* and *Test* and *Outcome*) 138. animal = yes 139. human = yes 140. 138 not 139 141. 137 not 140 142. PT = comment or PT = letter
11. 1 OR 2 OR 5 OR 10 (Captures *Population*)	**42. OR/12–41 (Captures history)**	**62. or/43–61 (Captures examination)** **98. 42 or 62 or 97 (Captures *Test*)**	**97. or/63–96 (Captures investigation)**	**136. or/99–135 (Captures *Outcome*)**	**143. 141 not 142 *Final citation set (animal only studies, comments and letters excluded)***

Key to commands and codes used in Dialog interface:
Adj = words adjacent;; near = words within five words of each other in any order;.DE. = descriptor (MeSH heading);# = Exploded MeSH heading
$ = Truncated to allow for variant word endings; QN = Quick analysis pre-exploded subheading (including analysis, blood, urine, cerebrospinal fluid, isolation and purification PT = Publication Type

regard for inter-coder agreement. In addition to using multiple coders to insure the reproducibility of the overview, sensitivity analyses around important or questionable judgments regarding the inclusion or exclusion of studies, the validity assessments and data extraction will be performed.

We will explore causes of variation in results from study to study (heterogeneity), synthesise results from individual studies (meta-analysis) if appropriate[8,15] and assess for the risk of publication bias. Heterogeneity of results between studies will be graphically assessed looking at the distribution of rates, sensitivities and specificities in the ROC (Receiver Operating Characteristics) curve and likelihood ratios using Forest plots. To explore causes of heterogeneity we will conduct a sensitivity analysis by subgroups to see whether variations in population characteristics, tests, outcomes and study quality affect the estimate accuracy. Conclusions regarding the typical estimate accuracy will be interpreted cautiously if there is significant heterogeneity. Individual factors explaining heterogeneity will also be analysed using meta-regression to determine their unique contribution allowing for other factors. We will conduct meta-analyses to generate summary estimates of likelihood ratios (LRs), diagnostic odds ratios (ratio of LRs) and area under receiver operating characteristic (ROC) curves as appropriate.[15,20,21]

The risk of publication bias is expected to be high in reviews of test accuracy.[22] Analysis for assessing the risk of publication bias will be carried out by producing funnel plots of accuracy estimates against corresponding variances. In the absence of publication bias it is to be expected that the point estimates will fill a funnel shape in the plot. Large gaps in the funnel indicate a group of possible 'missing' publications. These omissions are due to small studies showing limited accuracy and are unlikely to be missing at random. This phenomenon will also be statistically evaluated using Egger's test.[23]

Discussion

In the same way as systematic reviews of effectiveness of treatments in obstetrics have been pursued over the last decade, research on test accuracy also needs systematic reviewing.[14,24] One of the questions remaining after establishing effectiveness evidence for magnesium sulphate, steroids and anti hypertensives is to identify those who will benefit most from these interventions.[25,26] Relying on the inclusion and exclusion criteria of the trials alone is not sufficient for determining who should and shouldn't get these treatments. Women at high risk of complications of pre-eclampsia are likely to benefit most whilst in low risk women, therapy may cause more harm than good. Therefore, what is required is the prediction of risk of complications (such as eclampsia) of pre-eclampsia.

Information on women's risk stratification can be obtained from test accuracy reviews, which provide post test probabilities for a clinical outcome targeted by treatment. Integration of these with evidence for therapeutic effectiveness will enable generating

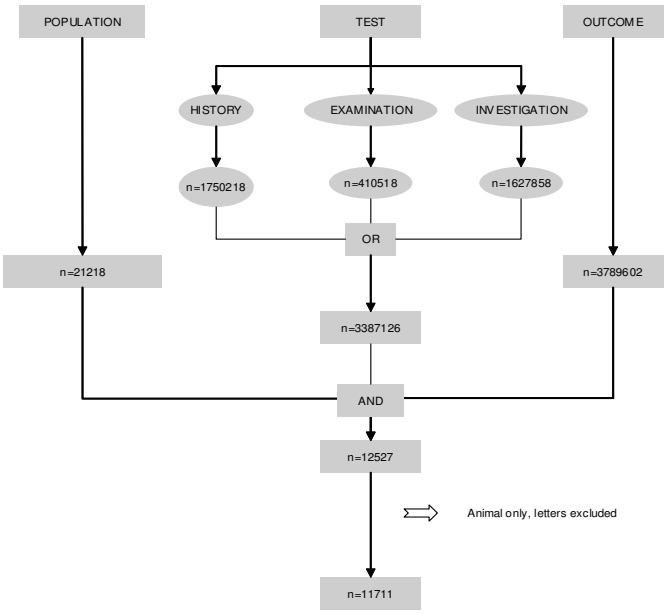

Figure 1. Flow diagram of study selection process in Medline.

estimates of Number Needed to Treat (NNT). The lower the risk, the higher the NNT and the lower are our and women's expectation of benefit from treatment. Conversely, the higher the baseline risk, the lower the NNT, the higher are our expectation of benefit and the more inclined we would be to recommend, and women to accept therapy.[24,27] This will serve to rationalise clinical decision-making.

This project will collate and synthesise the available evidence regarding the value of the tests for predicting complications of pre-eclampsia. The systematic overviews will assess the quality of the available evidence and provide estimates of rate (or risk) of complications of pre-eclampsia given various patient characteristics and other findings. It will identify a set of tests that have maximal predictive value to aid in therapeutic

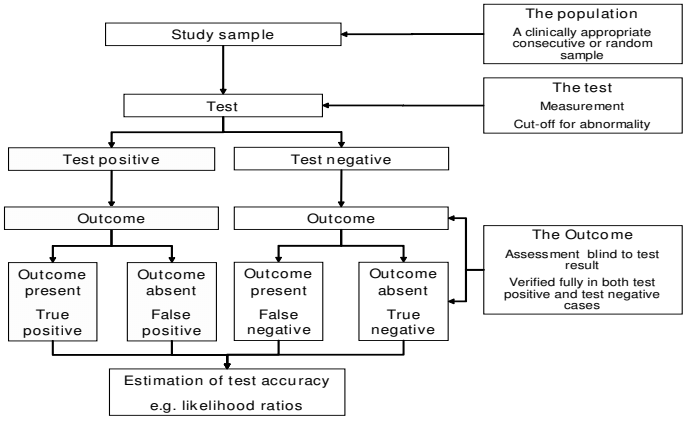

Figure 2. Criteria for quality assessment to be used in the review of tests predicting complications of pre eclampsia. a) Generic quality items · Recruitment of subjects (consecutive or random sample) · Blinding of observers assessing the outcome to the findings of the test · Verification of diagnosis by outcome in all tested cases · 90% or more of enrolled population followed up b) Specific quality items related to features of this project Population Description of spectrum composition Test Adequate description of test and its measurements determining cut-off level for abnormality a priori Outcome Complications of pre-eclampsia

decision-making. An estimate of the magnitude of the benefits will be gauged by integration of the knowledge about risk with evidence of therapeutic effectiveness for various interventions. This will help to formulate practice recommendations and specific recommendations for future research.

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MRC ORACLE Children Study: Long Term Outcomes Following Prescription of Antibiotics To Pregnant Women with Either Spontaneous Preterm Labor or Preterm Rupture of the Membranes

Sara Kenyon, Peter Brocklehurst, David Jones, Neil Marlow, Alison Salt, David Taylor

Abstract

Background: The Medical Research Council (MRC) ORACLE trial evaluated the use of co-amoxiclav 375 mg and/or erythromycin 250 mg in women presenting with preterm rupture of membranes (PROM) ORACLE I or in spontaneous preterm labor (SPL) ORACLE II using a factorial design. The results showed that for women with a singleton baby with PROM the prescription of erythromycin is associated with improvements in short term neonatal outcomes, although co-amoxiclav is associated with prolongation of pregnancy, a significantly higher rate of neonatal necrotising enterocolitis was found in these babies. Prescription of erythromycin is now established practice for women with PROM. For women with SPL antibiotics demonstrated no improvements in short term neonatal outcomes and are not recommended treatment. There is evidence that both these conditions are associated with subclinical infection so perinatal antibiotic administration may reduce the risk of later disabilities, including cerebral palsy, although the risk may be increased through exposure to inflammatory cytokines, so assessment of longer term functional and educational outcomes is appropriate.

Methods: The MRC ORACLE Children's Study will follow up UK children at age 7 years born to 4809 women with PROM and the 4266 women with SPL enrolled in the earlier ORACLE trials. We will use a parental questionnaire including validated tools to assess disability and behavior. We will collect the frequency of specific medical conditions: cerebral palsy, epilepsy, respiratory illness including asthma, diabetes, admission to hospital in last year and other diseases, as reported by parents.

National standard test results will be collected to assess educational attainment at Key Stage 1 for children in England.

Discussion: This study is designed to investigate whether or not peripartum antibiotics improve health and disability for children at 7 years of age.

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Background/Rationale

The sequaelae of preterm birth pose a significant public health problem. Children born before 37 weeks gestational age are at increasing risk of major disabilities, such as cerebral palsy, with decreasing gestation.[1] Furthermore, of the preterm children without disability, many will have important behavioral and educational difficulties. The ORACLE Children Study presents a unique opportunity to determine if a simple, inexpensive intervention reduces the long term sequaelae of preterm birth with benefit for individuals and their families.

The ORACLE trial evaluated the prescription of Co-amoxiclav 375 mg and/or erythromycin 250 mg to women either with PROM[2] or in SPL.[3] The trial reported that erythromycin did improve the composite primary outcome (death or major cerebral abnormality on ultrasound prior to discharge or chronic lung disease defined as needing oxygen therapy at 36/40 post conceptual age) in singleton babies born to women after PROM. The prescription of Erythromycin was also associated with improvement in other significant outcomes such as prolongation of pregnancy, reduction in the need for neonatal ventilation, oxygenation and treatment with surfactant, a decrease in oxygen dependence at 28 days of age or older, and fewer positive neonatal blood cultures. Although Co-amoxiclav was associated with prolongation of pregnancy, a significantly higher incidence of neonatal necrotising enterocolitis was found in these babies. In the group of women with SPL the use of neither Co-amoxiclav nor erythromycin were associated with any improvement in neonatal morbidity or mortality.

Following the ORACLE trial antibiotic treatment for preterm, prelabor rupture of the membranes (PROM) may become standard practice and so there will never be another opportunity to undertake this study and provide unbiased and reliable evidence on this subject.

There is increasing evidence that, in addition to preterm birth, perinatal infection is an independent antecedent of other disability, particularly cerebral palsy and chronic lung disease.

Table 1: For each sub-group (PROM or SPL), a response from 3700 babies will allow the following differences to be detected with 80% power:

Outcome	Incidence in erythromycin group	Incidence in erythromycin placebo group	Relative risk reduction
'3 or more attributes affected'	**3.1%**	**5%**	**38%**
	5.6%	8%	30%
	1.5%	3%	50%

Therefore, perinatal administration of antibiotics could prevent neurological and respiratory disability by two mechanisms, either by prolonging pregnancy and/or by eliminating infection. In contrast however, it is possible that prolongation of pregnancy may increase rather than decrease the risk of disability by continuing fetal exposure to inflammatory cytokines, which have also been implicated in the genesis of neurological damage4 and chronic lung disease.[5] Some clinical evidence to support this possibility comes from two observational studies of neurodevelopmental outcome in preterm infants born after PROM which showed a higher risk of cerebral palsy or neurological impairment compared with gestation matched controls.[6,7] In addition, duration of membrane rupture had a direct relationship with the risk of neurological impairment.[7]

The cerebral and respiratory benefits reported with erythromycin in women with PROM in the ORACLE trial may have been secondary to (a) prolongation of pregnancy and (b) a reduction of the effects of fetal and neonatal lung infection or inflammation. Supportive evidence for the latter comes from broncho-alveolar lavage fluid studies. Studies of the constituents of broncho alveolar lavage fluid have shown that infants who develop chronic lung disease have higher concentrations of neutrophils,[8] proinflammatory cytokines[9,10] and proxy markers of neutrophil recruitment, than those who recover from respiratory distress syndrome.[9,11] There is also evidence that intrauterine lung inflammation is implicated in the genesis of chronic lung disease, since high concentrations of the potent profibrotic agent, transforming growth factor, have been described in the first broncho-alveolar lavage fluid after birth of infants who go on to develop chronic lung disease.[5,12] The MRC ORACLE Children Study provides a unique opportunity to determine whether the reductions in chronic lung disease found at discharge from hospital in the erythromycin group are reflected in a decreased incidence of respiratory disease and the need for therapy at 7 years of age.

Follow-up of the infants of women who presented with SPL is important, even in the absence of an apparent effect of antibiotics from ORACLE II[3] on short term morbidity. Many clinicians and researchers are convinced from observational evidence that a substantial proportion of SPL is caused by sub-clinical infection.[13] If this evidence is indeed correct then differences in childhood neurodevelopment and respiratory function could be detected between children born to women randomised to antibiotics compared with those randomised to placebo even though crude measures of early neurological damage or respiratory disease were no different between the groups during the perinatal period.

Methods/Design

ORACLE was a double blind randomised controlled factorial design trial which evaluated whether giving broad spectrum antibiotics to women in SPL or with PROM improved neonatal mortality and morbidity.

Women were randomized to receive antibiotics and matching placebos 4 times daily for 10 days or until delivery, whichever was sooner. ORACLE tested Co-amoxiclav 375 mg and erythromycin 250 mg singularly and in combination.

This phase of the study—the MRC ORACLE Children Study—will follow up children of women randomised to ORACLE at 7 years of age to determine whether antibiotics have effects on their development, educational attainment, and the risk of conditions such as cerebral palsy and respiratory illness. The MRC ORACLE Children Study will include the 8942 children born to those women randomized in the UK.

The primary outcome is: 1) the overall level of disability (severe, moderate, mild, none) derived from the Multi-Attribute Health Status (MAHS) classification system.

The secondary outcomes are: 1) number of children with 3 or more abnormal attributes derived from the MAHS classification system; 2) degree of function (severe, moderate, mild, none) within the 9 domains of vision, hearing, speech, ambulation, dexterity, emotions, cognition, pain and self care; 3) behavior (Goodman's strengths and difficulties questionnaire); 4) educational achievement in reading, mathematics and writing at Key Stage 1. Data on both levels and raw scores will be collected; 5) incidence of specific medical conditions—cerebral palsy, epilepsy, respiratory illness including asthma, diabetes, admission to hospital in last year, other diseases, death—from trial entry to aged 7 years and from initial discharge from hospital to aged 7 years; covariates—family demographic information (housing status, ethnic group, smoking practice) will be collected.

Inclusions are: surviving children of mothers recruited to the ORACLE trial; child resident in UK. Exclusions are: recruited outside UK, adopted or fostered children and children who have emigrated. Children who have been adopted or fostered will not be followed-up to avoid potential distress to parents and child. Children born in Scotland, Northern Ireland or Wales have different National Tests to England and therefore will not have data collected to assess educational achievement.

Postal parent-report questionnaire

A parental questionnaire will be administered to determine the level of disability (severe, moderate, mild, none). This is based on the Multi-Attribute Health Status (MAHS) Mark II and III[14] classification system developed and widely tested by the Departments of Paediatrics and Clinical Epidemiology and Biostatistics of McMaster University, Canada. The additional domain of behaviour is being assessed using the strengths and difficulties questionnaire developed and validated by Robert Goodman.[15] Additional questions will assess the other health related outcomes. Deaths will be categorized hierarchically using the system below developed by PMG and with the advice of Steve Gould, Consultant Pathologist, John Radcliffe Hospital, Oxford.

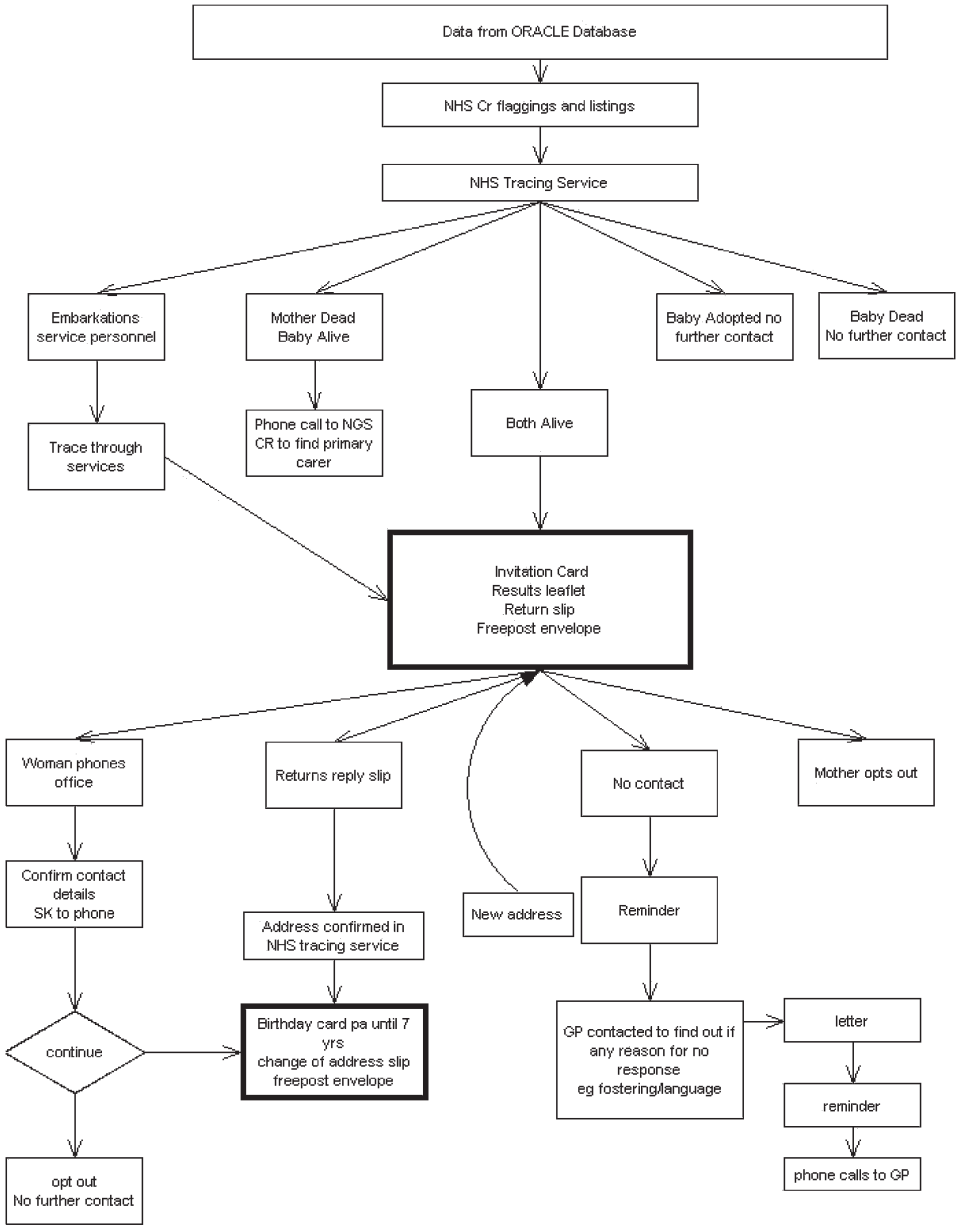

Figure 1. Tracing and contact mechanisms.

Death categorizations

1. Congenital abnormality
2. Cancer/Neoplasia
3. Complications of Prematurity

3a. Chronic lung disease
3b. CLD and CNS
3c. Central Nervous System related to prematurity

4. Central Nervous System
5. Infection
6. Miscellaneous
7. Sudden Unexpected Death in Infancy (SUDIs, SIDS and Unascertained)

National Tests

In England we will employ a unique and innovative approach of using the standard National Tests (Key Stage 1) to assess the children's educational ability supported by the Qualifications and Curriculum Authority (QCA). DFES will provide anonymized data for test level achieved and ethnicity of all children in each treatment group. For those children for whom parental consent is obtained level data will be obtained from the Local Education Authority (LEA) and the scores for each question will be collected from individual schools. Children in Northern Ireland and Wales have different National Tests and no such tests are conducted in Scotland therefore these children will not have data collected to assess educational achievement.

Estimated power of study

A total of 8,942 babies survived until the end of data collection in England, Scotland, Wales and Northern Ireland. Of these, 4521 were in the SPL group and 4421 were in the PROM group. Not all of these babies will have survived until age 7 years; assuming an 85% response rate to a parental questionnaire, 3843 responses can be expected from the SPL group and 3758 from the PROM group (7601 in total).

Table 1 demonstrates the differences detectable between any two intervention groups for the listed primary measure (eg erythromycin vs erythromycin-placebo) in each of the specified sub-groups (SPL and PROM). The estimates of prevalence of disability are based on data derived using the same instrument (MAHS Mark II)[14] on extremely low birth weight (ELBW) babies compared with a reference group of normal birth weight babies. As the majority of ELBW babies are born less than 28 weeks gestation they will have a higher prevalence of disability than the children included in the MRC ORACLE Children Study. For the measure of '3 or more attributes' affected, an incidence of 28% occurred in the ELBW group compared with 2% in the reference group. As the gestational age of the ORACLE population of children is between these extremes a conservative disability estimate of 5% has been taken as the principal estimate and sensitivity to variation of this value of the power of the study to detect differences is explored in the table. By ranking children into groups by their degree of disability (the number of attributes affected) the power of the study to demonstrate smaller differences will be increased by using tests for trends.

Analyses plan

The primary analysis will comprise comparison of MAHS disability prevalence by allocated treatment group, through fitting of logistic models including terms indicating allocation to Co-amoxiclav/not and to Erythromycin/not, together with an interaction term. Both HUI2 and HUI3 data will be collected and analysed as they have been designed to complement one another but are based on the same conceptual framework. HUI2 refers to worry and anxiety, HUI3 to happiness versus depression. Similarly while both refer to the degree of severity

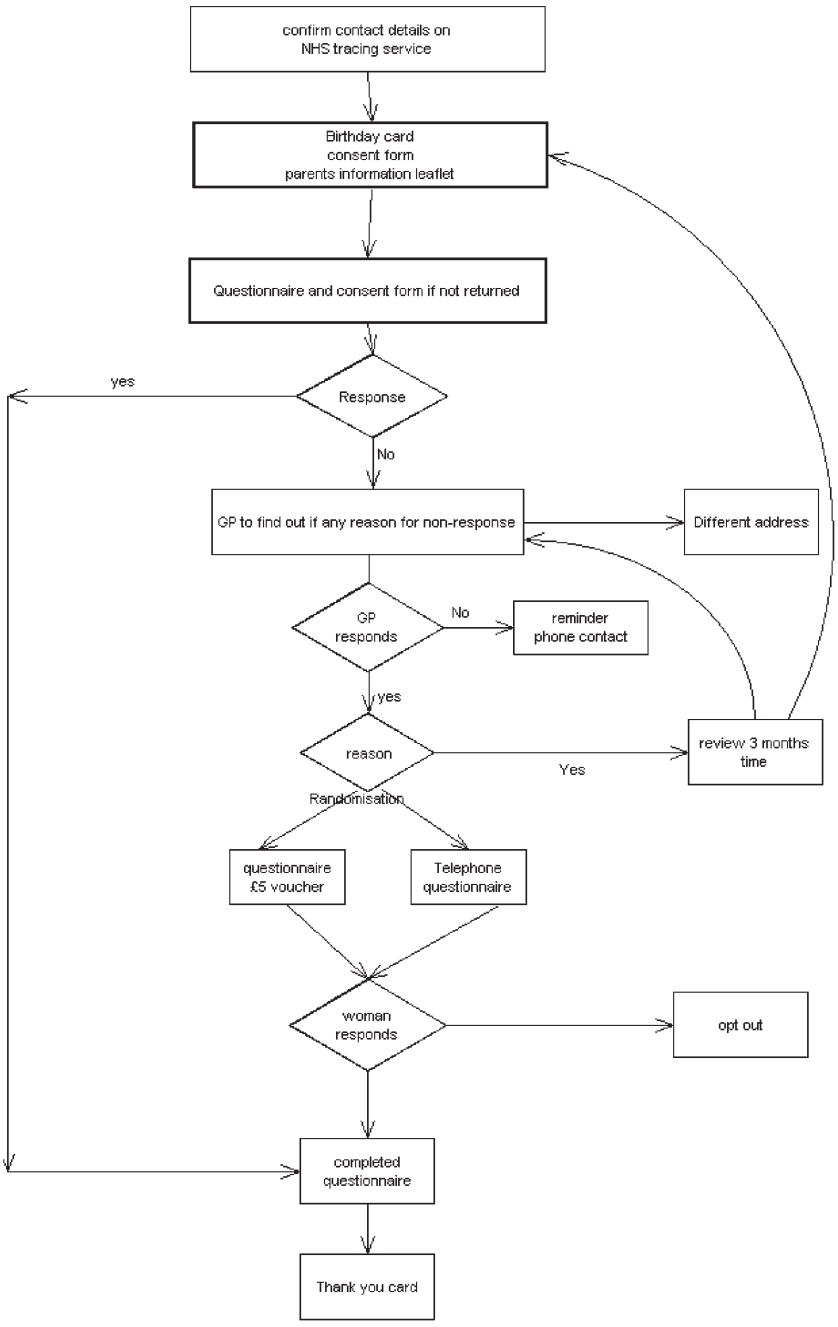

Figure 2. Child in 7th year.

of pain, HUI2 focuses on the use of analgesia while HUI3 focuses on the disruption of activities. Self-care is only available in HUI2 and dexterity only in HUI3. Sensitivity analyses will include i) logistic modeling of the MAHS level of disability, ii) corresponding models for risk differences, iii) alternative approaches to analyzing outcomes from multiple births, and iv) models adjusted for demographic covariates if their balance deteriorates during further follow up, and for other covariates including length of gestation, and year of KS1 assessment and original ORACLE outcomes.

Analyses of secondary outcomes will follow the approach for the primary outcome, appropriately modified where necessary to accommodate continuous or survival measures. Details of the analysis of KS1 data are to be developed in collaboration with colleagues in the agency responsible for collection and interpretation of these data. Explicit allowance for multiplicity of comparisons will be made in interpretation of the results.

Planned subgroup analyses

Comparisons of primary and secondary outcomes will be undertaken for the infants of women with: (1) SPL—intact membranes; (2) PROM; (3) multiple & singleton pregnancies; (4) >32 week gestation and < 32 week gestation; (5) > < 28 weeks gestation.

Data collection

The women were aware of the possibility of a Follow-Up Study when they were recruited to ORACLE. We will trace both mother and child through the Office of National Statistics (ONS) and will be informed of the mother or child's death since discharge from hospital to date. We will then send an invitation letter to the address obtained for the woman using the NHS Tracing Service (NSTS). If no response is obtained the child's GP will be contacted to check contact details and ascertain if there is a reason eg child is currently in care or non-English speaker etc. Translations of all study materials will be available should they be required and an inexpensive pen will be included with the invitation and information leaflets.

Once we have established contact with the woman and child we will make every effort to maintain this by the use of birthday cards and newsletters (to maintain regular contact) and change of address cards (to facilitate tracking of address changes). We will receive listings from ONS quarterly throughout the study so we are aware of embarkations and deaths are notified immediately. We may consider giving maternity units and GP's surgeries posters and information leaflets so women can contact us directly. We confirm current address using NSTS prior to contact when the child is 7 years old. The Information Leaflet is sent to the parents, and two weeks later a questionnaire. Should no response be obtained this is followed by two letters, a fortnight apart, to the GP to ascertain whether we have the correct address and contact information. Following this confirmation a reminder letter is sent to the parent's/carers the week of the child's 7th birthday including a ~5 voucher which is sent recorded delivery. Should no response be forthcoming the last reminder is done 3 weeks after that and involves either letter or telephone contact, where a phone number is available.

A consent form for educational outcomes (KS1) is sent to parents in England only. KS1 data is to be collected from either schools or Local Education Authority (LEA).

A thank you card will be sent to parents once the questionnaire has been completed and it is planned to send the results of the follow-up to parents, should they request them, in 2008.

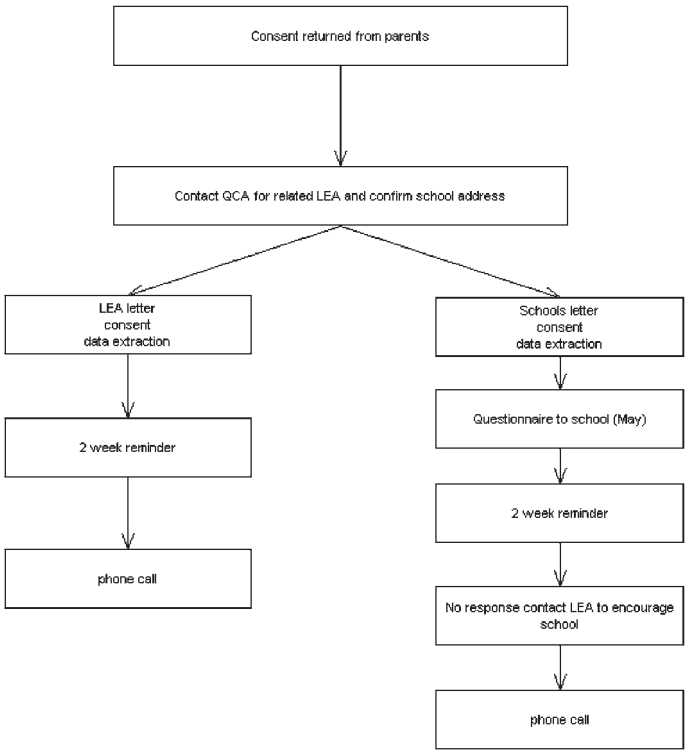

Figure 3. KSI data extraction.

Safety

This study is not actively treating women—it is the follow up of the children. However, clinical care is different for the two groups. It is recommended that women with preterm rupture of the membranes receive erythromycin and women with spontaneous preterm labor are not prescribed antibiotic therapy.

A Data Monitoring Committee (DMC) has been established and will meet annually to consider interim analyses. The Committee will determine if additional interim analyses of trial data should be undertaken. It will consider the data from interim analyses, unblinded if considered appropriate, plus any additional safety issues and relevant information from other sources. In the light of this, and ensuring that ethical considerations are of prime importance, to report (following each DMEC meeting) to the Trial Steering Committee (TSC) and to recommend on the continuation of the study. The DMC will consider any requests for release of interim trial data and to recommend to the TSC on the availability of this and in the event of further funding being required, to provide to the TSC and MRC appropriate information and advice on the data gathered to date that will not jeopardise the integrity of the study.

The DMC membership is Professor Diane Elbourne, Chair, Professor of Health Care Evaluation, London School of Hygiene and Tropical Medicine; Ms Helena McNally, ECMO Trial, NPEU; Professor Martin Whittle, Clinical Co-Director, National Collaborating Centre for Women and Children's Health, London.

Discussion

The ORACLE Children Study will provide important information about the health, development and educational attainment of children at 7 years of age whose mothers were exposed to peripartum antibiotics. This information will be important to both parents and clinicians when faced with either preterm ruptured membranes or threatened spontaneous preterm labor.

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Endnote

No Capital Budget? A Primer on Leasing.

John Campbell

To those reading this who may be intimidated by various financing options, welcome to the club. Very few people understand all the intricacies of equipment financing. Hopefully, the information to follow will help you understand how knowing even the most basic aspects of financial options can help you get what you need.

What is leasing?

Leasing is not rocket science. There are really just a few terms and ideas that you need to know to make this work for you. For starters, let's take the term "leasing" out of the equation and use the term "anything but a cash deal." How many times have you wanted or needed new equipment but were faced with no available capital dollars? You probably just wrote it down on your To Do list as something to follow up on for the next budget. After reading this, it should be clear that "no cash" should never mean "no new equipment" for you.

By the way, all hospitals use borrowed money of one sort or another. Your hospital may claim that you don't lease, but you rent. Or you don't rent, but you do lease. All you need to understand is that in one way or another, all hospitals use borrowed money.

How does a lease work?

You decide you want more equipment but you have no cash. Very simply, a hospital can go to the bank and borrow enough to buy that equipment and make payments each month. [Or maybe, these days, you can't go to the bank—Ed] In a lease, a hospital goes to a leasing company which buys the equipment from the manufacturer and the hospital makes payments to the leasing company instead of the bank.

So why doesn't a hospital just borrow the money and buy versus using the leasing company? Good question!

Why would/should a hospital lease equipment?

Equipment Management. No technology obsolescence or life expectancy problem and nothing to dispose of at the end of the term. At the end of the contract you can either give the equipment back to the leasing company or continue to rent. This eliminates the burden and risk of outdated equipment in the hospital inventory.

Reasons for leasing:

- Operating leases and rentals are paid out of the hospitals operating budget and thus do not show up on balance sheets. This means it doesn't become a liability to the hospital's overall financial status.
- Locks in a price and an interest rate right now, not when the budget comes in.
- No need to use cash or lines of credit to finance deals. This helps preserve the hospital's working capital.
- Convenience. Less paperwork than for loans. One of the misconceptions about leasing is a perceived complexity of paperwork.
- Tax considerations are often applicable. Depreciation vs operating costs.
- Leasing usually costs less per month than paying cash or acquiring debt.
- Lower monthly payments than for a loan. Like an auto lease, you get more equipment for the same monthly payment.

What are some terms I need to know?

Capital Budget – This is what the hospital uses to pay for new construction, remodeling, beds, ventilators, or any "hard" asset.

Operating Budget – This is what is used to pay for wages, utilities and any disposable products like IV fluids or light bulbs.

By the way, these budgets are in separate accounts and cannot be moved from one to the other. If the capital budget is used up, you can't take money from the operating budget to buy your equipment.

What are the different types of leases that I need to know about?

Capital Lease – Other names used might be Rent-to-Own or Dollar Buy-Out. This is like buying a house. The hospital pays a number of monthly payments with each payment going toward the eventual payoff of the equipment. Funding comes out of the capital budget.

Operating Lease – This is like leasing a car. The hospital only pays for the use of the equipment for a set period of time, like a rental. At the end of the term you have a return, purchase or extension option. The return option paves the way for a new lease on brand new equipment. Funding for an operating lease comes out of the operating budget.

Rental Rewards – If your hospital is renting to fill basic long-term equipment needs, this gives you an opportunity to acquire brand new equipment. Through each payment made, you earn credits and ultimately would own the equipment if you continue renting. Funding comes from the operating budget.

OK, this is an oversimplification but it will get you started. There are many options and variations for the lease, depending on how it is set up. Suffice it to say, you probably will not be interested any further than the three choices above.

How do I use leasing with my equipment supplier?

Find out if they have a leasing program within their company. Just about every company that sells capital equipment over $5,000 has a relationship with a source to help you through this and they will then put you in touch with these people. Some leasing companies can usually have the paperwork done in hours and the form is short, as few as two pages. There is no obligation to do the lease. After all is laid out for you, all they would need from you would be a P.O. stating the terms. Simple and fast.

Remember, leasing is just another tool for you to get what you want and need now rather than later. For additional information, visit MedOne Capital.

John Campbell is with MedOne Capital. This article was provided by Hamilton Medical, from its newsletter.

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- ICD-9 00.12 may trigger contractual payment mechanisms

[a] HCPCS, Healthcare Common Procedure Coding System.
[b] CPT, current procedural terminology.

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