Vol. 22 No. 5
September 2009

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The Journal of Perinatology-Neonatology

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Vol. 22 No. 5
September 2009

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Editorial

Trials and Tribulations

A recent article in BioMed Central discussed parental attitudes toward enrolling children in randomized trials. I thought you might be interested in the discussion. Here are the highlights from the article pertaining specifically to neonatology.

For parents the diagnosis of serious illness in a child can be a shattering experience. When consent is sought soon after diagnosis, parents will be making decisions when they are distressed and vulnerable. Being approached about a trial confronts parents with a volume and complexity of information well beyond their everyday experience and they can never be certain about what is the "right" decision. However, while they may be vulnerable, protecting their child is fundamental to the parental role and this will shape how they think about trials. Parents who participated in a survey investigating different types of consent to hypothetical neonatal resuscitation trials were more comfortable with prospective consent than with consent which was deferred, waived or required the parent to "opt-out." They wanted to be informed about the trial and make the decision themselves. Other surveys provide further evidence that parents value their role in decisions about trial entry—over 90% say they do not want the doctor or nurse to decide on their behalf. Parents upheld these views even when they realized that the quality of their consent was limited or experienced the informed consent process as an additional burden, indicating that consent could indeed serve important symbolic functions.

In one neonatal study three-quarters of parents believed their doctors would not ask to do research if it might put babies in real danger and half indicated that they trusted their doctor, and if he or she suggested their baby should enter a trial, they would agree. Though they have authority for their child, parents lack expertise in matters related to the child's illness, and as a consequence, are likely to rely heavily upon the expertise of medical practitioners.

Parents considering neonatal trials report particularly high levels of distress during trial discussions and a sense that this impairs their ability to ask questions or seek additional information, occasionally leading them to later doubt their decisions. Some parents will see trials as a threat to their child or fear regretting their decision, while others see trials as offering hope of better treatments for their child. Almost all parents cherish their role in protecting children and want to secure the best outcome for them, but many are aware of complexities of the medical and research context and how this constrains their fulfillment of this role.

Interactions at the time of trial recruitment offer scope for negotiating these complexities if practitioners have the flexibility to tailor discussions to the needs and situation of individual parents. In this way, parents may be helped to retain a sense that they have acted as good parents to their child whatever decision they make.

Les Plesko

From the article, How do parents experience being asked to enter a child in a randomised controlled trial? by Valerie Shilling and Bridget Young, Division of Clinical Psychology, School of Population, Community and Behavioural Sciences, University of Liverpool, UK, BMC Medical Ethics 2009,

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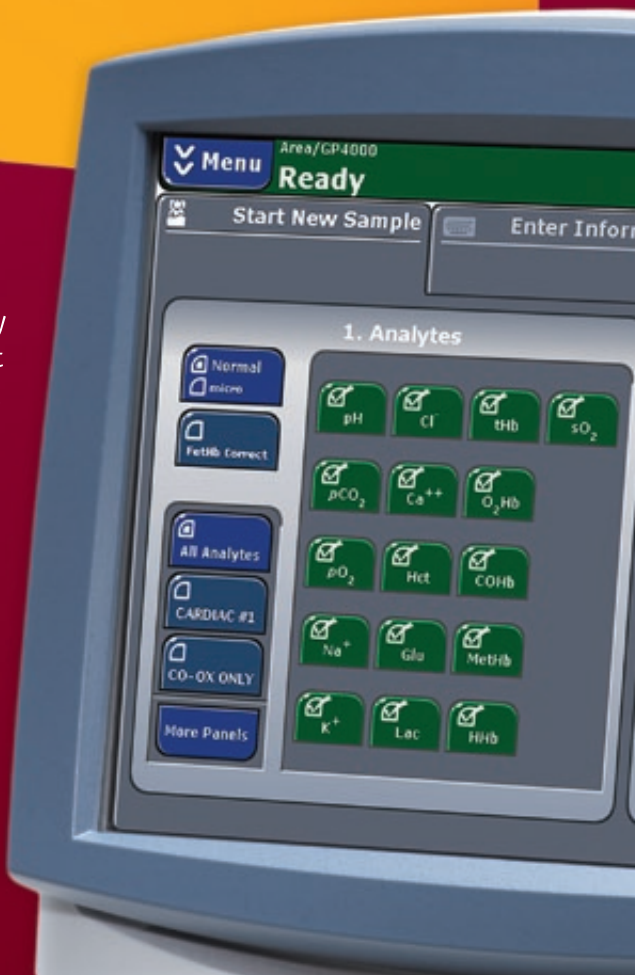

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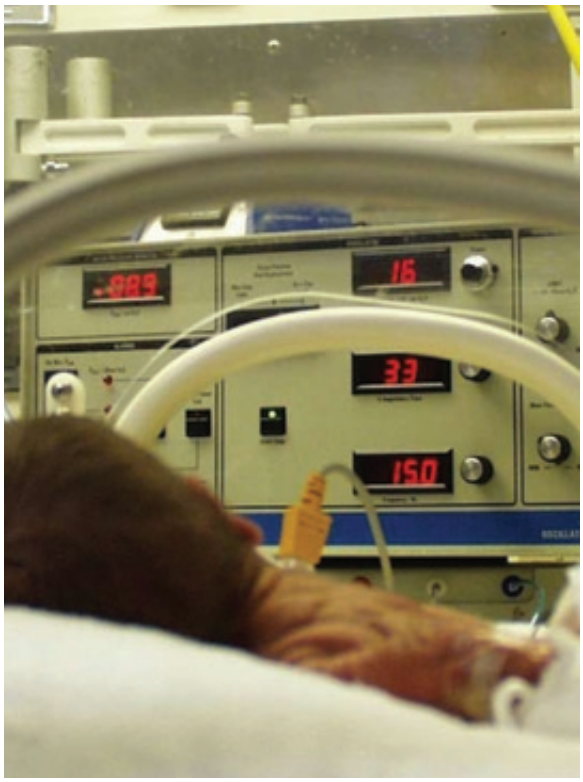

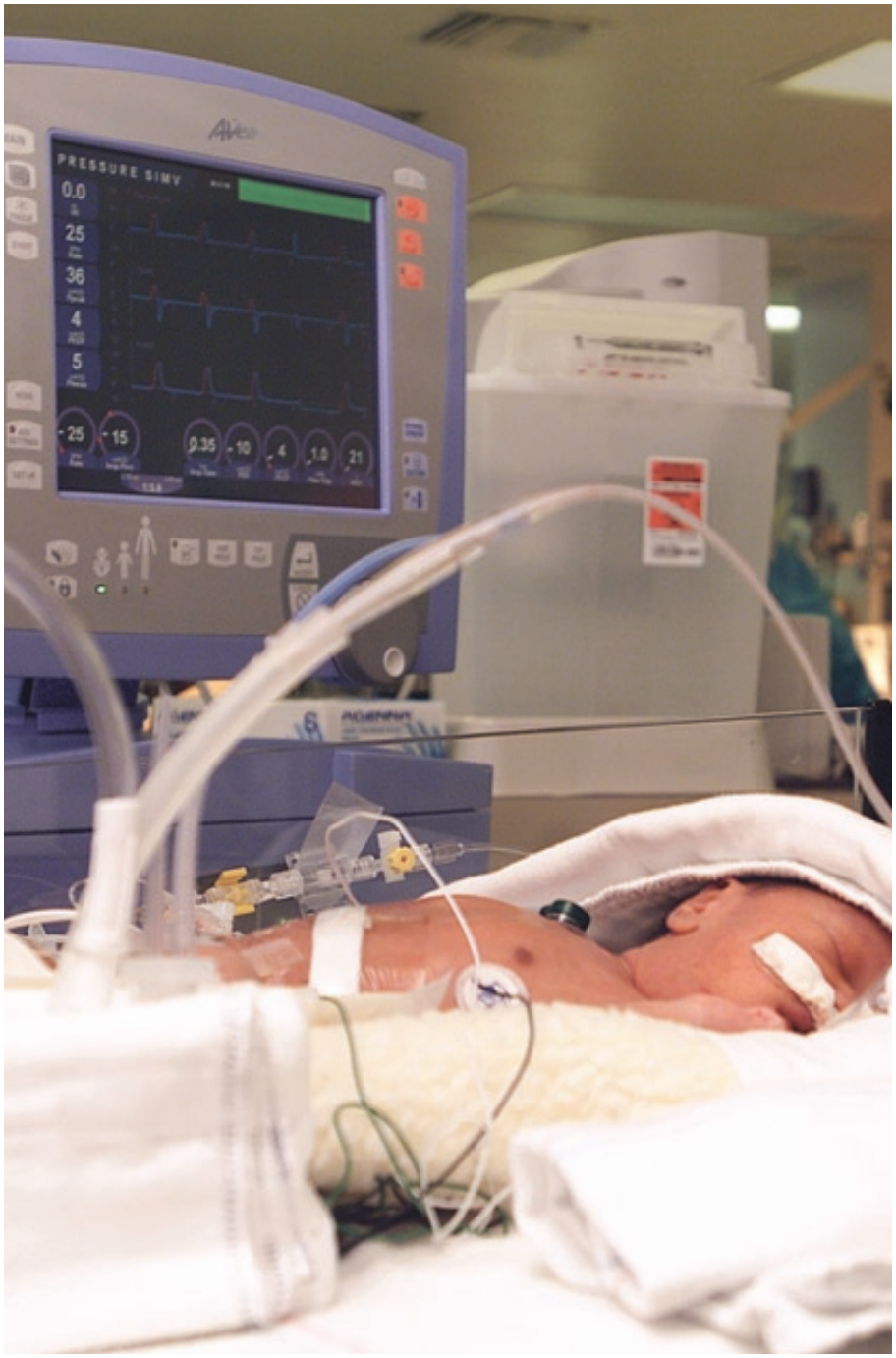

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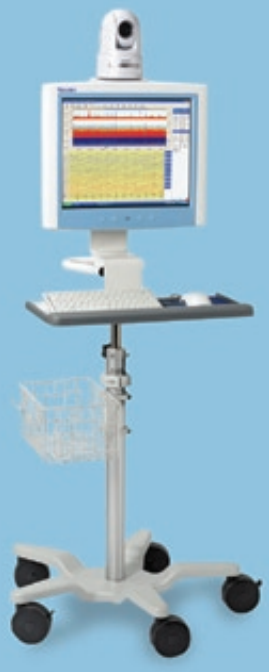

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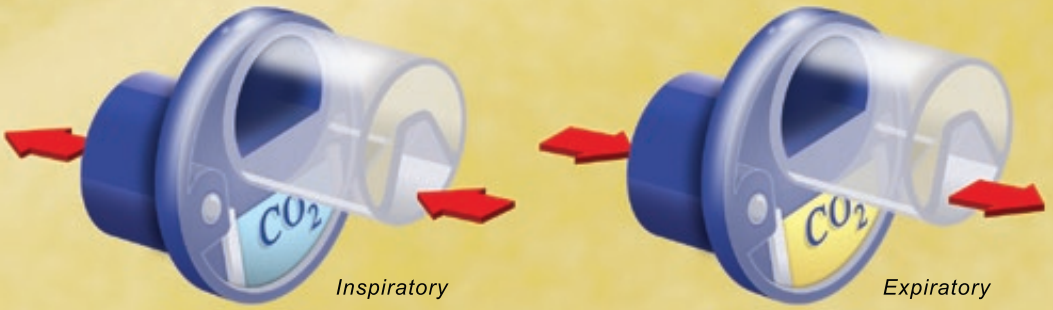

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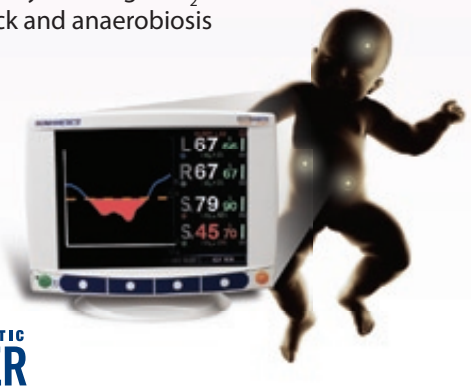

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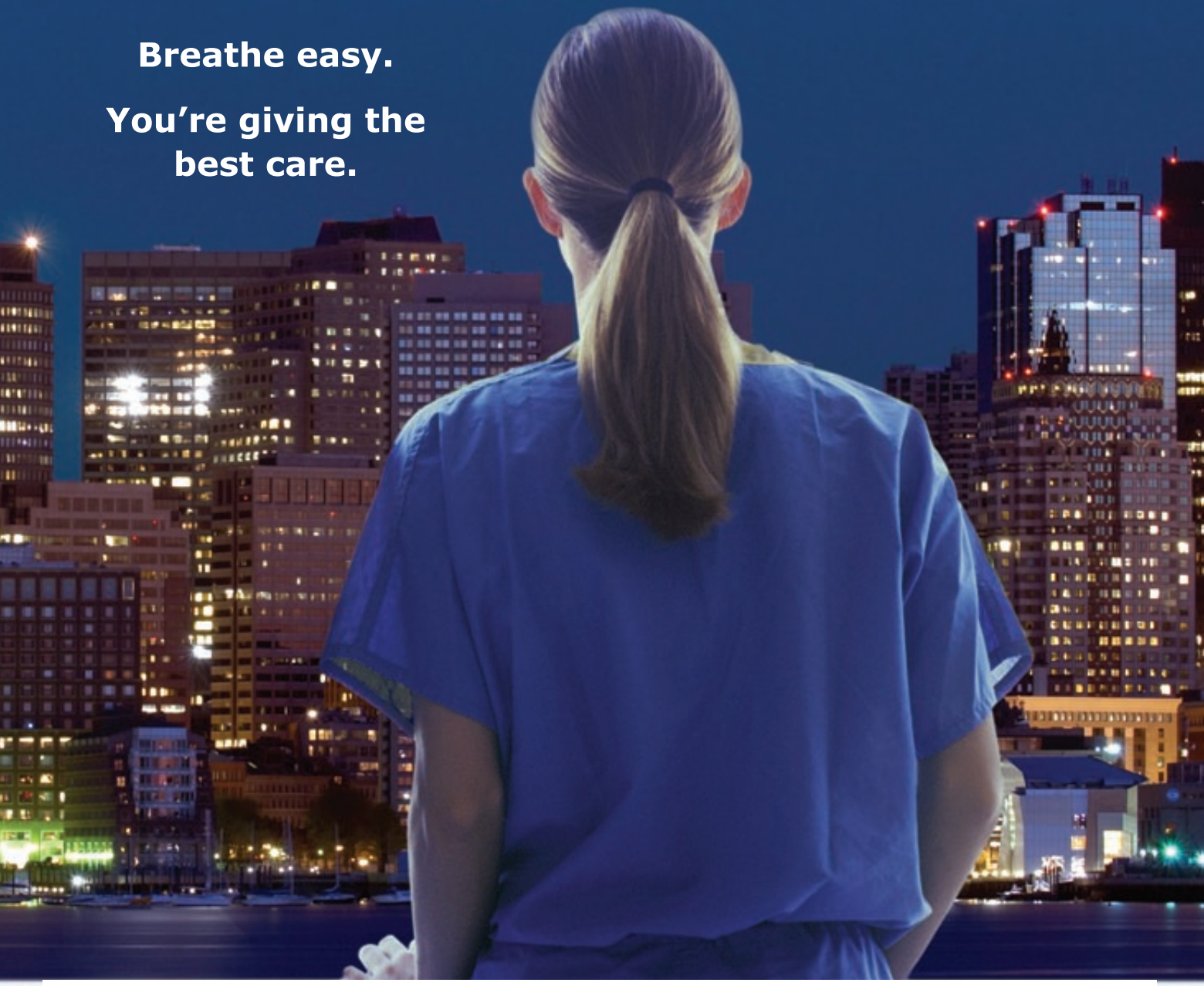

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News

☐ September 2009

NEW STUDIES

FORE-SIGHT's accuracy and proven performance helps clinicians make decisions that protect the brain and improve outcomes. New research includes: **Simultaneous Comparison of FORE-SIGHT and INVOS Cerebral Oximeters to Jugular Bulb and Arterial Co-Oximetry Measurements in Healthy Volunteers,** MacLeod D; Ikeda K; Vacchiano C, Duke University School of Nursing, Durham, NC. Conclusion: The results demonstrate that the FORE-SIGHT cerebral oximeter monitor has greater precision with respect to measuring absolute cerebral tissue oxygen saturation than the INVOS cerebral oximeter monitor… **Decreased Forebrain Cerebral Tissue Oxygen Saturation is Associated with Cognitive Decline after Cardiac Surgery,** MacLeod D; White W; Ikeda K; Newman M; Mathew J, Duke University Medical Center, Durham, NC. Conclusion: Decreases in intraoperative $SctO_2$ are associated with POCD. Declines in $SctO_2$ below several thresholds were significantly associated with 6-week decline in the Domain 2, 3, & 4 average in unadjusted Spearman correlations. After adjustment for baseline variables $SctO_2$ minutes <60% remained significantly associated with this cognitive decline (p=.040, R-Squared=.09). Verbal memory (Domain 1), measured by the Randt test, was not associated with decreased $SctO_2$… **Decreased Cerebral Tissue Oxygen Saturation during Aortic Surgery Increases Risk of Post-Operative Complications,** Fischer G; Lin H; DiLuozzo G; Griepp R; Reich D, Departments of Anesthesiology and Cardiothoracic Surgery, Mount Sinai Medical Center, New York, NY… **Continuous Monitoring of Cerebral Blood Flow Autoregulation During Cardiac Surgery in Adults with Near Infra-Red Spectroscopy: Preliminary Results,** Johsi B; Brady K; Stearns J; Hogue C, The Johns Hopkins Hospital, Baltimore, MD. Conclusion: These data suggests that NIRS based COx monitoring provides an accurate detection of the lower CBF autoregulatory threshold in patients undergoing cardiac surgery. This promising non-invasive monitoring method might provide a means for individualizing MAP during surgery potentially reducing the frequency of brain injury due to cerebral hypoperfusion. Results: Despite the low number of subjects enrolled in this study, decreased $SctO_2$ values and prolonged DHCA times were found to be associated with major complications, prolonged extubation times, and ICU/Hospital LOS. This study suggests that prolonged intraoperative periods of time with $SctO_2$<60% correlate significantly with an increased risk of having major complications and an increased LOS. You can find the above studies at scahq.org/sca3/events/2009/annual/show_abstract.iphtml?id+6, 53, 62 and 5.

LETTER TO THE EDITOR

As the Associate Director of Marketing for Respiratory Care Systems at Draeger Medical, Inc, I am writing to clarify a statement made in the recent article "Ventilator Care Takes 2 Safety Hits" regarding the principle of operation regarding SmartCare/PS [July-August 2009].

In Mr Garbarini's article, he states that "SmartCare follows a set of rules to wean pressure support during a wean trial. So if the tidal volume is too small, pressure support will titrate up to prevent tachypnea."

This statement requires clarification to your readers. SmartCare/PS is an automated weaning feature in the Evita XL ventilator that controls the ventilator settings to maintain a spontaneously breathing patient in a "comfortable zone" and reduce the inspiratory support until the patient is ready for extubation. All of the Evita XL alarms remain in place and continuously monitor for any changes in the patient's condition.

Physiologic monitors of tidal volume, respiratory rate, and end-tidal CO_2 are all considered when SmartCare determines the patient's response fits one of eight diagnoses—Normal Ventilation, Hyperventilation, Tachypnea, Severe Tachypnea, Insufficient Ventilation, Hypoventilation, Central Hypoventilation, and Unexplained Hyperventilation. According to these diagnoses, SmartCare will continue to initiate adjustments in pressure support as the patient requires.

SmartCare/PS will take three actions before declaring the patient ready for separation from the ventilator – that being adaptation, observation, and maintenance. Once the patient is considered ready to be extubated, the ventilator gives an indication to the clinician "consider separation."

Thank you for the opportunity to briefly clarify the SmartCare/PS option by Dräger. If readers have any further questions, they may contact me directly at edwin.coombs@draeger.com.

Edwin Coombs, MA, RRT, Associate Director of Marketing, Respiratory Care Systems, Draeger Medical.

BE AFRAID

A New York Times, June 28th editorial warns about genetic mutations affecting fetal development and causing sexual changes. The Times' Nicholas Kristof, in the piece titled, It's Time to Learn From Frogs, writes: Some of the first eerie signs of a potential health catastrophe came as bizarre deformities in water animals, often in their sexual organs. Frogs, salamanders and other amphibians began to sprout extra legs. In heavily polluted Lake Apoka, FL, male alligators developed stunted genitals. In the Potomac watershed near Washington, male smallmouth bass have rapidly transformed into "intersex fish" that display female characteristics. More than 80% of the male smallmouth bass in the Potomac are producing eggs. Now scientists are connecting the dots with evidence in humans, for example, large increases in numbers of genital deformities among newborn boys. Up to 7% of boys are now born with undescended testicles, and up to 1% of boys in the US are now born with hypospadias. Scientists say the cause may be from endocrine disruptors, used in agriculture, industry and consumer products, and entering the water supply when estrogens in human urine, compounded when a woman is on the pill, pass through sewage systems and water treatment plants. There is accumulating evidence that male sperm count is dropping and that genital abnormalities in newborn boys are increasing. Some studies show correlations between these abnormalities and mothers who have greater exposure to these chemicals during pregnancy, through everything from hair spray to the water they drink. In women, the endocrine disruptor DES, given in the '30s to '70s to prevent miscarriages, caused abnormalities in their children, who seemed fine at birth, but later girl children were more likely to develop misshaped sexual organs and cancer. There is also evidence from both humans and monkeys that endometriosis is linked to endocrine disruptor exposure, and can cause early puberty in girls. New research has tied endocrine disruptors to obesity, insulin resistance and diabetes. Mice exposed in utero even to low doses appear normal at first but develop excess abdominal body fat as adults.

In June, the Endocrine Society issued a landmark statement: "We present the evidence that endocrine disruptors have effects on male and female reproduction, breast development and cancer, prostate cancer, neuroendocrinology, thyroid, metabolism and obesity, and cardiovascular endocrinology… The rise in the incidence in obesity matches the rise in the use and distribution of industrial chemicals that may be playing a role in generation of obesity." The EPA is very slowly moving toward screening for endocrine disrupting chemicals. For now, these chemicals continue to be widely used in agricultural pesticides and industrial compounds. Everybody is exposed. *The foregoing is edited or quoted directly from the New York Times opinion section, June 28, "It's Time to Learn From Frogs," by Nicholas D. Kristof.*

GUIDING LIGHT

The New York Times reported on new guidelines on fetal monitoring, published in July, that aim to bring more consistency to how doctors interpret the results and act on them. An obstetrician at Washington University was quoted, "Technology got rolled out before we knew if it worked or not." The use of fetal monitoring has produced both negative and positive results: electronic monitoring has led to a significant increase in both cesarean deliveries and forceps vaginal deliveries. Monitoring results are widely used by lawyers to bolster malpractice cases of spurious merit, which has led to soaring costs for malpractice insurance and, in turn, prompted many obstetricians to stop delivering babies. Monitoring has not reduced the risk of either cerebral palsy or fetal deaths. The revised guidelines are based on recommendations by the NICHHD, and published recently by ACOG. The new guidelines refine the meaning of different readings from the monitors, in the hopes of helping doctors make better decisions during labor about when to intervene and when to let nature take its course. Previous guidelines divided readings into two categories—reassuring and nonreassuring—and it was up to the doctor to decide whether a nonreassuring reading meant the fetus was at serious risk of oxygen deprivation. With fear of liability, many babies with nonreassuring readings who might have done just fine with a natural vaginal delivery are being delivered surgically or with forceps. The new guidelines divide monitor readings into three categories. In Category I, tracings of the fetal heart rate are normal and no specific action is required. In Category II, indeterminate tracings require evaluation and continuous surveillance and re-evaluation, and consider factors like the mom's blood pressure, heart rate and temperature, what medicines she might have been given, the frequency of contractions and how fast labor is progressing. Depending on what makes the reading Category II, the doctor can take steps to see if the reading will go back to Category I. In Category III, tracings are clearly abnormal, requiring prompt evaluation and efforts to reverse the abnormal heart rate. This could involve giving the mother oxygen, changing her position, treating her low blood pressure and stopping stimulation of labor if that is being done. If the tracing does not improve with such measures, the new guidelines say that "delivery should be undertaken." The above article is edited from the New York Times, July 7, "Updating a Standard: Fetal Monitoring," by Jane E. Brody.

TAKE DIRECTION

Mothers who breastfeed their babies are also more likely to follow recommendations to delay the introduction of solid foods, according to a study at Children's Hospital, Munich. In the study, 1,500 fomula-fed infants from five European countries were given solid foods on average two weeks earlier than breast fed infants and were also twice as likely to be introduced to solid foods before the age of four months, the recommended minimum age of solids introduction in Europe. Around 37% of formula fed infants had received solid foods before four months compared to only 17% of breastfed infants. Breast fed babies were also more likely to be given family foods than formula fed infants, who were more likely to be given commercial infant foods.

GESUNDHEIT

The EAACI, Pediatric Allergy & Asthma Meeting 2009 will take place in Venice, Italy, from November 12th to 14th. Main topics will be: asthma management and research, food allergy, drug allergy and anaphylaxis in children, allergic rhinitis and immunodeficiencies. Practical sessions will give delegates the opportunity for hands-on training to be applied in daily clinical practice. Contact eaaci.net.

MISINTERPRETATION

Some parents may be unnecessarily switching infant milk formulas for their healthy infants. A study published in BioMed Central's open access Nutrition Journal, found that many parents misinterpret common baby behaviors as milk intolerance and needlessly switch formulas. Researchers at Mead Johnson Nutrition found that up to half of formula-fed infants experience a formula change during the first six months of life. The randomized study of 335 healthy term infants was

designed to test the hypothesis that there is no advantage in choosing a partially hydrolyzed protein formula as a first-choice for most healthy infants. The study demonstrated no difference in infant tolerance of two cow milk formulas, intact vs partially hydrolyzed cow milk protein, over a 60-day feeding trial. While regurgitation, crying, fussiness, and colic can be signs of intolerances, similar episodes are also normal during early infancy, but anxious parents may mistake these normal episodes as formula intolerance.

ALL'S NOT WELL

The Vancouver Sun reports that an increased risk of acute myeloid leukemia appears to be associated with the high and low extremes of birth weight. There is a growing body of evidence indicating that childhood leukemia is initiated in utero. Researchers at Harvard School of Public Health and Brigham and Women's Hospital, Boston, conducted an analysis of 32 studies to examine the association between birth weight, childhood leukemia, plus ALL and AML. Included in the analysis were 16,501 cases of all types of leukemia, 10,974 cases of ALL, and 1832 cases of AML. Compared with normal birth weight, high birth weight was associated with a 35% increased risk of leukemia, a 23% increased risk of ALL and a 40% increased risk of AML. For every 1000 gram increase in birth weight, the odds ratio for overall leukemia increased by 1.18. Researchers aid leukemia risk may be affected by epigenetic factors, including the addition of molecules, like methyl groups, to the DNA backbone and other factors that may indirectly influence the expression of the genome. Reported in the International Journal of Cancer and reported by the Vancouver Sun.

LAST STEP

Parents of babies and young children are being urged to stop using the First Steps medicine feeder manufactured by RSW International Ltd after a six month old baby was admitted to a hospital from an overdose while using the device. The feeders are marketed for the administration of liquid medicines to babies and young children. A UK government agency said the product could pose a potential risk to babies or young children as the measuring scale is confusing and could be inaccurate.

BALLS

Recent epidemiological studies have revealed an increase in the frequency of genital malformations in male newborns such as un-descended testes and a decrease in male fertility. Researchers said environmental contaminants that reduce male hormone action were likely to blame. Researchers showed a sustained decrease in birth weight differences between boys and girls, which supports the hypothesis of growing endocrine disruption related to environmental contaminants, especially those found in plastics.

HOW IMMATURE

Researchers at Children's Hospital Boston believe they have found a way to enhance the immune system at birth and boost newborns' vaccine responses, making infections like respiratory syncytial virus, pneumococcus and rotavirus much less of a threat. Doctors at the Children's Division of Infectious Diseases showed that the newborn immune system functions differently than that of adults, but that one portion of the immune response is fully functional and can be harnessed to boost innate immunity. Researchers found that when most of a newborn's toll-like receptors were stimulated, their responses were very impaired, with one exception, TLR8, which triggered a robust immune response in antigen-presenting cells crucial for vaccine responses. The study suggested that agents that stimulate TLR8 could be used to enhance immune responses in newborns, perhaps as adjuvants given along with vaccines. Researchers are now validating their work in human cells and in animal models, and eventually want to test TLR8 stimulators, some of which are already available, in human babies.

SAY YOUR PRAYERS

All serious cases of maternal mortality in Jehovah's Witnesses over a two year period in the Netherlands were caused by major obstetric hemorrhage, because the sect refuses blood transfusions. According to the researchers, as such, the group's members expose themselves to a serious risk during childbirth. A major survey has showed a maternal mortality ratio due to obstetric hemorrhage of 68 per 100,000 live births in this group, a 130 times higher risk than the average.

BARFY

Metoclopramide, used to control nausea, vomiting and heartburn, is safe for the fetus, according to researchers at Ben Gurion University. Metoclopramide is the drug of choice in Europe and Israel for morning sickness, but it's only approved for off-label use in the US. The Israel study examined a large cohort of moms exposed to the drug in the first trimester. The study linked a database of medications dispensed over 10 years, with 3,458 babies out of 81,703 exposed to the drug. The rate of major congenital malformations identified in the exposed group was 5.3% (182 of 3,458 infants), as compared with a rate of 4.9% in the unexposed group. Thus, exposure to metoclopramide was not associated with significantly increased risks. The results were unchanged when therapeutic abortions of exposed fetuses were included in the analysis. In addition, infants exposed in utero had no increased risk of perinatal mortality, low birth weight or premature birth.

UNINSURED

Researchers at the Yale School of Medicine and Yale-New Haven Children's Hospital have found that babies from uninsured families who are born with congenital defects are far more likely than those whose families have insurance to be transferred out of the large community hospitals where they are born and into children's hospitals for corrective surgery, and that these uninsured babies may receive better care at the children's hospitals, which are fully staffed with pediatric specialists. The research comprised data from 6,000 infants with major congenital defects born in community hospitals between 1997 and 2006. The uninsured babies were three times as likely than the insured to be sent to children's hospitals. The mean hospitalization cost for newborns with complex congenital anomalies is more than $155,000, with care for some infants rising above $1 million. The researchers noted that care of newborns with major anomalies can produce either a huge financial gain or loss to a hospital, depending upon the patient's insurance status. Researchers also noted that children's hospitals are being asked to shoulder a disproportionate burden of caring for such uninsured babies, without the appropriate reimbursement and that this threatens the viability of all children's hospitals in the US.

FIGHTING BACK

The mystery of why the immune system of pregnant women doesn't attack the developing fetus is closer to being solved by a study at NYU School of Medicine. Experiments with

mice revealed that once an embryo implants into the wall of the uterus, the formation of the decidua prevents immune sentinel cells (DCs) from leaving the maternal/fetal interface and traveling to the local lymph nodes to activate an immune response toward the fetus. The research suggests that impaired formation or function of the human decidua might allow DCs to leave the decidua to initiate an aggressive immune response toward the fetus, something that might contribute to poor pregnancy outcomes. For the complete study go to Medline and type: Dendritic cell entrapment within the pregnant uterus inhibits immune surveillance of the maternal/fetal interface in mice.

ACCIDENTAL

Childbirth-related injuries have declined significantly in the past six years, according to the Agency for Healthcare Research and Quality. There were nearly 158,000 potentially avoidable childbirth-related injuries to women and their infants in 2006. The report used data submitted for 15 million discharges from 1,900 hospitals in 25 states. Between 2000 and 2006, the rate of potentially avoidable injuries during vaginal childbirth without the use of instruments declined by 30%. The injury rate declined by 21.3% for vaginal childbirth using instruments and by 16.7% for women with c-sections. Rates of injury were higher when instruments were used during childbirth. Trauma during vaginal delivery with the use of instruments occurred 160.5 times per 1,000 discharges, compared with 36.2 times when instruments weren't used. The most common injuries were perineum tears. Traumatic injury to infants during childbirth occurred 1.6 times per 1,000 discharges. Women giving birth in high-income areas had 44% more injuries during vaginal delivery than their counterparts in low-income areas. Black and Hispanic women experienced fewer injuries than white women, while Asian American and Pacific Islander women experienced the highest rate of injuries. Women covered by Medicaid were less likely to be injured during childbirth, at 127 per 1,000, as opposed to women with private insurance, at 185 per 1,000. The rate of injury for infants covered under Medicaid was slightly higher, at 1.7/1,000 vs 1.5 for private insurance. Information for the above is from Medical News Today, nationalpartnership.org, © 2009 The Advisory Board Company.

SHOW US YOUR BIRTHS

Thousands of women have posted videos of giving birth on YouTube, according to an article in the New York Times. Is it voyeurism or education? The videos are challenging YouTube's "rules" about graphic content and propriety, according to the Times. Some say the trend is helping to "demystify" childbirth, which has been around a long time and is really no great mystery, though one would suppose it could be scary to contemplate for people who've never experienced it, especially since most births now take place in hospitals where visitors can't stand around gawking. Others have argued that the graphic videos would actually instill more fear of childbirth, not less. Most of the videos show home births because most hospitals prohibit patients from recording births due to liability concerns.

AUTISM STUDY

The NIH and the group Autism Speaks are enrolling 1,200 pregnant women who have other children with autism to participate in a study to identify its early signs. The EARLI study (Early Autism Risk Longitudinal Investigation) participants will be monitored throughout their pregnancies, and their infants will be monitored until age three. The study will focus on women who already have one child with autism because these moms have a higher chance of having another child with the condition. Researchers will collect blood and urine for DNA analysis, and samples from the umbilical cord, placenta and the infant's meconium. Reported in the Wall Street Journal, from Medical News Today, © 2009 The Advisory Board Company.

DIDN'T DO SQUAT

Progesterone is ineffective at preventing premature births for women with twins, though it works for single pregnancies, according to a study by the University of Edinburgh. Its study involved 500 women who took either progesterone or a placebo daily for 10 weeks. Twenty-five percent of women delivered or had a fetus die before 34 weeks in the progesterone group, compared with 20% in the placebo group.

BIRTHING WHILE BLACK

Black women have nearly two times the odds of having a preterm birth as white women, according to researchers at the University of Washington. The researchers surmised that the higher rate was because of declining health over time among black women. In the study 18.1% of the black women had a preterm birth compared to 8.5% of the whites. According to one of the researchers, being black takes a toll on the physiological system and chronic exposure to stressors leads to health disparities between the two groups.

WATCH OUT

The New York Times reports that pregnant women who get swine flu are at such high risk of complications like pneumonia, dehydration and premature labor that they should be treated at once with the antiviral drug Tamiflu, even though it is not normally recommended in pregnancy, according to the CDC. Because a positive test for the new H1N1 flu can take days, the agency said, Tamiflu should be given to any pregnant patient with flu symptoms and a history of likely contact with someone else with swine flu. Tamiflu is not normally recommended for use by pregnant women because the effects on the unborn child are unknown. The CDC and WHO said case histories in Mexico and the United States suggested that pregnancy was emerging as a risk factor rivaling asthma, diabetes, immunosuppression and cardiovascular disease. One of the three deaths in the United States involved a pregnant Texas woman who was on no medication other than prenatal vitamins, the disease centers said. The agency knows of 20 confirmed or probable swine flu infections in pregnant Americans, and a few had severe complications. The outbreak of swine flu is said to be spreading more slowly in Europe because the Europeans aggressively treat every suspected mild case with Tamiflu.

PRIZE WINNER

Basil S. Hetzel, AC, MD, FRCP is the 2009 recipient of the Pollin Prize for outstanding achievement in pediatric research. His pioneering work led to our understanding of the effects of iodine deficiency on brain development—and the importance of incorporating iodized salt in the diet to prevent brain damage in newborns. Dr Hetzel's research team in Papua New Guinea (1964-1972) established that brain damage could be prevented by correction of iodine deficiency before pregnancy. This groundbreaking research led him to begin a worldwide campaign to incorporate iodized salt into the diets of more than two billion people in some 130 countries where iodine is lacking. Dr Hetzel's efforts have prevented brain damage in millions of children. The Pollin Prize in Pediatric Research recognizes outstanding

lifetime achievement in biomedical or public health research related to the health of children. Established in 2002, the award was created by Irene and Abe Pollin and their family.

FIT NOT FAT

Breast milk has less protein than formula, which could be why bottle-fed babies grow faster, according to a three-year, five country study. The international study of 1,000 babies suggests that protein levels in formula should fall. Parents were recruited in the first few weeks of their babies' lives. A third were given a low protein content formula milk (around 2g per 100kcal), a third had a formula with a higher level of protein (3-4g per 10kcal), while the rest were breast-fed during their first year. The infants were all then followed up to the age of two with regular weight, height and body mass index measurements taken. At the age of two, there was no difference in height between the groups, but the high protein group were the heaviest. The researchers suggested that lower protein intakes in infancy might protect against later obesity. However, others have warned that low protein formula should definitely not be prescribed to infants. Reported by the BBC.

A LITTLE RSV

Babies who are only mildly premature are at increased risk of respiratory syncytial virus, according to researchers at Kaiser Permanente. Its study included 108,794 babies born at 33 weeks' gestation or later who were discharged from six hospitals between January 1, 1996 and December 11, 2002. The neonatal characteristics assessed included gestational age, race, birth weight, sex, oxygen exposure in the neonatal period, neonatal discharge month, siblings, and being small for gestational age. Results showed that the rate of use of supplemental oxygen during the neonatal period was 6.32% among babies 33 to 36 weeks and 1.63% among babies ≥37 weeks, and the rate of use of assisted ventilation was 9.92% and 0.86% in the two groups, respectively. Overall, the risk of RSV infection was greater in infants who were siblings, had a lower gestational age, were males, and were oxygen-exposed in the neonatal period. Researchers said the results demonstrated that medically attended RSV infection is more common in premature infants, even if they are not very premature. The above information was written by Jill Stein, a Paris-based medical writer, copyright Medical News Today.

FOLIC ACID

The Los Angeles Times' Thomas Maugh II reports, taking folic acid supplements for a year before conception reduces the risk of very premature birth by at least 50%. Shorter courses of the supplement were not as effective, according to a study of nearly 35,000 women. The finding reinforces the recommendation that all women of child-bearing age should take multivitamin supplements. Only 35% to 40% of such women currently take supplements. Previous research had shown that women who deliver prematurely have lower-than-normal levels of folate in their blood. Small trials of folic acid supplements to prevent premature birth have given mixed results. In the latest trial, women were questioned during the first trimester of pregnancy about their health behaviors, including use of supplements. The researchers found that for women who had been taking folate for at least a year before conception, the risk of birth between 28 and 32 weeks was reduced by 50%. The risk of birth between 20 and 28 weeks was reduced by 70%. The latter reduction is particularly significant because researchers had previously found no way to reduce the proportion of preterm babies born so early. The supplementation had no effect on the risk of preterm birth after 32 weeks, the researchers found. And beginning supplementation around the time of conception did little to reduce preterm births, even though such timing does reduce the risk of neural-tube defects. Health authorities recommend that women of childbearing age—whether or not they plan to become pregnant—consume an additional 400 micrograms per day. There has been recent debate about whether even higher amounts would be more beneficial—although some critics believe that higher amounts could mask vitamin B12 deficiency and might raise the risk of certain cancers. But the study suggested that dose is not as important as duration.

UPCHUCK

The WAO reports the following trial: Multicenter, double-blind, randomized, placebo-controlled trial assessing the efficacy and safety of proton pump inhibitor (PPI) lansoprazole (Lan) in infants with symptoms of gastroesophageal reflux disease. This study compared treatment with placebo (P) versus Lan with the primary outcome of reducing feeding-related crying by 50% and secondarily by changing other symptoms and global assessments and other alleged GERD symptoms. Infants (n=162) with symptomatic GERD were randomized to P or Lan (0.2-0.3 mg/kg/day for 10 wks of age; 1.0-1.5 mg/kg/day for ≤10 wks of age) groups and treated for 4 weeks. Number and duration of feeding-related crying episodes were recorded and a modified. Infant Gastroesophageal Reflux Questionnaire was completed daily. No change in symptom scores was found with Lan versus P, and there were significantly more adverse events (AE), particularly lower respiratory tract infections, in the Lan group. WAO noted: The lack of efficacy of the PPI, together with the increase in AE, suggest that these medications should not be routinely used in infant GERD. See J Pediatr 2009; 154:514-520.

ONE PER CUSTOMER

Progesterone gel to prevent premature births in single pregnancies may be ineffective in women expecting more than one child, according to researchers at Edinburgh University. The study looked at almost 500 women around the country expecting twins. Half of the women in the study group were given progesterone gel to protect the lining of the womb, while the other half were given a placebo. Researchers found that contrary to single pregnancies, the hormone gel did not reduce rates of premature births in those expecting twins. About 20% of multiple pregnancies result in preterm delivery before 34 weeks, compared with 2% to 3% of pregnancies for women expecting one child. The research was said to underscore the lack of effective treatments in the prevention of preterm birth in multiple pregnancy.

HOME BIRTHS

The Huffington Post reports: One factor driving up the cost of healthcare is the US cesarean rate, which is now performed in 31% of births, up from 4.5% in 1965. As the number one reason for hospital admissions, childbirth is a huge part of the nation's $2.4-trillion annual healthcare expenditure, accounting in hospital charges alone for more than $79 billion. Because spending on the average uncomplicated cesarean for all patients runs about $4,500, nearly twice as much as a comparable vaginal birth, cesareans account for a disproportionate amount (45%) of delivery costs. Among privately insured patients, uncomplicated cesareans run about $13,000. Pregnancy is the most expensive condition for both private insurers and Medicaid, according to a 2008 report. However, the Huffpost

notes, off-site birthing centers and home deliveries have lower C-section rates and healthier outcomes. For decades, ACOG, the website says, has managed to prevent any truly rigorous review of statistics, preferring to use data that counts miscarriages as home deliveries. But the Netherlands has provided alternate information. Researchers there have found that births where women actually prepared to deliver at home (as opposed to precipitous labors where sudden complications forced them to deliver there) were just as likely to have a safe delivery and healthy baby as those who delivered in a hospital under the care of a midwife. The group who chose to give birth in hospitals rather than at home were more likely to be first-time mothers or of an ethnic minority background, and the risk of complications is higher in both these groups. Some other interesting info to come out of the Netherlands about other advantages of home births: You can avoid hospital "supergerms"; birthing positions there can actually make fetal distress (and thus, a C-section) more likely; the use of powerful labor-inducing drugs not only increases the likelihood of a C-section, but also of uterine rupture. One commenter on the Huffpost site wrote: "I did it both ways: a hospital birth with a doctor and nurse-midwife, and a home delivery attended by lay midwives. (I told my then-husband I would never have another child in a hospital after they almost killed my first-born and then bragged about how they "saved" him.) Not only did I give birth at home with my youngest, I was up cooking breakfast for everyone just a few hours later. It was an experience I wouldn't trade for the world. It was better in every possible way."

SOOTHES THE SAVAGE (LITTLE)…

A Canadian study says hospitals that play music to premature babies help them grow and thrive, mounting evidence suggests. Researchers reviewed nine studies and found music reduced pain and encouraged better oral feeding. Music also appeared to have beneficial effects on physiological measures like heart and respiratory rate. In six of the studies the University of Alberta looked at music played to babies during circumcisions and heel prick tests and another study looked at the effect of music on feeding rates. The remaining two looked at the effect of music on physiology and behaviors. The studies used lullabies with or without added sounds like heartbeats and womb noises. Another used a specially-composed wordless lullaby accompanied by a harp, and some hospitals have been playing the great composers, though presumably not the 1812 Overture.

DON'T BOTHER

Learning relaxation and breathing techniques does not reduce the need for an epidural in labor, a new study shows. More than 1,000 mothers-to-be took part in a Swedish trial in which prospective moms took one of two classes: the first taught natural coping methods, the other emphasized pain relief. The study found no difference in the use of epidurals between the women when they went into labor, with over half the women in each group ultimately opting for them. About 70% of the women who had attended the natural childbirth class said they employed the psychoprophylaxis techniques they had learned, which included breathing and relaxation methods as well as ways of coping with pain such as positive imaging. The perceptions of pain, the proportion of vaginal births and emergency cesareans was also the same between the two groups. In the natural childbirth group, there was a slightly higher rate of instrumental births, involving forceps or a ventouse. Regardless, the women in both groups were satisfied with their birth experience, with the same small minority in both describing it as negative.

HISTORY

From the Wall Street Journal, by Melinda Beck: In the 1950s, babies named Linda and Bobby came home from the hospital in Studebakers with Fats Domino on the radio. Many were given a new score a minute after birth to assess how well they made the transition from womb to room. Today, the Apgar score is still given to nearly every baby born in a hospital world-wide. Many parents know Apgar as an acronym for what it measures: Appearance, Pulse, Grimace, Activity and Respiration. But the score was first named for Virginia Apgar, the anesthesiologist who, in 1949, scribbled it on the back of a card in a hospital cafeteria that read "Please Bus Your Trays." The score laid the foundation for the field of neonatology, and Dr Apgar became a legendary figure in medicine. She died in 1974. She would have been 100 years old last month. The score came about, indirectly, because of the sexism long rampant in medicine. The cash-strapped graduate of Mount Holyoke waited tables and caught stray cats to sell to the lab while earning her medical degree from Columbia University in 1933. She excelled at surgery, but a mentor convinced her she'd never make a living that way. She went into anesthesiology and helped build it into a medical specialty. But she was passed over for a man to head the new department at Columbia. So she threw herself into teaching and patient care, becoming the first woman full professor at Columbia's College of Physicians and Surgeons. She was particularly drawn to obstetrical anesthesia, and was increasingly concerned about what she saw. As late as the 1940s, delivery-room doctors focused on mothers and paid little attention to babies. Those who were small or struggling were often left to die, since doctors assumed little could be done for them. It was considered better not to be aggressive. You dried them, you shook them, and some doctors patted them on the backside and that was it. In the cafeteria one morning, a med student asked Dr Apgar how a newborn might be evaluated. "That's easy, you'd do it like this," she said, dashing down heart rate, respiration, muscle tone, color and reflexes. Then she rushed off to try it, according to Selma Calmes, a retired anesthesiologist who has written about her. After testing the score on more than 1,000 newborns, Dr Apgar presented it at a conference in 1952 and it caught on quickly. As simple as it was, the score transformed deliveries by requiring staffers to carefully observe and assess each baby, assigning a score of 0, 1 or 2 to each of the five categories. Then, as now, few babies get a perfect 10 one minute after birth, since most have bluish toes and fingers until oxygenated blood starts circulating fully. Some doctors became competitive about the scores, and many hospitals began repeating the test at five or 10 minutes to measure whether newborns had improved. Babies who needed care started to get it, gradually spurring the development of newborn-size resuscitation tools, infant heart-rate monitors and neonatal intensive care units. Thanks to all those efforts, and the philosophy that came with them, US infant mortality dropped from 58 per 1,000 in the 1930s to 7 per 1,000 today. By the 1970s, it was said, every baby born in a hospital around the world is looked at first through the eyes of Virginia Apgar. Dr Apgar, who never made any money from the test, moved on to become a senior medical official at the March of Dimes in 1959, devoting the rest of her life to preventing birth defects and other conditions that caused newborns to have low Apgar scores. She was among the first to recognize and warn pregnant women about the dangers that infections, viruses, RH incompatibility and certain medications could pose to unborn babies. After a rubella outbreak in 1964 caused 20,000 birth defects and 30,000 fetal deaths, she helped win funding for widespread vaccinations.

Dr Apgar was also one of the first at the March of Dimes to look for ways to prevent preterm birth, the organization's current focus, and coined the slogan, "Be good to your baby before it's born." Dr Apgar took up flying in her 50s, and also played, and made, stringed instruments. One night, she and a colleague famously snuck into Columbia-Presbyterian Hospital and stole a maple shelf from a phone booth that she thought would make a splendid violin. She died in 1974, having never married. "I never found a man who could cook," she often said.

MONEY

In 2008, the CMS considered adding VAP to their list of "Never Events." Due to a concerted effort by the respiratory and critical care field, VAP is currently listed as an "often unavoidable" condition. While VAP has not yet become a "Never Event," the costs of a single case can exceed $35,000. The financial impact if such costs are not reimbursed in the future would be significant. To further decrease occurrences of VAP, the AARC has established recommendations based on Evidence Based Clinical Practice Guidelines. The recommendations include: Ventilator circuits should not be changed routinely for infection control purposes; Even though evidence supports a lower VAP rate with passive humidification than with active humidification, other issues related to use of passive humidifiers preclude a recommendation; Passive humidifiers do not need to be changed daily; Use of closed suction catheters should not be considered part of a VAP prevention strategy. High Flow Therapy, and Vapotherm, can be a key tool in potentially reducing or avoiding more invasive (and costly) procedures by eliminating MV when possible and reducing total ventilation time. For additional clinical information, contact clinicalsupport@vtherm.com.

REIMBURSEMENT

Vapotherm reported on how to code its equipment for a maximum reimbursement: "As with all of our products, you will want to code through the HCPCS Coding System under E0550 for 'Heated Humidification.' The average monthly reimbursement is about $50. If the patient is a Medicare patient or Medicare is going to be a co-insurer you would have to bill them using the E0550 code. Vapotherm cannot make any recommendations on how to bill private insurers. In some instances, the Vapotherm 2000h has been billed for a specified payment via the E1399 'Miscellaneous Code.' This is normally the process with non-Medicare neonatal and pediatric patients who are currently in the hospital but ready for discharge, taking into account equipment, supplies and servicing. This approach is best supported by putting together an argument stating that paying 'X' to the DME company a month is less expensive than paying 'X+' a day to keep them in the hospital. This justification has also been a successful approach with some secondary or non-Medicare payers for adult patients. No matter which insurer or code you use, it is best to support your reimbursement request with documentation from the physician and/or hospital discharge planners to ensure maximum reimbursement."

PRODUCTS

REFORM SCHOOL

Siemens Healthcare announced that Thomas Miller, Chief Executive Officer (CEO) for the Workflow & Solutions Division, Siemens Healthcare, testified before the Health Subcommittee, Committee on Energy and Commerce, US House of Representatives on the need for healthcare reform. During the hearing, Comprehensive Health Reform Discussion Draft, Day 2, Miller testified on ways to improve the quality of healthcare delivery while reducing its overall costs. He noted that there is undeniable evidence that medical imaging finds disease earlier, renders some invasive procedures obsolete, and saves lives. The medical imaging industry has worked hard to generate savings and efficiencies by developing physician-driven appropriateness guidelines that will ensure appropriate and effective use of diagnostic technologies, while assuring every patient has access. Miller presented to the Committee the facts about medical imaging: Diagnostic technologies support more cost-effective care by enabling earlier, faster and more accurate diagnosis, eliminating the need for expensive and invasive surgeries and inappropriate therapies, reducing hospital admissions, and, in many cases, avoiding costs of long-term chronic conditions. The growth in medical imaging can be attributed to its transformational effect on medicine for almost every facet of every disease. Physicians know that medical imaging is simply the best tool they have to diagnose disease with confidence. And, the great majority of physicians have one overriding interest: to achieve the best possible outcomes for their patients. The best means to reduce costs and overuse is by creating a more efficient healthcare system through Healthcare Information Technology and to manage medical imaging utilization through physician-driven appropriateness guidelines. Contact usa.siemens.com.

SOFTWARE

Siemens Healthcare announced the launch of its newest version of Inveon Research Workplace, IRW 3.0, at the 2009 SNM Annual Meeting in Toronto. This new software provides Inveon users with an expanded set of tools for image visualization and data analysis, and new solutions for important applications in cardiac PET imaging. As part of Siemens' ongoing commitment to preclinical imaging solutions, this new software is one more tool in the comprehensive array of solutions offered with Inveon hardware and software technology for preclinical research. A significant challenge for preclinical researchers is the ability to derive accurate quantitative information in an expedient and efficient manner. The new IRW 3.0 software is equipped with image visualization, analysis and data management features that increase overall ease-of-use. Specifically, IRW 3.0 enables visualization and analysis of dual-gated dynamic PET data. With support for both acquisition and analysis of these types of data, Inveon users are able to carry out complex and demanding preclinical studies which are affected by cardiac and/or respiratory motion artifacts. In addition, IRW 3.0 allows for quick and accurate high resolution image data export, representation and interpretation, while delivering features such as arbitrary image reorientation and image filtering. Inveon•Workplace also provides improved kinetic modeling and parametric analysis tools. Contact usa.siemens.com.

GOING 4-WARD

Discovery Labs announced the results of its latest meeting with the FDA regarding Surfaxin (lucinactant) for the prevention of RDS in premature infants. The meeting was convened to discuss resolution of the remaining issue necessary for marketing approval and focused on the Surfaxin fetal rabbit biological activity test. The FDA stated that it would apply a newly-refined standard to determine whether Discovery Labs has adequately demonstrated the comparability of Surfaxin clinical to commercial drug product. The FDA insisted that data generated from the preterm lamb model study and BAT studies

must demonstrate the same relative changes in respiratory compliance, and that it believed such a demonstration would present Discovery with a high hurdle. In light of this new standard, Discovery is now focusing on maximizing the inherent value of its KL_4 surfactant and aerosolization platforms and will minimize development risk by leveraging Surfaxin's established proof-of-efficacy in RDS. The two highest priority programs are Surfaxin LS and Aerosurf. The synthetic nature and formulation flexibility of KL_4 supports expansion into a wide range of respiratory disease conditions. Discovery Labs intends to pursue these opportunities through strategic alliances. While proceeding with BAT as a validation method, Discovery believes that the best way to address the global RDS patient population is to advance its KL_4 surfactant programs and target traditional endotracheal tube delivery and less invasive surfactant administration through aerosolization. Aerosurf may provide benefits that will advance the management of RDS and represent a significant improvement from a medical and economic perspective. As for Surfaxin approval, Discovery Labs may further interact with the FDA to assess whether Surfaxin approval can be gained without additional clinical trials, or may exercise its right of appeal through the FDA's Formal Dispute Resolution process. In addition to focusing on Surfaxin LS as a KL_4 formulation and Aerosurf, Discovery Labs had initiated exploratory development programs targeting ARF, ALI, CF, and the feasibility of drug combination therapies utilizing KL_4 surfactant. Contact discoverylabs.com.

NEW BOSS

Michael Reitermann has been appointed the new CEO of Siemens Healthcare's US organization. Reitermann will lead the marketing, sales and service functions for Siemens Healthcare in the US, including the medical imaging, therapy and healthcare information technology businesses. He will be based at the US headquarters in Malvern, PA. Reitmann worked as a senior project manager at the corporate strategies division as well as a partner in Siemens Management Consulting. He also served as vice president for sales, marketing and innovation of the Siemens Angiography, Fluoroscopy and X-ray business unit. Most recently, as CEO of Siemens Molecular Imaging (MI) Business Unit, and president of the former Nuclear Medicine division, he was responsible for the establishment and implementation of MI's business objectives around the world.

CLEARED FOR TAKEOFF

Hamilton Medical, Inc announced FDA 501(k) market clearance of the Hamilton Medical C2 Ventilation System. The Hamilton C2 is designed for adults and children requiring invasive or non-invasive ventilation support. With its compact design, a weight of only 19.5 lbs, built-in batteries and an ultra-quiet turbine, this ICU ventilator can accompany your patient anywhere within the hospital, independent of central gas and power supplies. You do not have to disconnect a patient for transport, thus increasing patient safety and comfort, while at the same time reducing your workload. Hot-swappable batteries permit extended ventilator operation for a virtually unlimited period of time. The touch screen provides easy operation and clear data display. The compact design of the Hamilton C2, the integrated blower and innovative battery management make the Hamilton C2 the perfect choice for patient transport inside the hospital. It is no longer necessary to change the ventilator for transports, which provides for continued patient improvement, as the C2 is a transport and a true critical care ventilator. Two batteries, fully charged, allow the Hamilton C2 to run for up to five hours without AC power. The batteries are hot-swappable, which means with additional batteries the Hamilton C2 can run indefinitely on battery power. The optional universal bed trolley is a comprehensive solution for mounting the patient monitoring system, perfusion pumps and the Hamilton C2 to the bed. Synchrony between patient and the ventilator is one of the main issues in ventilation. Using patient proximal flow measurement, the C2 and all Hamilton Medical ventilators, perfectly adapt to the patient's needs. The C2 supports the patient in all conventional volume and pressure controlled modes. The biphasic concept allows the patient to breathe freely at anytime. Part of Hamilton Medical's Intelligent Ventilation strategy is ASV (Adaptive Support Ventilation), an innovative mode that is able to adapt to the patient's lung mechanics. Breath by breath, the patient's resistance and compliance are measured, evaluated and visualized in the Dynamic Lung panel. In an effort to facilitate and improve patient weaning, the innovative Ventilation Status panel provides the user an overview of patient-ventilator dependency at a glance. Non-invasive ventilation is used more often as an alternative to intubation and conventional ventilation. NIV addresses well known complications such as, but not limited to, trauma during intubation, infections, and is more comfortable for the patient. The use of NIV is not trivial and some precautions have to be taken. The appropriate interface must be selected and proper mask fit is critical; however, this cannot always be done and leaks can occur. Leaks are a major problem of non-invasive ventilation resulting in dyssynchrony between patient and the ventilator. To combat this issue, the C2 incorporates Hamilton's innovative IntelliTrig technology to compensate for leaks and assure a perfect synchronization between the patient and the ventilator. Contact hamilton-medical.com.

RICKETS

New clinical data was released on a new drug that may help save the lives of babies born with a rare bone disease. Enobia Pharma's Enzyme Replacement Therapy (ERT) ENB-0040 is being used to treat hypophosphatasia, a disease which can prevent bones from properly forming, or weaken bones already formed. When the onset of the disease begins in infancy, the results are particularly severe. Globe Newsire reported: A new experimental targeted enzyme replacement therapy strengthens the bones of infants with a severe, sometimes deadly, genetic bone disorder known as hypophosphatasia (HPP), according to early clinical data presented by Michael P. Whyte, MD, medical/scientific director of the center for metabolic bone disease and molecular research at Shriners Hospitals for Children St Louis. Dr Whyte presented the results of a Phase I safety trial of the experimental treatment in adults, and early safety and efficacy findings from an ongoing study on severely affected infants at The Endocrine Society's 91st Annual Meeting (the ENDO 09 Conference) in Washington, DC. There were no drug-related serious adverse events reported in either study, nor did any of the patients develop anti-ENB-0040 antibodies. ENB-0040 is an enzyme replacement therapy designed to specifically target TNSALP to the bones, with the goal of "normalizing" bone mineralization. In the infant trial, all patients had undermineralized and deformed bones (rickets) when they entered the study. After an initial single intravenous dose, the patients received thrice-weekly subcutaneous doses of ENB-0040 for up to six months. X-rays at three months showed substantial new mineralization in the ribs, wrists, knees and long bones in the first three of five patients. The patients' overall

clinical status improved as well, with most showing improved growth and requiring less respiratory support over the course of treatment. Enobia Pharma, the Montreal, Canada-based company developing ENB-0040, sponsored both studies.

COMFORTABLE

Comfort Flo Humidification System: "The Difference is Easy to "C". Comfort Flo and ConchaTherm from Teleflex Medical combine to deliver high flow nasal cannula therapy, without compromise. The Comfort Flo Humidification system allows you to safely and effectively deliver heated, humidified oxygen therapy to a broad range of patients. Featuring an adjustable airway temperature and gradient control, the Conchatherm Neptune allows you to customize therapy to enhance patient comfort while minimizing condensation build-up. The disposable delivery system and line of specialty cannula allow flow rates ranging from 1 to 40 LPM. Contact (866) 246-6990, teleflexmedical.com.

GETTING WARMER

The EC390L from Enthermics Medical Systems is a single-chamber fluid warming cabinet with an 18" depth for built-in applications or counter-top placement. Its pull-out basket holds up to 29 liters and can be set to warm either irrigation or injection fluids. Temperature range for injection fluids is 95° to 104°F, while the range for irrigation fluid is 95° to 150°F. An option is the WarmWatch feature, a glass door for inventory at-a-glance. The stainless steel EC390L has rugged hinges and latches, and fluid warming chambers help manage core body temperature. The warmer has three variable-control temperature environments, for blankets, injection fluids and irrigation fluids. Contact enthermics.com.

NOT A FLUKE

Fluke Biomedical's used equipment purchase program allows customers to purchase like-new equipment from its demonstration-showcase inventory, some models less than a year old, at a fraction of new-product cost. Customers who take advantage of this program enjoy the same new-product warranty as all Fluke Biomedical equipment, fresh calibration, and the benchmark quality of design only available from Fluke Biomedical. For complete promotional details on the used-equipment purchase program, visit the Fluke Biomedical website at flukebiomedical.com.

GOING UP

B&B Medical Technologies has introduced two new medical grade Heliox regulators with DISS fittings. The compact and versatile Heliox 70/30 DISS and Heliox 80/20 DISS regulators will help medical facilities reduce costs by eliminating the need for two separate regulators for low flow Heliox therapy and high pressure gas delivery devices. Designed for use in critical care, special procedure units and emergency departments, the B&B regulators are easy to set up with either 70/30 or 80/20 Heliox H cylinders. Calibrated for delivery of precise flow and MRI compatible, no conversion or calibration of flow is needed to determine accurate Heliox flow. Easy to set up on H cylinders, the permanent O-ring design eliminates the need for a washer and provides hand tight seal at the yoke connection. The Heliox 70/30 DISS and Heliox 80/20 DISS regulators combine a calibrated "click style" flowmeter with barbed nipple for flows up to 25 Lpm plus an additional 50 psi male air connector for ventilator and other high pressure applications. Each regulator has a built-in unique color coded tank pressure indicator with 0-3000 psi operating range. The CGA yoke connector has a special inlet filter and all-brass construction in the high-pressure zones. The regulators are single stage, piston type with backpressure compensation and internal relief valve. The Heliox 70/30 DISS Regulator and the Heliox 80/20 DISS Regulator provide a complete system for simultaneous and independent delivery of metered constant flow Heliox and regulated high pressure gas. Contact bandb-medical.com.

NEWS FROM CASMED

CAS Medical Systems, Inc announced the introduction of Non-Adhesive Small Sensors for its **FORE-SIGHT** Absolute Cerebral Oximeter. This sensor is designed specifically for preserving the skin integrity of newborns and preterm infants. Coupled with CASMED's unique COOL-LIGHT technology which eliminates heat at the site of the sensor, the FORE-SIGHT Non-Adhesive Small Sensors help to maintain skin integrity with the use of either a headband system or a hydrogel adhesive—the same gel adhesive used on CASMED's premium Klear-Trace neonatal electrodes… The company announced that **four studies** were presented at the Society of Cardiovascular Anesthesiologists (SCA) Annual Meeting in San Antonio, TX, demonstrating the efficacy and accuracy of the FORE-SIGHT Absolute Cerebral Oximeter. These observational studies show initial evidence of the relationships between low cerebral tissue oxygen saturation measured by FORE-SIGHT and: a) longer term post-surgical cognitive decline, b) increased time to extubation, c) increased length of ICU stay, and d) post operative complications following cardiac surgery. In addition, one study demonstrates the superior accuracy of the FORE-SIGHT system. Simultaneous Comparison of FORE-SIGHT and INVOS Cerebral Oximeters to Jugular Bulb and Arterial Co-Oximetry Measurements in Healthy Volunteers, led by Dr David MacLeod of Duke University Medical Center in Durham, NC, compared simultaneous measurements from two cerebral oximeters against the gold-standard of weighted invasive jugular bulb and arterial oxygen saturation measurements. This study indicated that the FORE-SIGHT absolute cerebral tissue oxygen saturation measurements are three times more accurate than the comparison product. Decreased Forebrain Cerebral Tissue Oxygen Saturation is Associated with Cognitive Decline after Cardiac Surgery, a clinical evaluation led by Dr MacLeod, examined the relationship of cerebral tissue oxygen saturation ($SctO_2$) measured by FORE-SIGHT to longer term post-operative cognitive decline 6 weeks post surgery. Subjects were given a battery of cognitive tests both before and 6 weeks after surgery for verbal memory and language comprehension, figural memory, attention and concentration, and psychomotor and processing speed. This observational study showed that decreased intraoperative $SctO_2$ levels are potentially associated with longer term forebrain post-operative cognitive decline. It is believed that this was the first study to demonstrate initial evidence that longer term post-operative cognitive decline may be associated with decreased cerebral tissue oxygen saturation measured by cerebral oximetry. Decreased Cerebral Tissue Oxygen Saturation during Aortic Surgery Increases Risk of Post-Operative Complications was led by Dr Gregory Fischer of the Mount Sinai School of Medicine in New York, NY. This study examined the relationship between decreased intraoperative cerebral tissue oxygen saturation values and post-operative complications following aortic surgery. This study indicated that decreased $SctO_2$ values were potentially associated with major

post-operative complications, prolonged extubation times, and increased ICU length-of-stay. Continuous Monitoring of Cerebral Blood Flow Autoregulation during Cardiac Surgery in Adults with Near Infra-Red Spectroscopy: Preliminary Results, led by Dr Brijen Johsi of The Johns Hopkins Hospital in Baltimore, MD, demonstrated that cerebral oximetry using near infra-red spectroscopy provides accurate detection of the lower cerebral blood flow threshold in patients undergoing cardiac surgery. For more about these studies, contact cereabraloximetry.com… CASMED announced that the Company's FORE-SIGHT Absolute Cerebral Oximeter now has the **capability to interface** with the Philips Healthcare IntelliVue monitoring system. FORE-SIGHT absolute cerebral tissue oxygen saturation ($SctO_2$) measured values can be transmitted through the Philips VueLink module and displayed in real-time on the IntelliVue patient monitor display screen. IntelliVue monitors collect, combine, and cross-reference physiologic data for comparison and storage. This patient data integration reduces the number of displays, control, alarm and documentation points at the bedside—providing a clear view of patient information that supports clinical thought processes. FORE-SIGHT's new communication ability with Philips IntelliVue allows absolute $SctO_2$ data to be displayed with a wide array of critical care and operating room physiologic measurements, offering convenient central viewing of decision support variables. The FORE-SIGHT Absolute Cerebral Oximeter is compatible with the many Philips IntelliVue and CMS patient monitors already installed worldwide. Current users of these Philips systems can simply connect the FORE-SIGHT monitor to existing systems via the VueLink AUXPLUS module… The company announced that **five studies were presented** at Euroanaesthesia 2009, the annual meeting of the European Society of Anaesthesia, in Milan, Italy, demonstrating utility of the FORE-SIGHT Absolute Cerebral Oximetry technology in monitoring during surgery and critical care. These studies were all conducted by Cathy S. DeDeyne, MD and her colleagues at the Department of Anaesthesia & Neurosurgery, Ziekenhuis Oost-Limburg, Genk, Belgium. Data from these early studies demonstrate that cerebral tissue oxygen saturation ($SctO_2$) provided clinicians with new information that can be used to manage patients in neuro-critical care. Applications include cerebral aneurysm surgery, craniotomy following acute intracerebral bleeding, endoscopic shoulder surgery, hyperthermic intraperitoneal chemotherapy (HIPEC), and carotid endarterectomy. In addition, three abstracts demonstrating the clinical utility of FORE-SIGHT were also recently presented at 2009 OUTCOMES in Barbados. These studies demonstrated a link between the use of absolute cerebral oximetry during aortic surgery and length of stay; clinical utility of cerebral oximetry in detecting desaturation events associated with patients receiving anesthetics in the beach chair position for shoulder surgery and the link between patient positional changes to total hemoglobin and cerebral tissue saturation. These studies were all conducted at Mt Sinai Medical Center in New York City… CASMED announced the **FDA 510(k) clearance** of its Medium (Pediatric) Sensor for use with the company's FORE-SIGHT Absolute Cerebral Oximeter. The Medium Sensor is the latest in the FORE-SIGHT family of absolute cerebral oximeter sensors. This new product is indicated for use on patients weighing between 4kg and 80kg. CASMED plans a limited release of the Medium Sensor in April to select customers, with full commercial release scheduled for the end of Q2. Along with the original Large (Adult) Sensor and the Small (Neonatal/Infant) Sensor released last year, the FORE-SIGHT sensor line now covers the full range of patient populations in the hospital. The target markets for the Medium Sensor are in the areas of pediatric intensive care, pediatric cardiovascular OR and cardiovascular intensive care…. The FORE-SIGHT Absolute Cerebral Oximeter offers a new, sophisticated approach to cerebral oximetry with its patient-tailored algorithms. Only the FORE-SIGHT Absolute Cerebral Oximeter incorporates age and weight into its advanced algorithms to account for brain and head development stages. This exclusive approach refines the sensor light path to optimally interrogate brain tissue, ensuring absolute accuracy. This represents another cerebral oximetry breakthrough from FORE-SIGHT Absolute Cerebral Oximeter. The FORE-SIGHT sensor kits now use less plastic with their new, smaller, recyclable package, leaving a reduced carbon footprint. Contact casmed.com.

PRODUCT REVIEW

Edi (Electrical Diaphragm Activity)—a new respiratory vital sign? The ability to measure the electrical activity of the heart with an electrocardiogram (ECG) has been a standard of care for so long we take its importance for granted. Now, for the first time, the ability to measure the electrical activity of the diaphragm (Edi) is available for bedside use with MAQUET SERVO-i Ventilators. An Edi catheter, designed like a typical naso- or orogastric tube, incorporates 10 miniaturized sensors. The Edi catheter enables the clinician access to the neural respiratory impulse, while providing feeding capability. The Edi directly reflects the neural input from the brain to the diaphragm (Sinderby C, Beck J. Proportional assist ventilaltion and neurally adjusted ventilatory assist—better approaches to patient ventilator synchrony? Clin Chest Med. 2008;29[2]329–342). Upon esophageal insertion the catheter relays electrical diaphragmatic signals to the SERVO-i ventilator where digital Edi values and waveform are displayed. With Edi monitoring capability, clinicians can confirm spontaneous breathing effort in all modes of ventilation. When Edi is used with NAVA mode (Neurally Adjusted Ventilatory Assist) the SERVO i can adapt ventilator output to the patient's own respiratory drive for improved synchrony. NAVA is the latest mode available with the MAQUET SERVO-i ventilator that uses the Edi signal to synchronize breath delivery providing pressure assistance in proportion to the Edi (Sinderby C, Navalesi P, Beck J, et al. Neural control of mechanical ventilation. Nat Med. 1999;5:1433–1436). Contact (888) 627-8383, maquet-inc.com.

FACILITY REPORT

Vapotherm's Newsletter reports: The NICU at Children's Hospital of Wisconsin, Fox Valley Campus is part of a state-of-the-art unit that was rated number 5 in the nation by Parents magazine. More than 700 infants with a wide variety of health and respiratory problems are cared for by Children's Hospital of Wisconsin each year. The NICU features private newborn bed spaces that are specially designed to care for the patient from admission to discharge, the ability to perform certain procedures at the patient's bedside, rooms that allow parents to practice caring for their baby before it goes home and an in-unit pharmacy with staff that is specially trained in the unique needs of the NICU. Daneen Klehn, RT, NICU Specialist, joined the department about two and a half years ago but she says that Vapotherm had already made its impact on the NICU long before she became a part of the team. Kehn favors Vapotherm technology for her patients because there is less equipment on the face of the baby and it is less invasive than CPAP. She also adds that when a patient is 28 weeks or older, she weans him off the ventilator to High Flow Therapy (HFT) within a 24 hour period. She does this because

she says she notices a difference right away when the babies are placed on HFT. "The babies seem more relaxed. It's as if they know the therapy will help them get better." The NICU currently has four to five Vapotherm 2000i units running on a daily basis. The department has trialed the Precision Flow and is eager to add more units to the floor.

BALANCED

The quest for optimal humidification is a balancing act. How do you deliver the right amount of humidity to maximize clinical outcomes without creating additional challenges? Introducing the ConchaTherm Neptune, the heated humidifier that has the flexibility to deliver the perfect balance. Featuring an adjustable airway temperature and gradient control, you can customize the therapy to maximize humidification, while minimizing challenges like circuit or interface condensation. Compatible with a wide range of circuits and accessories, the Neptune can be used across a broad spectrum of patients from neonates to adults and with therapies ranging from Invasive Mechanical Ventilation, to High Flow Nasal Cannula Therapy, to Non-Invasive Ventilation. To find out how the ConchaTherm Neptune can help you achieve the perfect humidification balance call (866) 246-6990 or contact teleflexmedical.com.

SPOTLIGHT ON VENTILATION

INSPIRATIONAL

eVent Medical's Inspiration ventilators are versatile, high performance ventilators designed with the clinician in mind. The patented Swiss pneumatic design allows high performance PSOL valves to provide outstanding breath delivery. Users find exceptional value in the straightforward interface, ease of transport, comprehensive monitoring and simple preventive maintenance. A unique capability within the Inspiration line is the built-in MiniWeb Server that allows display of all settings, monitoring and alarms on computers, hospital network or on the internet using standard hardware and Windows software. Practical advantages include standard battery, emergency backup compressor, integral nebulizer, Heliox and extreme ease of use. Contact event-medical.com.

HEY BABY

Your tiniest patients often present the biggest ventilation challenges. Dräger's Babylog 8000 plus serves the neonatal population with advanced features such as dynamic leakage compensation and volume guarantee for very low birthweight babies. With leakage compensation, ventilation is more reliable. Clinicians rely on the versatility of using both pressure and volume modes of ventilation—including the Babylog's pressure support volume guarantee mode of ventilation. Learn how you and your patients can benefit from Dräger's 100 years of ventilation experience—in the NICU and throughout the ventilation care process. Contact (800) 437-2437, draeger.com\respiratorycare.

HIGH FREQUENCY

The Bunnell Life Pulse High Frequency Ventilator provides improved oxygenation and ventilation of infants at lower mean and peak pressures than other high frequency or conventional ventilators. Jet pulse technology, passive exhalation, and a wide range of I:E ratios are the keys to achieving the lowest therapeutic pressures. The Life Pulse is easy to use, with only three control settings: PIP, Rate, and I-Time. All other functions are controlled automatically. Bunnell's LifePort adapter has eliminated the need to reintubate with a special endotracheal tube and the new WhisperJet inspiratory valve has significantly reduced noise levels. Call (800) 800-4358 for a trial evaluation. Contact bunl.com.

G-WHIZ

Ventilation may be required for the infant who is depressed, experiences apnea or during prolonged periods of respiratory failure. Inflammation caused by lung overdistension is thought to be important in the pathogenesis of bronchopulmonary dysplasia. Neonates with variable lung compliance are particularly at risk. The Hamilton G5 delivers consistent tidal volumes as low as 2cc with the goal of reducing lung damage. This lung protective ventilation can provide a safer means of ventilating the neonate. Proximal monitoring enables precise volume measurement. The Hamilton G5 provides ergonomically advanced features to help the clinician assess patient status. The Graphic User Interface simplifies the interaction between clinicians and the ventilator, thereby minimizing the chances of human error in ventilator management. The award winning user interface is scientifically proven to reduce workload and improve safety. Contact hamilton-medical.com.

PRODUCT CASE STUDY

The following information was provided by Philips.

Isabella Rivers is one of the 5,000-10,000 infants born annually with bronchopulmonary dysplasia. Born three months premature, Isabella weighed only one-pound, six ounces. She spent the first 11 months of her life in a hospital where she underwent a battery of procedures, including open-heart surgery to repair two holes in her heart. At 19-months, Isabella is a typical toddler even though she requires a ventilator and oxygen to support her breathing. To accommodate her curiosity and active nature, Isabella's father built a wheeled cart for the equipment. Isabella can take baths, easily get into the kitchen and is mobile within the house. When the family goes for walks or on errands, Isabella and her equipment ride in a double stroller. Right now, the oxygen tank and ventilator weigh almost as much as Isabella. Despite the challenges, Isabella's family is committed to her experiencing all that life has to offer. They recently took her to the beach so that she could play in the sand. The daily challenges of caring for a medically fragile child are immeasurable; simple, everyday tasks such as bathing and going for a walk or to the store can be difficult. Isabella's mother, Heather, feels that lighter, more simplified equipment would make their lives easier and help her daughter remain active. To meet such challenges, Philips introduced its Trilogy 100 portable at-home life-support ventilator. The versatile, lightweight 5 kg device is from Respironics, which introduced bi-level positive airway pressure for noninvasive ventilation nearly 20 years ago. Philips Respironics offers a broad range of clinically proven solutions intended to support breathing in the intensive care, sub-acute, and home care settings. Developed to meet the needs of a wide range of patients, Trilogy100 offers both volume- and pressure-control ventilation for adult and pediatric use with features intended to help caregivers and clinicians administer patient care in the home and alternative care settings through ease of use, versatility, and portability. Trilogy100 features Respironics' bi-level technology with advanced leak compensation, enabling the patient to receive

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Heliox Therapy— A Clinical Review for Neonatal Use

Justin Tse, BS, RRT

Airflow through the airways under normal conditions is laminar. Airflow through a constricted orifice or through an obstruction can be turbulent, causing increased airway resistance and air trapping. Heliox has been used in many institutions for the treatment of airway obstruction due to its inherent properties. Heliox is a mixture of helium and oxygen. Heliox has a density three times less than that of air and eight times less than that of oxygen. Because of these properties, heliox changes areas of turbulence into areas of laminar flow. Heliox has found its place in the neonatal intensive care unit. Heliox has been used with mechanical ventilation where the air supply is replaced with an 80/20 tank of helium and oxygen. The concentration of heliox can change based on the oxygen needs of the patient. Mechanical ventilation has been used frequently in the treatment of acute severe asthma and bronchiolitis.

A study by Migliori et al examined the effects of heliox before and after extubation in long term mechanically ventilated very low birth weight infants. In this study, Migliori enrolled ten preterm infants.

All patients were ventilated with synchronized intermittent mandatory ventilation (SIMV). All patients were stable before the inclusion in the study.

Each patient's pulmonary mechanics were recorded before heliox administration and one hour after heliox administration. Also monitored were patients' vital signs. Patients were then evaluated for extubation to BiPAP. Each patient was extubated to BiPAP of 9/5 (cmH_2O), rate of 30 bpm, and Ti of 0.5 seconds.

"Subjects with subsequent occurrences of apnea, clinical signs of severe respiratory distress, respiratory acidosis (pH ≤ 7.23; PCO_2 ≥ 65 mm Hg), or hypoxemia (PO_2 ≤ 50 mm Hg or O_2 saturation ≤ 85% with FIO_2 ≥ 0.40) were reintubated."

Migliori et al reported all ten (10) patients finished the study. They concluded that their "data show that mechanical ventilation with heliox support improves gas exchange in long-term ventilated preterm infants."

This article was provided by Hamilton Medical.

An assessment of the patient must be done to determine the effectiveness of heliox therapy.

The benefit of heliox should be immediate. If no benefit occurs within thirty minutes of start, heliox therapy should be stopped.

Today, heliox is becoming an important part of the medical arsenal. Clinicians need to know the properties of heliox and how these properties interact with physiology. As technology advances and our understanding of disease processes improve, heliox has taken its role as a standard in the treatment of many disorders. I have included studies below for regarding information on heliox and its role in medicine.

Information On Heliox

1 The Effects of Helium/Oxygen Mixture (Heliox) Before and After Extubation in Long-term Mechanically Ventilated Very Low Birth Weight Infants. Claudio Migliori, Paolo Gancia, Elena Garzoli, Vania Spinoni and Gaetano Chirico. Pediatrics 2009;123;1524-1528
2 Comprehensive Perinatal and Pediatric Respiratory Care. K.B. Whitaker. Chapter 7,565-566, 2001.
3 Heliox therapy in acute severe asthma. Kass, JE and Castriotta, RJ. Chest Vol 107, 757-760. 1995
4 Room Air Entrainment During {beta}-Agonist Delivery With Heliox. S. Dhuper, S. Choksi, S. Selvaraj, G. Jha, A. Ahmed, H. Babbar, B. Walia, A. Chandra, V. Chung, and C. Shim, Chest, October 1, 2006; 130(4): 1063 - 1071.
5 I. K. Kim, E. Phrampus, S. Venkataraman, R. Pitetti, A. Saville, T. Corcoran, E. Gracely, N. Funt, and A. Thompson. Helium/Oxygen-Driven Albuterol Nebulization in the Treatment of Children With Moderate to Severe Asthma Exacerbations: A Randomized, Controlled Trial Pediatrics, November 1, 2005; 116(5): 1127 - 1133.
6 J. M. Haynes, R. J. Sargent, and E. L. Sweeney. Use of Heliox to Avoid Intubation in a Child With Acute Severe Asthma and Hypercapnia Am. J. Crit. Care., January 1, 2003; 12(1): 28 - 30.
7 Helium oxygen mixtures in the intensive care unit. Jean-Claude Chevrolet. Crit Care. 2001; 5(4): 179-181. Published online 2001 July 13.

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Maternal Care in Rural China: A Case Study from Anhui Province

Zhuochun Wu, Kirsi Viisainen, Xiaohong Li, Elina Hemminki

Abstract

Background: Studies on prenatal care in China have focused on the timing and frequency of prenatal care and relatively little information can be found on how maternal care has been organized and funded or on the actual content of the visits, especially in the less developed rural areas. This study explored maternal care in a rural county from Anhui province in terms of care organization, provision and utilization.

Methods: A total of 699 mothers of infants under one year of age were interviewed with structured questionnaires; the county health bureau officials and managers of township hospitals (n = 10) and county level hospitals (n = 2) were interviewed; the process of the maternal care services was observed by the researchers. In addition, statistics from the local government were used.

Results: The county level hospitals were well staffed and equipped and served as a referral centre for women with a high-risk pregnancy. Township hospitals had, on average, 1.7 midwives serving an average population of 15,000 people. Only 10–20% of the current costs in county level hospitals and township hospitals were funded by the local government, and women paid for delivery care. There was no systematic organized prenatal care and referrals were not mandatory. About half of the women had their first prenatal visit before the 13th gestational week, 36% had fewer than 5 prenatal visits, and about 9% had no prenatal visits. A major reason for not having prenatal care visits was that women considered it unnecessary. Most women (87%) gave birth in public health facilities, and the rest in a private clinic or at home. A total of 8% of births were delivered by caesarean section. Very few women had any postnatal visits. About half of the women received the recommended number of prenatal blood pressure and haemoglobin measurements.

Conclusion: Delivery care was better provided than both prenatal and postnatal care in the study area. Reliance on user fees gave the hospitals an incentive to put more emphasis on revenue generating activities such as delivery care instead of prenatal and postnatal care.

Authors Wu and Li are with the Department of Health Statistics and Social Medicine, Fudan University School of Public Health, Shanghai; Wu is also with the Department of Public Health, University of Helsinki, Helsinki, Finland; Li and Hemminki are with the National Research and Development Centre for Welfare and Health (STAKES), Helsinki, Finland.
The authors wish to thank Haifeng Xu, Rengui Zhang, Ying Wang for their contribution to the data collection. Reprinted from BioMed Central, BMC Health Services Research, For references, go to BioMed Central on the internet and type the full title of the article.

Background

The appropriate care of pregnant women during the prenatal, delivery and postnatal periods in order to identify risks of adverse events for both the women and their fetuses or newborn children (ie maternal care), is considered a priority in most healthcare systems. In China, a systematic maternal care program was introduced in the 1980s and its utilisation and outcomes have been the target of many studies. However, only a few of these studies are in English. The studies showed that the utilization of maternal care increased and that perinatal and maternal health indicators have improved since the early 1980s.

The results of national household surveys showed that the proportion of pregnant women with the first prenatal care visit before 13 weeks of gestation increased from 19.9% to 58.1% and hospital delivery rate increased from 37.6% to 73.7% between 1993 and 2003. According to the results of national maternal and infant mortality surveillance, maternal mortality rate (MMR) fell from 94.7 to 53.4 per 100000 live births between 1989 and 2000 and infant mortality rate (IMR) decreased from 37.9 per thousand live births in 1982 to 32.5 per 1000 in 1998. In the study province MMR fell also from 62 to 50 per 100,000 live births and IMR decreased from 33 to 29 per 1000 live births between 1995 and 1999.

However, socioeconomic and geographic inequalities have remained. There were great differences in the use of maternal care between richer and poorer regions and between urban and rural areas, as well as in maternal and infant health status. In 1997, in urban areas, women had on average 6.4 prenatal visits in comparison to 3.2 visits in rural areas. Furthermore, while 92% of urban women gave birth in hospitals and 61% attended postnatal care, only 41% and 50% of rural women did so, respectively.

Table 1: Timing of first prenatal care visit.

Parity	No visit	< = 12 weeks	13–27 weeks	> = 28 weeks	Total
1 (n = 450)	8.7	44.2	45.1	2.0	100.0
2+ (n = 139)	10.1	44.6	43.2	2.1	100.0
Parity unknown (n = 110)	10.9	43.6	43.6	1.8	100.0
Total	9.3	44.2	44.5	2.0	100.0

In 2000, MMR in urban and rural areas were 28.9 and 67.2 per 100,000 live births. MMR in richer east coast area was below 21.2 while in poorer remote west the MMR reached as high as 114.9 per 100,000 live births. IMR in urban and rural areas was 25.8 and 37 per 1,000 live births respectively. Provincial or county level studies have showed that the reported MMR and IMR from census or surveillance data were underestimated and that the underreporting rate varied: that of MMR from less than 10% to about 30% while that of IMR from 10% to 50%. No nation-wide study has been done to evaluate the quality of the data.

The studies on prenatal care in China have focused on the timing and frequency of prenatal care and relatively little information can be found on how maternal care has been organized and funded, and the actual content of the prenatal visits, especially in the less developed rural areas. The purpose of the study is to explore maternal care in rural China in terms of care organization, provision, and utilizations.

Methods

The study was conducted in a rural county of 900,000 people in Anhui province, in eastern China. The total area of the county is almost 3,000 square kilometres, mostly of flatland. The majority of the population of the county is engaged in farming. In terms of national GDP rankings, the study county is typical of less developed rural areas in China. This paper is based on the experiences of a community-based randomised control trial on prenatal care. Twenty townships (10 interventions and 10 control) out of a total of 55 were selected—on the basis of having sufficient health facilities and staff—for a controlled trial on the introduction of systematic prenatal care in the area. The purpose of this randomized trial was to evaluate the effects of prenatal care on infant and maternal outcomes in the specific context of rural China, as well as to describe the process of conducting such a trial using community resources. This paper is based on the knowledge, attitudes and practices survey (KAP survey) data from the 10 townships used as controls. In addition, the data of the interviews of local government officials, interviews of healthcare managers, observations of service providers and local government statistics were used.

Table 2: Frequency of prenatal care visit by parity and place of delivery (%).

	0	1–4	5+	Total
Parity				
Parity 1 (n = 450)	8.7	37.6	54.4	100.0
Parity 2+ (n = 139)	10.1	36.2	54.3	100.0
Parity unknown (n = 110)	11.8	30.0	58.2	100.0
Total (n = 699)	9.0	36.1	54.9	100.0
Place of delivery				
County hospitals (n = 175)	7.9	35.4	56.7	100.0
Township hospitals (n = 438)	4.6	37.1	58.3	100.0
Private clinics (n = 65)	33.8	33.9	32.3	100.0
At home (n = 21)	38.1	23.8	38.1	100.0

Each township in the study county was administratively divided into 6–15 villages. About 10, 20 and 30 percent of villages in ten control townships were randomly selected to be surveyed in October- December in 2001, 2002 and 2003, respectively. All women who had given birth within 12 months prior to the three KAP survey periods in these villages were approached for an interview. During that time, there were 722 women who were eligible for the study according to the records kept by the local family planning system.

In the villages, the mothers of infants aged 0–12 months were identified according to lists provided by the family planning system and were asked to participate in the interviews. The interview was conducted at the respondent's home and was based on a structured questionnaire. If the woman was not at home at the time of the survey, the father or some other family member responded on her behalf. Altogether, the survey gathered data on 699 (out of 722) women, 90% of respondents being the mothers themselves. Three percent of the sample did not provide useful data: 1 (0.14%) refused, 15 families (2.1%) were out of village, 7 (1.0%) for other reasons. Women with dead infants were not approached for interviews.

Interviewers were recruited among the local health workers in the townships. They were trained to conduct interviews by a researcher (Wu Z.) from Fudan University. The structured questionnaire used in the survey included 60 questions covering infant outcomes, women's knowledge and attitudes, and practices relevant to prenatal, delivery, postnatal care and health, including infant care and breastfeeding. Only the questions concerning prenatal, postnatal and delivery care were used in this particular study.

The director and vice director of the county health bureau, the directors of the county maternal and child healthcare station, the directors of the county hospital and the directors of the 10 study township hospitals were interviewed in their offices with a semi-structured questionnaire concerning the provision and organization of services, the characteristics of the township hospital, the availability of equipment and staff, the funding of the hospital and the level of providers' income in mid-2000 and mid-2003 by one of the researchers from Fudan University (Li X.).

Direct observations of care providers and facilities were done ad hoc by the researchers from both the Fudan University and the Finnish National Research and Development Centre for Welfare and Health (STAKES) during field visits and systematically by the field research assistant who observed the implementation

Table 3: Comparison of the recommendations from the government and the care reported by the women.

	MOH recommendation	% complying
Timing of first prenatal visit	Before 13 weeks of gestation	44
Frequency of prenatal care visit	At least 5 times	55
Frequency of postnatal visit	At least 3 time	0
Measure of blood pressure	Every time during 5 visits	54
Haemoglobin test	At least once during the visits	45
Education on maternal nutrition	After 28 weeks of gestation	77
Education on maternal health care	During the pregnancy	84
Education on baby care	During the pregnancy	73

of maternal care trial in all the study townships and reported her findings to the researchers regularly. The observation activities included site visits to all study township hospitals and family planning services stations, to all county level hospitals including maternal and child healthcare institutes, and to some randomly selected village family planning posts and health clinics. The observations covered study settings, activities, and services provided by both the healthcare and the family planning facilities. The field research assistant visited each township at least once every month between 2000 and 2003. The researchers from Fudan University visited each of the above-mentioned institutes at least once during 2000 and 2003. The researchers from STAKES visited a selection of townships every year between 2000 and 2003. Some births occurred in private facilities but the county health authorities did not allow the researchers to visit such facilities.

The statistics of health facilities and obstetrical staff were collected from the county health bureau. The document "Management method of systematic maternal care in rural areas" issued by the Ministry of Health of China in 1989 was used to compare the provision and utilization of maternal care in the study townships with the national norms. This document gives norms for the management of maternal care at village, township and county levels by healthcare providers and recommends the content, number and timing of prenatal and postnatal care and gives advices on the referral and delivery services; the 1989 version was the most recent one at the time of the study. The above mentioned document does not cover the issues of financing of maternal care or whether the care should be free for users. There were no official recommendations for the number of healthcare professionals per population.

Results

The public maternal care system in the study county, like the healthcare system in general, was organized into three levels of care: the county, township and village level. At the county level, secondary to tertiary obstetric care was provided at two general hospitals (the county hospital and the hospital of traditional Chinese medicine) and at one specialised hospital (the maternal and child healthcare station). These hospitals each had 100–300 beds, 2 delivery beds, and 10–15 obstetrical staff members.

Most delivery care was taken care of in township hospitals and most prenatal care services were provided by township midwives. Township hospitals had on average 1.7 midwives serving an average population of 15,000 people. All midwives were female, from 26 to 55 years of age (mean = 36.4) with experience ranging between one and 37 years. The majority (88%) had three years of training in nursing after junior high school (9 years) and an additional six months of midwifery training.

At the village level, there were small private clinics staffed by one or two village health workers with 2–3 years of general medical training. There was no limitation for private practitioners to provide prenatal and postnatal care by the county legislation. However, they were not permitted to provide delivery care according to the county health bureau, but as some 12% of all births occurred either at home or at private

Table 4: Content of prenatal care (%).

Content of prenatal care	Parity 1 (n = 450)	Parity 2+ (n = 139)	Parity unknown (n = 110)	Total (n = 669)
Blood pressure measurement				
During every visit	54	54	54	54
Sometimes	33	36	37	34
Never	13	10	9	12
Times of haemoglobin measurement				
0	57	58	44	55
1	30	32	38	32
2+	13	10	18	13
Ultrasound screening				
0	39	51	45	43
1	35	31	29	33
2	19	16	23	19
3+	7	2	3	5
Health education on nutrition given	77	71	84	77
Health education on baby care given	71	70	86	73
Health education on maternal care given	83	79	95	84

Table 5: Place of delivery by parity (%).

	County hospitals	Township hospitals	Private clinics	At home	Total
Parity 1 (n = 450)	27.9	59.7	10.0	2.4	100.0
Parity 2+ (n = 139)	21.2	63.7	10.9	4.3	100.0
Parity unknown (n = 110)	19.2	72.7	4.5	3.6	100.0
Total (n = 699)	25.0	62.7	9.3	3.0	100.0

clinics, some village health workers might have been involved. There was also a vast network of larger private clinics and individual practitioners in townships and cities, which were also not permitted by the county health authority to deliver babies, but may still have been involved in the births registered to have occurred outside of the public sector. If discovered to be involved in delivery care, the private practitioners would have been required to pay a fine. For the baby's family there were no consequences financially or in registering the baby.

The county level hospitals served as the referral centres for the township hospitals in the county. However, there were no formal regulations or guidelines on how the referral system should have worked. Referral to a higher level hospital depended on the individual midwife's professional judgment and on the clients' compliance. A referral was not mandatory even in critical conditions. However, women could freely seek care at the higher level hospitals if they wished and could afford the cost of travel and higher fees. Most women who went to county level hospitals did so without a formal referral.

In the study county, the county health bureau had little power over township hospitals, because township hospitals had, in the decentralisation process, become directly accountable to the township government. Some of the health bureau officials were health professionals, but that was not the case of the township's government officials.

In parallel there were three levels of family planning services: the county institute, the township service station and the village service post. The family planning institutes were in charge of implementing and supervising the national family planning policy by performing mandatory pregnancy tests regularly on all married women. The family planning staff also provided maternal care consultations and performed simple obstetric examinations during the routine pregnancy test sessions. Posters related to maternal care were hung on the walls of the family planning offices. In addition to family planning services, these facilities at the county and township level could also provide delivery services. The family planning activities were by law fully funded by the county and township government and were free for the users. However, families paid for delivery care provided by family planning services.

In the township and county hospitals, only 10–20% of the current costs were funded by the local government (by the township government and the county government respectively) and the hospitals collected user fees to balance their budgets. The staff's salaries were dependent upon the level of activity and thereby of fee income of the hospital. The midwives' income per month varied from 36.3 to 108.8 USD (mean = 74.7 USD).

The hospitals were able to determine the user fees on their own; however, prenatal care consultations were free in most township hospitals. Only one township hospital charged 0.36 USD for a consultation. The cost of an ultrasound test ranged from 1.81 to 3.63 USD (mean = 2.65 USD), the fee for urine and haemoglobin testing were from 0.48 to 1.21 USD (mean = 0.78USD), the fee for normal delivery were from 15.72 to 36.28 USD (mean = 24.91 USD) and Caesarean sections (at county level) cost from 133.01 to 145.10 USD (mean = 139.06 USD) respectively. Farmers' annual net income per capita in the study area was about 260 USD, which was very close to that of national level (266 USD) and a bit higher than that of the average of the whole study province (240 USD).

One township carried out a prepaid maternal care program which was organized by the township hospital and supported by the township government. In the prepaid maternal care program, the pregnant woman paid a lump sum of money to the township hospital for a package of systematic maternal care, including prenatal, delivery and postnatal care. If the child died during the delivery because of a midwife's mistakes, the hospital reimbursed some of the money back to the woman.

Each study township hospital had a midwifery department with two to five rooms with basic delivery care equipment. In the department, the midwives saw women for prenatal and postnatal appointments. Delivery rooms were basic rooms with a simple delivery bed; all had electric lights but only 40% had running water. Manual suction pumps for infant airway clearance were available in 30% of rooms. Only two delivery rooms in the study area were equipped with air conditioners (combination heater/cooler), most used charcoal for warming up the rooms in cold winter months when temperatures can drop to minus 2–6 degrees centigrade. A total of 80% of the township hospitals had an ultrasound machine and a technician to use it, but only 50% had a scale for weighing the mother during pregnancy. Basic laboratory equipment for urine and haemoglobin tests was available in 90% of the township hospitals. Only one township hospital had an operating room and a surgeon who could perform caesarean sections. No medical records were kept in six of the 10 study township hospitals. Individual prenatal care cards were used in two out of the 10 township hospitals.

The average age of the mothers interviewed was 26.3 years. 23% had two children, and very few of them had three or more. The great majority (87%) of the mothers were farmers. 79% of them had at least 6 years of education, 21% were illiterate or semi-illiterate (less than 6 years of schooling).

Most prenatal care took place in public facilities; but 15% reported having visited a private practitioner during pregnancy. The first prenatal visit took place on average at 15.7 gestational weeks (see Table 1). About half of the women had their first prenatal visit before 13 gestational weeks and 2% sought prenatal care only after 28 weeks of gestation. The timing of the first prenatal visit did not change with parity (Table 1).

The average number of prenatal visits was 5.2. More than half of the women interviewed had 5 or more prenatal visits during their last pregnancy. Some 9% of primiparous and multiparous women had similarly made no prenatal visits.

The reasons for not attending prenatal care were: felt the care was unnecessary or worthless (42%), lack of time (17%), transportation issues (15%), cost (4%), other reasons (4%), no reply (19%). The reasons given were similar among primiparous and multiparous women. Only 50% of women had received the recommended prenatal care in terms of timing, frequency and content. Blood pressure was measured on every visit for 54% of the women, 34% were measured on some occasions, and for 12% it was not measured at all. Hemoglobin measurement was performed once on 32% of women, more than once on 13% of women, and not at all on 55% of women. Ultrasound screenings during pregnancy were common: 58% had had an examination at least once. Over 70% of women received health education on maternal nutrition (77%), baby care (73%), maternal healthcare during pregnancy (84%) from midwives (Table 4).

Most of the women gave birth in public health facilities, but 12% of the women gave birth in a private clinic or at home (Table 5). A total 8% of deliveries were caesarean sections, of which more than 90% were performed in county level hospitals. There was an association between frequencies of prenatal visits and the place of delivery (Table 2). The women who delivered in public facilities had on average almost twice as many prenatal visits as the women who delivered in private clinic or at home. A total of 35% of women who delivered outside of public health facilities had not received prenatal care at all. In comparison, 5% of the women who delivered in public health facilities had not used prenatal care.

According to interviews of the township hospital managers and township midwives, most of the women left the hospital within 24 hours of the delivery; the women only made postnatal visits to the clinic if the baby or the woman herself was sick; none of the midwives made postnatal home visits.

Discussion

Prenatal care in the study area was generally available in every township: there was a midwifery department in every township hospital with at least one midwife, though the equipment was not always adequate. However, the public facilities and resources were under-used in terms of timing and frequency of prenatal care. Further, the content of care did not follow government recommendations: some simple procedures were not carried out, while prenatal ultrasound testing in pregnancy was becoming more frequent than might be medically necessary. The document "Management method of systematic maternal care in rural areas" issued by the Chinese Ministry of Health (MOH) stipulated that the pregnant women should have their first prenatal visit before 13 weeks of gestation and have at least 5 prenatal visits and at least 3 postnatal visits (within 42 days of delivery).

In the study area, only about half of pregnant women complied with MOH requirement on timing and frequency of prenatal care visit. Furthermore, no women complied with the recommended postnatal visits, either by women to clinics or by midwives to mother's homes. The Chinese recommendation for the frequency of postnatal visits was higher than that of WHO. Despite the low number of prenatal visits, hospital deliveries were common, the rate almost reaching the level of urban areas of China.

Given the local family planning policy—a farmer couple is permitted to have another child if their first child is a girl—and the son preference in the study area, it was surprising that there was no difference in the timing or number of prenatal visits or hospital deliveries by parity. Reported ultrasound screening was not more common in higher parities. To explain these findings, further data would be needed.

The proportion of pregnant women who had their first prenatal care visit before 13 weeks gestation in study area was lower than the average level for rural areas nationally (55%). The proportion of women who had more than 4 prenatal visits was a bit higher (55%) than the average level of rural areas (36%) at the same period of time.

The Ministry of Health (MOH) recommended that pregnant women with serious condition should be referred to county level hospitals. The MOH norms for systematic maternal care stipulated that the county, township, and village networks of prenatal care system should be set up by the local government, but did not state where the financial resources should come from.

According to the county regulation, private practitioners were not permitted to provide delivery services, but they could be involved in prenatal care. However, one in six women sought delivery care from private practitioners.

The Minister of Health recommended that the pregnant woman could take an ultrasound test after 28 weeks of gestation if medically necessary. It was very likely that many women received an ultrasound before 28 weeks of gestation because the study showed that as many as 58% of women had received at least one ultrasound scan.

Previous studies in many underdeveloped or poor rural areas of China have shown that expensive user fees, long travelling distances or a lack of transportation were the most important obstacles to gaining access to available prenatal care. In this study, the most important factor reported as a hindrance to prenatal care by the women was their lack of recognition of the importance of prenatal care. While a lack of time and transportation were mentioned as reasons for not seeking prenatal care, by the far the most important reason given was a perception of the uselessness and insignificance of prenatal care. Two possible reasons may explain this finding: either the women did not accept the importance of the prenatal care in preventing adverse events, or they recognized the importance but did not believe that the local health services could deliver care adequately. The lack of basic equipment in the health facilities supports the latter belief. Further the proportion of women who did not seek prenatal care was higher among those who gave birth in the private clinics. Some of these women might have wanted to have private delivery care because of the illegal status of their pregnancy. Due to the sensitivity of the family planning policy, this issue could not be directly discussed with the women.

The equipment in the prenatal care facilities in townships did not match the needs of good prenatal care. Rather it seems that investments in equipment were based on the ability to generate income for the hospital. In terms of providing prenatal care, weighing scales would be a priority as they are cheap, readily available in the market and important for the monitoring of

every pregnancy. In contrast, the ultrasound machine is of less importance at the primary care level: it is useful for a lesser number of patients and is more expensive. However, more township hospitals owned ultrasound machines than weighing scales and height-measuring equipment. Apparently, women were either encouraged to use the ultrasound machine, or the women asked for scans themselves.

The consultations were almost always free for pregnant women. There was little incentive to adequately equip hospitals for routine prenatal care as it generated no extra income for the hospital. Hospitals profit from laboratory tests and birth services, so these services were promoted by the hospital. The high hospital delivery rate may also be attributed to the "Healthy mother and well baby" campaign launched by the health-related international organizations such as WHO and UNICEF and supported by the Chinese Government since the early 1990s.

The Chinese Ministry of Health and local health authorities had set requirements for conducting prenatal care and recommendations for its content, but had not offered funding or guidance on how to fund preventive activities. If township hospitals conducted systematic maternal care with little or no payment, they would not generate enough income to support the hospital. In rural areas of a western province, a new Cooperative Medical Scheme has been initiated. It involves risk sharing among farmers, financed jointly by individual farmers and local and central government. If the scheme is extended to cover maternal care, it might be one solution to the current problems of financing prenatal care.

Because of the decentralization of state administration, policies or regulations from a high level of government have less impact on lower level government. In our study, this was seen in the lack of authority the county health bureau had over township hospitals. Their management decisions were made from an economic standpoint, rather than from a medical view; that is, balancing the income and expenses of the facilities was more important than complying with accepted medical recommendations and regulations. This management model has been questioned by many researchers, but is also still defended by some. From the point of view of the quality of healthcare, health policies should be supported with financing schemes that do not work against the intent of the policy.

Few studies describing maternal care in China in detail are published in English. This is the first paper aimed toward an international audience that explores the organization, provision and use of maternal care in rural China, while covering both service providers and users.

One drawback of the study is that only one county was studied, and the results may not be applicable to other areas. The second limitation of our study is that study townships were purposely selected and did not cover townships without a township hospital. The third limitation is that mothers with dead infants were not included in the study. The second and third limitations might result in overestimation of the maternal care use in the study county. For example, the hospital delivery rate in the townships without hospital might be lower than that in townships with a hospital. The number of stillborn children was small, and can not effect the study results much.

The fourth limitation is that even though our description covers various elements of maternal care, it still lacks important details, such as the detailed content of pre- and postnatal care. The interviews of the women were conducted by local health workers, which may have facilitated them because they came from the same area as the interviewees. However, women may have perceived that they represented health authorities, which might have decreased women's willingness to speak freely in interviews. We do not know whether this decreased the reliability of the results, and if so, to what direction.

Further, to do the study required collaboration with the county health officials. As a result, we were not allowed to visit or interview private practitioners, because the government officials thought this to give credit to that illegal activity; private provision of delivery care was declared illegal in the county. Studying private delivery care might have been interesting taking into account the differences in prenatal care usage between women delivering in private and public facilities.

Conclusion

Delivery care was better accepted by women and more systematically provided than prenatal and postnatal care in the study area. Reliance on user fees gave the hospitals an incentive to put more emphasis on revenue generating activities such as delivery care instead of prenatal and postnatal care.

Against the Odds

R. Holland

Summary
The history of the development of humidifiers as a necessary accompaniment to mechanical ventilation is a fascinating one. In New Zealand in the 1960s, Fisher and Paykel, an established importer of a variety of household appliances, launched into the design and manufacture of humidifiers following the requirements envisaged at that time for optimal use in the intensive care setting. This was a completely new venture for the company and led to the establishment of a separate Fisher and Paykel Health Care company for medical equipment manufacture, which has continued successfully to the present day.

The recent history of the Australasian manufacturing industry is not a happy one, and once-thriving companies with connections to anesthesia have failed for a variety of reasons.[1] Much more cheerful has been the success of two antipodean businesses, both of which have contributed significantly to anesthesia and intensive care.

Woolf Fisher and Maurice Paykel both descended from Jewish refugees fleeing from Czarist anti-Semitic persecution and had made New Zealand their final destination—perhaps because it was as far away from Russia as possible.

The families were to be linked by romance—Woolf courted and later married Maurice's sister Joyce—and then commercially in 1934 when they founded a company to import refrigerators, radios and washing machines.[2]

Fisher and Paykel complemented each other perfectly: Woolf the born salesman, extrovert and networker, Maurice meticulous and precise, with a streak of frugality. These talents saw them through the economic abyss of the Great Depression, during which no country was harder hit than New Zealand.

Steadily, the business grew and new products were added to their range—vacuum cleaners, record players, irons and toasters; until by the outbreak of World War II, Fisher and Paykel were the largest importers of household appliances in New Zealand. On one voyage, 75% of the cargo on the SS Mariposa from the US was consigned to Fisher and Paykel Ltd.

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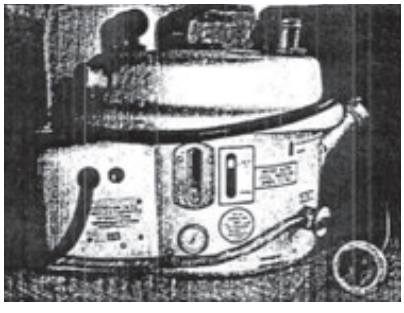
For a company so dependent on the importation of foreign goods, severe restrictions imposed by a nearly bankrupt government could have meant the end. No other threat could have been of such daunting magnitude, and Fisher and Paykel's survival was almost miraculous. Yet in one respect the seeds of future greatness were germinating, because the ban on imported products forced Woolf and Maurice to consider either local manufacture or assembly, or both.

The outbreak of hostilities in 1939 emphasized the need for national self-sufficiency and later, the arrival of large numbers of American troops created another opportunity: the demand for ice-cream making machinery!

At the war's end, Fisher and Paykel were well placed to take advantage of the pent-up domestic demand. A contract with Nash-Kelvinator to manufacture its refrigerators under license was followed by a similar deal with Bendix for washing machines. The company also ventured timidly into manufacturing its own wholly-local clothes dryers. From such a modest beginning, the capability which would enable the company to enter the healthcare business started to grow.

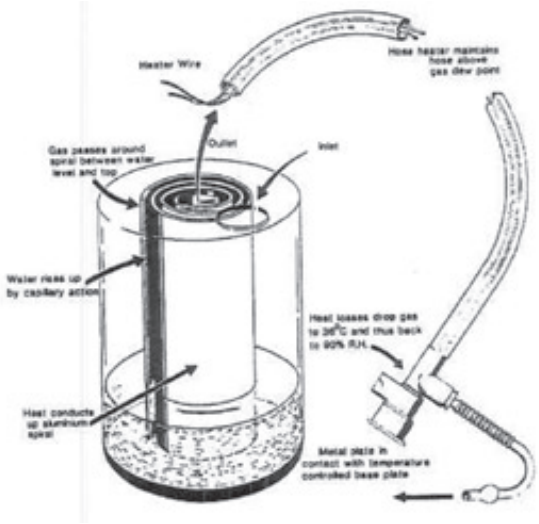
In the 1960s, intensive care in Australia and New Zealand was dominated by the imposing, albeting controversial, personality of Matthew Spence,[3] whose expertise in mechanical ventilation was unexcelled. His early appreciation of the need to humidify inspired gases was frustrated by the deficiencies of commercially available humidifiers, based as they were, for the most part, on modified pressure-cooker designs.

Spence was therefore very receptive to the device based on a new principle—the brainchild of Alf Melville, at that time

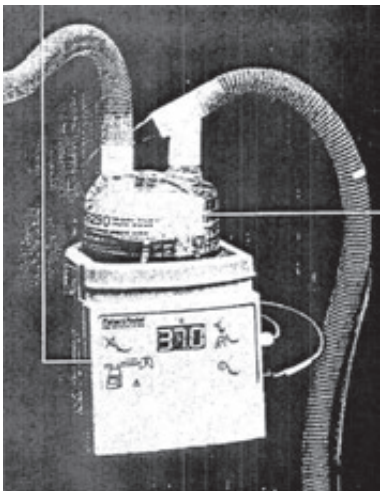


Typical example of the "modified pressure cooker" type humidifier, which was less than satisfactory.

The "Jam-Jar."



A new principle for humidifiers.



The MR850a—an early production model.

Dave O'Hare with the first prototype humidifier.

working for the New Zealand Government's Department of Scientific and Industrial Research.[3]

Actually, Melville had already been introduced to the arcane world of high-tech medicine and surgery via Brian Barratt Boyes' Cardiothoracic Unit at Green Lane Hospital, Auckland, so he was not intimidated by Spence's request that he turn his attention to the problems of humidifiers, especially that of "rain-out," was a major curse of all existing devices at that time.

Melville's elegant solution, a heating element in the inspiratory limb of the breathing circuit, plus a feedback control of temperature and moisture content—actually met the need for a fail-safe heating system as well. His experimental prototype—the famous "Jam Jar"— now resides at the Fisher and Paykel head office in Auckland.

It was Woolf Fisher's networking which created the link between Fisher and Paykel and the Department of Scientific and Industrial Research, since Woolf was a friend of Jack Brooke, Director of Industrial Development in the department. He also knew the Chairman of the Auckland Hospital Board, so that the company was already taking an interest in medical devices.

It was into that fertile soil that Alf Melville's throwaway line fell when he mentioned the device he was developing with Matt Spence. Within a fairly short time a pre-production version was ready, but this was only the beginning of a complex process of refinement which tried the patience of Woolf Fisher, who threatened the more patient Maurice Paykel with the following outburst: "Any more money for this humidifier and it had better be yours."

Maurice had realized that the development of a medical device on which lives of very sick patients would depend was a lot more complicated than debugging an automatic washing machine. But eventually the humidifier which came to dominate the market was ready, allowing Spence and Melville to submit their paper to Anesthesiology, describing this ground-breaking apparatus.

It is not clear just when the concept of continuing research and development was adopted to keep the humidifier ahead of the competition, but more and more user-friendly improvement such as the single-use ("disposable") chamber were incorporated into the original design.

The company's sales personnel now had access to the specialist community in hospitals, namely the anesthetists and intensivists, and were encouraged to seek other opportunities for the company in the healthcare field. The emerging subspecialty of sleep apnea attracted their attention, with the realization that humidification of the positive pressure devices used to treat this condition would be a considerable advance.

By now Fisher and Paykel had a large staff with expertise in large-scale plastics manufacture and sterile packaging, ensuring the company's ability to compete in the huge North American market. Within a relatively short time, 80% of Fisher and Paykel's output of medical devices was exported, mostly to the USA. With an annual turnover of $190 million, the time had come for healthcare to be hived off, so a new entity entitled Fisher and Paykel Health Care was floated as a public company, listed on both the Australian and New Zealand Stock Exchanges.

By then both Woolf Fisher and Maurice Paykel had gone, but the latter's descendants still play important roles in the business their ancestor had established 70 years ago.

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Neonatal High Pressure Hydrocephalus is Associated With Elevation of Pro-Inflammatory Cytokines IL-18 and IFNγ in Cerebrospinal Fluid

Deborah A. Sival, Ursula Felderhoff-Müser, Thomas Schmitz, Eelco W. Hoving, Carlo Schaller, Axel Heep

Abstract

Background: In human neonatal high pressure hydrocephalus (HPHC), diffuse white matter injury and gliosis predispose to poor neuro-developmental outcome. The underlying mechanism for diffuse white matter damage in neonatal HPHC is still unclear. Analogous to inflammatory white matter damage after neonatal hypoxemia/ischemia, we hypothesized that pro-inflammatory cytokines could be involved in neonatal HPHC. If so, early anti-inflammatory therapy could ameliorate white matter damage in HPHC, before irreversible apoptosis has occurred. In HPHC and control neonates, we therefore aimed to compare cerebrospinal fluid (CSF) concentrations of IL18, IFNγ and sFasL (interleukin 18, interferon gamma and apoptosis marker soluble-Fas ligand, respectively).

Methods: In neonatal HPHC (n = 30) and controls (n = 15), we compared CSF concentrations of IL18, IFNγ and sFasL using sandwich ELISA. HPHC was grouped according to etiology: spina bifida aperta (n = 20), aqueduct stenosis (n = 4), and fetal intra-cerebral hemorrhage (n = 6). Neonatal control CSF was derived from otherwise healthy neonates (n = 15), who underwent lumbar puncture for exclusion of meningitis.

Results: In all three HPHC groups, CSF IL18 concentrations were significantly higher than control values, and the fetal intracranial hemorrhage group was significantly higher than SBA group. Similarly, in all HPHC groups CSF-IFNγ concentrations significantly exceeded the control group. In both HPHC and control neonates, CSF FasL concentrations remained within the range of reference values.

Conclusion: Independent of the pathogenesis, neonatal HPHC is associated with the activation of the pro-inflammatory cytokines (IL-18 and IFNγ) in the CSF, whereas CSF apoptosis biomarkers (sFasL) were unchanged. This suggests that anti-inflammatory treatment (in addition to shunting) could be helpful to preserve cerebral white matter.

Background

Since the introduction of innovative drainage valves and third ventricular endoscopy, neurosurgical treatment strategies for neonatal HPHC have improved. Nevertheless, HPHC is still associated with irreversible white matter damage and adverse neurological outcome.[1-4] After hypoxemia/ischemia, white matter damage consists of a diffuse, inflammatory pattern involving pro-inflammatory cytokines, oligodendrocytic injury, gliosis and myelin loss.[5-7] Pro-inflammatory cytokines are biologically active proteins produced by T cells, astrocytes and microglial cells. After cytokine release, immune cells invade the brain and subsequently activate astrocytes and microglial cells, which results in apoptosis and gliosis.[5-8]

Especially, the immature central nervous system is vulnerable for inflammatory damage. This is attributed to the specific sensitivity of immature oligodendrocytes for microglial cells, glutamate and free radicals.[9-10] Although shunting will improve cerebral perfusion and prevent gliosis,[11] shunting does not address inflammatory consequences. Thus, long-acting cytokines (released before shunting), could theoretically continue to damage oligodendrocytes after shunting.[6,12] In the neonatal CNS, inflammatory mechanisms may contribute to diffuse white matter damage not only in the periventricular regions, but also at a distance from the ventricles.[9] Hypoxemia/ischemia is associated with cytokine IL18 release and cystic white matter damage.[6] Cytokine IL18 can induce other pro-inflammatory cytokines, such as IFNγ, IL-1β and TNFα.[13] In contrast to elevated CSF IL18 concentrations which last for months, IL-1β and TNFα concentrations are only elevated for hours.[14-15] This may explain our previously reported negative association between CSF IL-1β concentration and cystic white matter damage.[6] Cytokine IFNγ is also involved in the regulation of the

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inflammatory response by activation of cytotoxic T-cells and macrophages.[16] Upon activation, this may result in apoptosis, myelin loss and gliosis.[5,12,17-20] In neonates with post-hemorrhagic hydrocephalus and cystic white matter damage, we have subsequently shown that enhanced growth factor concentrations (i.e. vascular endothelial growth factor (VEGF) and transforming growth factor β1 (TGF-β1)) will finally reflect tissue repair.[21,22]

In this perspective, we hypothesized that hypoxemia/ischemia-related up-regulation of longer acting cytokines (IL18 and IFNγ) could be involved in neonatal white matter damage by HPHC. If cytokines are involved in ongoing white matter damage, early anti-inflammatory therapy could be beneficial, before irreversible apoptosis has occurred. The apoptosis biomarkers Fas and Fas-ligand (FasL) are members of the tumour-necrosis factor super family. The death Fas (CD95/Apo-1) is located on the cell surface. It plays a pivotal role in transduction of the apoptotic cell death program. Fas and its FasL exist in membrane bound form and soluble forms and can be detected in neonatal CSF.[23] Soluble FasL (sFasL) is expressed on activated T cells and released by metalloproteinase. SFasL can regulate extracellular apoptosis by pro- and anti-apoptotic properties. Expression of sFasL indicates ongoing apoptosis.

In neonatal HPHC characterized by progressive ventriculomegaly and increased head circumference > P_{75}, and control patients, this study aimed to determine and compare CSF IL18, IFNγ and sFasL concentrations. We hypothesized that CSF IL-18 and IFNγ concentrations are increased in HPHC, irrespective of underlying etiology. To investigate this, HPHC patients were grouped according to three different aetiologies: spina bifida aperta (SBA), aqueduct stenosis, and hydrocephalus after fetal intra-cranial hemorrhage.

Methods

After informed consent by the parents, 30 HPHC and 15 control neonates were included. In neonatal HPHC, CSF was obtained during initial neonatal shunt surgery. Indications for shunting consisted of clinical signs for high intracranial pressure, bulging fontanel, widening of the sagittal suture, progressive ventriculomegaly and increased head circumference (> P_{75}). Since anaesthesia, artificial respiration and internal pressure compensation may quantitatively influence the assessment of intracranial pressure, CSF pressure was not measured routinely during shunt placement. Neonatal HPHC was grouped according to aetiology: SBA (n = 20; characterized by presence of meningomyelocele), aqueduct stenosis (n = 4); HC after fetal intra-cranial hemorrhage (n = 6). Selection of HC after fetal intra-cranial hemorrhage (i.e. hemorrhage 4–6 weeks before delivery) allowed avoidance of the potentially confounding influence by disintegration of platelets. The diagnosis of fetal post-hemorrhagic hydrocephalus was confirmed by prenatal ultrasound (ATL 500, 3.5 MHz transducer), postnatal ultrasound (Vingmed Vivid5, multi-frequency transducer (5–7.5–10 MHz crystals) and magnetic resonance imaging (Philips Healthcare, Best, Netherlands, 1.5 Tesla). Low risk neonates, undergoing lumbar puncture for exclusion of meningitis, served as controls (n = 15). Gestational ages in the three hydrocephalic groups and control group were similar, i.e. between 27–54 and 24–54 weeks, respectively. CSF samples obtained during shunt revisions, neonatal asphyxia and CNS infections were excluded. Cerebral infection was excluded by negative CSF cultures, cellular count, total protein concentration and by assessment of CSF-IL6 concentrations (in CNS infection, CSF IL-6 concentrations are increased). CSF-IL6 concentrations were measured by commercially available solid-phase enzyme-labelled chemiluminescent sequential immunometric assay on an Immulite analyzer (DPC Biermann, Bad Naunheim, Germany). All CSF IL-6 concentrations were within the normal range 5 pg/ml – 200 pg/ml (i.e. far below CSF IL-6 levels in newborns with bacterial ventriculitis).[24] Total CSF protein content varied between 0.1 – 2.5 g/l.

All CSF samples were immediately centrifuged and stored at -40°C for further analysis. CSF concentrations of IL-18 and IFNγ were determined by sandwich ELISA (R&D systems, Wiesbaden, Germany) according to the manufacturer's instructions. The sensitivity of the assay was 12.5 pg/ml for IL18, 8.0 pg/ml for IFNγ and 0.5 ng/ml for sFasL using Mab for coating and binding (clones 4H9 and 4A5).[6,23] The intra-assay coefficient of variation was 5.0% for IL18 and 4.7% for IFNγ. All ELISA 96-well micro titer plates were analyzed using a microplate photometer (Dynotech MR5000, Denkendorf, Germany). Neonatal control CSF sFasL data were derived from our previous study by application of the same analytical technique, performed by the same laboratory.[23]

Results

Irrespective of the underlying cause, IL-18 concentrations were significantly higher in HPHC neonates than in controls, median and range: SBA: 80 (23–232) pg/ml; aqueduct stenosis: 66 (55–226) pg/ml; fetal intracranial hemorrhage: 223 (103–406) pg/ml; controls: 12.5 (12.5–158) pg/ml. Each group was significantly higher than control, $p < 0.01$, and the fetal intracranial hemorrhage group was significantly higher than SBA, $p < 0.01$; figure 1A). Similarly, CSF IFNγ concentrations were also significantly higher in the three HPHC groups than in controls, median and range: SBA: 35 (12–139) pg/ml; aqueduct stenosis: 22 (15–28) pg/mL; fetal intracranial hemorrhage: 22 (17–56) pg/mL; controls: 8 (8–22) pg/ml. Each group was significantly higher than controls, $p < 0.01$; but not significantly different between the groups (figure 1B). In all three neonatal HPHC groups, CSF sFasL concentrations remained within control limits, < 0.5 ng/ml.[23]

Discussion

Under diverse cerebral pathological circumstances, both astroglial and microglial alterations may be involved in white matter damage and adverse neurological outcome. It is indicated that hydrocephalus-associated brain tissue compression can instigate proliferation of astrocytes and microglial cells resulting in gliosis.[11] This study has shown that irrespective of the underlying aetiology, early indications for HPHC (derived from concurring ventriculomegaly and macrocephaly) are accompanied by pro-inflammatory cytokine activation (IL-18 and IFNγ) with highest IL18 concentrations in post-hemorrhagic HPHC. Despite cytokine release into the CSF, the CSF concentrations of the apoptosis biomarker sFasL remained within control limits. These results are contrasted by our previous findings of high CSF sFasL concentrations in neonatal cystic white matter damage.[23] In the present study, normal CSF sFasL concentrations are explained by early assessment of CSF samples during the first shunt implantation and before cystic white matter alterations have occurred. All together in early neonatal HPHC, present data indicate that inflammation precedes irreversible apoptosis, which may provide a theoretical basis for early anti-inflammatory therapy (at about the time of first shunt implantation). In children with leucomalacia and post-hemorrhagic hydrocephalus, similar cytokine activation is

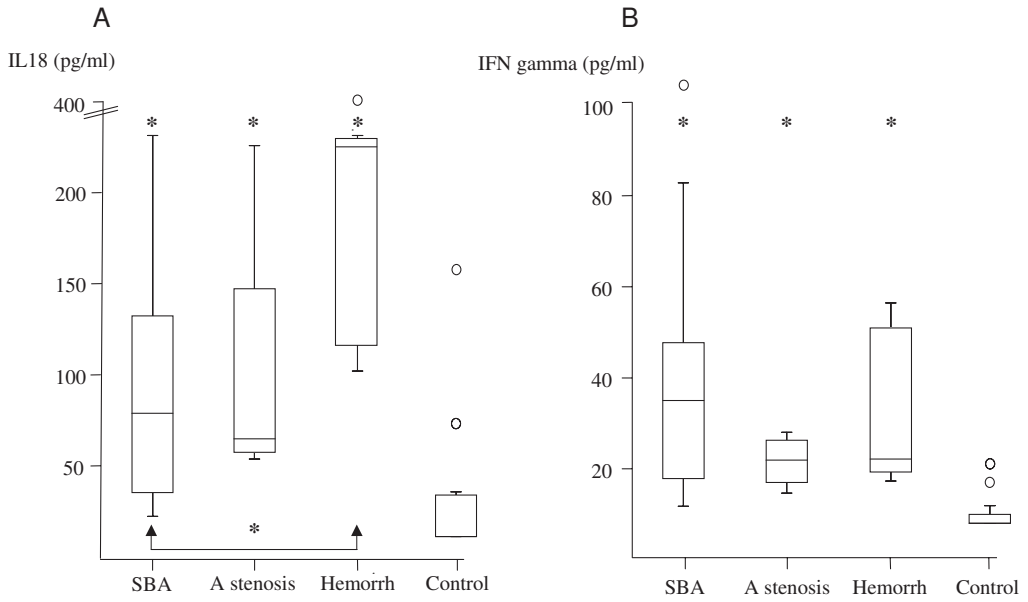

Figure 1. (A) Graphs of CSF interleukin-18 (IL-18) concentration and (B) CSF interferon gamma (IFN gamma) concentration in CSF from neonatal HPHC. The vertical axes indicate concentration (pg/ml). The horizontal axes indicates three different age-matched aetiologies for neonatal HPHC: spina bifida aperta (SBA), aqueduct stenosis (A stenosis), and fetal intracranial hemorrhage (Hemorrh) and neonatal controls (Control). Data are median and range plus 25th and 75th percentiles Encircled symbols in the figures indicate single parameters that appeared out of range. A: In all three neonatal HPHC groups, IL-18 concentrations were significantly higher than in controls (* $p < 0.01$). Furthermore, the fetal intracranial hemorrhage hydrocephalus group was significantly higher than the SBA hydrocephalus group (indicated by arrows at the bottom * $p < 0.01$). B: In all three neonatal HPHC groups, CSF IFNγ concentrations were significantly higher than in controls (* $p < 0.01$).

associated with a diffuse component of white matter damage, prolonged myelination delay (for months) and even permanent myelin deficiency.[5,6] From a neuro-pathological point of view, concurrent white matter lesions of varying appearance and age (acute, organizing and chronic) suggest various, ongoing insults in the same patient.[5] However, before these data can be extrapolated to all groups of neonatal HPHC, histological examination (by immunostaining) will be required. Analogous to pediatric HPHC, adult patients with normal pressure hydrocephalus and/or vascular dementia may also have elevated pro-inflammatory cytokine concentrations (TNFα) in association with white matter damage.[25,26] However, because of patient heterogeneity, age-specific cytokine sensitivity and variability in disease progression, it is not possible to speculate further about similarities in inflammatory involvement between ages.

In neonatal H-Tx rat (i.e. an animal model for congenital hydrocephalus by aqueduct stenosis), it was shown that shunting could ameliorate gliosis.[11] Since gliosis may be associated with both reactive astrocytosis and microgliosis, one would expect that anti-inflammatory therapy could have a beneficial effect in addition to shunting. Accordingly, it was shown that minocycline, a semi-synthetic second generation tetracycline with anti-inflammatory, anti-apoptotic and anti-glutaminergic properties,[27] reduces gliotic scarring in H-Tx rat.[28] Although minocycline is contra-indicated in young children, present human neonatal HPHC data suggest that other anti-inflammatory compounds could theoretically ameliorate diffuse cytokine-coupled, white matter damage.[11] In multiple sclerosis (characterized by up-regulation of pro-inflammatory cytokines), different anti-inflammatory agents (such as interferon beta (IFNβ) and glatiramer acetate) are known to ameliorate white matter damage.[29] Although there may be a rational basis for early neonatal (or perhaps even fetal) application of such anti-inflammatory compounds, potentially harmful adverse reactions should first be considered.

Conclusion

Neonatal HPHC irrespective of cause, is accompanied by pro-inflammatory cytokine activation (IL-18 and IFNγ) in the CSF. These data suggest that anti-inflammatory treatment (in addition to shunting) could be helpful to preserve cerebral white matter in these patients.

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The Use of Absolute Cerebral Oximetry in Cardiovascular Surgery

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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).[2,3,4] 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 $SctO_2 = 100\%* HbO_2 / (Hb + HbO_2)$.

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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 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 "snap shot" information about cerebral oxygenation, but cannot be used at the bedside. Since cerebral oximetry can provide an immediate indication of cerebral blood flow changes and 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.[48-54]

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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Table 1.

Patients	Mean Gestational Age	Mean Birth Weight	Mean Weight	Mean Postnatal Age	Mean Ventilator Days
10 (7 male, 3 female)	26.3 weeks	859g	1027g	22 days	22 days

Table 2.

Inclusion criteria for the study:
- PIP of > 21 Cm H2O
- Inspiratory time of ≥ 0.33 seconds
- IMV of ≥ 30 breaths per minute
- These parameters ensured Vt of 5 ml/kg and a minute ventilation of ≥ 200 ml/kg/minute.
- Maximum FiO2 was 0.40 (mean FiO2 0.33 during mechanical ventilation phase of test).

Table 3.

Spontaneous Breathing Patients	Mechanically Ventilated Patients
1. Decreased use of accessory muscles	1. Decreased wheezing
2. Improved air entry by auscultation	2. Improved air entry by auscultation
3. Decreased wheezing or stridor	3. Lower PaCO2
4. Decreased respiratory rate	4. Decreased use of accessory muscles
5. Less dyspnea reported by the patient	5. Improved vital Signs
6. Improved vital signs	6. Lower auto-PEEP
7. Lower PaCO2	

The Impact on Neonatal Mortality of Shifting Childbirth Services Among Levels of Hospitals: Taiwan's Experience During the SARS Epidemic

Shi-Yi Wang, Sylvia H. Hsu, Li-Kuei Chen

The concentration of high-risk deliveries in a smaller number of advanced hospitals increases patient volume in neonatal intensive care units (NICUs), and leads to better outcomes for high-risk infants.

Abstract

Background: There is considerable discussion surrounding whether advanced hospitals provide better childbirth care than local community hospitals. This study examines the effect of shifting childbirth services from advanced hospitals (ie, medical centers and regional hospitals) to local community hospitals (ie, clinics and district hospitals). The sample population was tracked over a seven-year period, which includes the four months of the 2003 severe acute respiratory syndrome (SARS) epidemic in Taiwan. During the SARS epidemic, pregnant women avoided using maternity services in advanced hospitals. Concerns have been raised about maintaining the quality of maternity care with increased demands on childbirth services in local community hospitals. In this study, we analyzed the impact of shifting maternity services among hospitals of different levels on neonatal mortality and maternal deaths.

Methods: A population-based study was conducted using data from Taiwan's National Health Insurance annual statistics of monthly county neonatal morality rates. Based on a pre-SARS sample from January 1998 to December 2002, we estimated a linear regression model which included "trend," a continuous variable representing the effect of yearly changes, and two binary variables, "month" and "county," controlling for seasonal and county-specific effects. With the estimated coefficients, we obtained predicted neonatal mortality rates for each county-month. We compared the differences between observed mortality rates of the SARS period and predicted rates to examine whether the shifting in maternity services during the SARS epidemic significantly affected neonatal mortality rates.

Results: With an analysis of a total of 1,848 observations between 1998 and 2004, an insignificantly negative mean of standardized predicted errors during the SARS period was found. The result of a sub-sample containing areas with advanced hospitals showed a significant negative mean of standardized predicted errors during the SARS period. These findings indicate that despite increased use of local community hospitals, neonatal mortality during the SARS epidemic did not increase, and even decreased in areas with advanced hospitals.

Conclusions: An increased use of maternity services in local community hospitals occurred during the SARS epidemic in Taiwan. However, we observed no increase in neonatal and maternity mortality associated with these increased demands on local community hospitals.

Background

Regionalization of perinatal care, which links a tiered structure of facilities and refers women with high-risk pregnancies to a central facility with advanced technology and increased staff, has been established to improve perinatal health care and decrease neonatal mortality.[1-3] Studies have demonstrated that the relative risk for low birthweight infants in local community hospitals is significantly higher than that in advanced hospitals, ranging from 1.3 to 2.3.[4-6] Although the benefits of perinatal care for low birthweight infants in advanced hospitals are well established, the data on the outcome of infants of normal birthweight are still inconclusive.[7-15] The public considers advanced hospitals, with their sophisticated technology and equipment, safe places for both high- and low-risk deliveries because undetectable prenatal conditions can cause unexpected complications during childbirth. Even though several studies on low-risk pregnancy show no statistically significant difference in neonatal mortality rates between low technology facilities and advanced technology hospitals.[7-10] there is still evidence of increased risks for low-risk deliveries in local community hospitals.[11-15] For example, Heller et al. reported a more than three-fold risk of neonatal death in

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Table 1. Neonatal and maternal mortality of Taiwan Island, 1998-2004

	Neonatal mortality		Maternal mortality	
	Deaths	Rate (‰)	Deaths	Rate (‰)
1998	918	3.38	24	0.09
1999	980	3.45	24	0.08
2000	1,038	3.40	24	0.08
2001	865	3.32	18	0.07
2002	745	3.01	19	0.08
2003	624	2.75	15	0.07
2004	623	2.88	12	0.06

Data are extracted from Health and Vital Statistics of Taiwan 2004.

Table 2. Descriptive data on neonatal mortality, categorized by four-month periods: January to April, May to August, September to December, 1998-2004

	January to April		May to August		September to December	
	Number of Deaths	Rate (‰)	Number of Deaths	Rate (‰)	Number of Deaths	Rate (‰)
1998	304	3.32	318	3.59	292	3.25
1999	319	3.48	305	3.25	349	3.65
2000	322	3.41	356	3.65	355	3.19
2001	267	3.04	302	3.59	287	3.32
2002	240	3.05	271	3.41	229	2.62
2003	203	2.74	201	2.83	214	2.67
2004	189	2.74	213	3.16	211	2.70

small hospitals compared to large hospitals.[15] These inconsistent results have raised concerns about the impact of regionalization on the outcome of low-risk deliveries.

In Taiwan, the accreditation system classifies medical institutions into four categories: medical centers, regional hospitals, district hospitals and clinics. Medical centers and regional hospitals provide neonatal intensive care for high-risk pregnancies, while district hospitals provide premature observation care for mild-risk pregnancies. Ob-gyn clinics are run by obstetrics-gynecology specialists and provide medical care for women, including lowrisk child deliveries. In Taiwan, low-risk pregnant women are allowed to seek services from medical centers without restrictions. During the 2003 SARS epidemic in Taiwan, the general population avoided seeking health care due to a combination of factors, including the vulnerability of health-care workers, and the rapid transmission of and limited knowledge about the disease.[16] In particular, people avoided seeking care from advanced hospitals (i.e., regional hospitals and medical centers) because SARS patients were being treated there. Therefore, expectant mothers began seeking maternity services at local community hospitals instead of at advanced hospitals to avoid becoming exposed to SARS.[17] This change in expectant mothers' preference of healthcare providers led to an increase of 7.1 % and 2.1% of the market share of total childbirth deliveries in clinics and in district hospitals, respectively.[17] Due to inconclusive evidence surrounding birth outcomes in local community hospitals, this large shift in childbirth services to local community hospitals has led to serious concerns about quality of care.[17] Therefore, this study undertook a population-based examination of neonatal and maternal mortality between 1998 and 2004 to investigate the impact of an increase in deliveries in district hospitals and clinics during the 2003 SARS epidemic.

Methods

The analysis was based on data from Taiwan's National Health Insurance annual statistics, which included detailed monthly and county maternal and neonatal mortality numbers. We retrieved the data from 1998 to 2004 to compare the impact of the shift in childbirth services during the SARS epidemic, which took place from May 2003 to August 2003.[17] Examining the data from the period after the SARS epidemic (ie, post September 2003) allowed us to rule out the effect of technological progress on the outcome of maternity services, which might mitigate the potential negative impact of the shift in treatment from May to August 2003. We applied an interrupted time-series design to analyze the effect of shifting childbirth services from one hospital level to another.

Both neonatal and maternal mortalities were analyzed to examine the impact of shifting hospital services on childbirth outcomes. For each county, monthly neonatal and maternal mortality rates were calculated; neonatal rates were determined by dividing the number of neonatal deaths by the number of childbirths, and maternal mortality rates were determined by dividing the number of maternity deaths by the number of childbirths. Because the small number of maternal mortality cases precludes a meaningful analysis, descriptive statistics are presented.

Linear regressions were estimated using data from the years 1998 to 2002 to examine the changes in neonatal mortality rates for the pre-SARS period. A total of 22 counties were included in the analysis. We excluded the data from three isolated islands with no advanced medical institutions and small populations because the expense of transportation in these locations may have prevented expectant mothers from voluntarily selecting advanced hospitals and little shifting would have occurred. Furthermore, the SARS patients were found only on Taiwan's main island.

The dependent variables were monthly county neonatal mortality rates; the independent variables included "trend," a continuous variable that measured for the effect of yearly changes, and two binary variables, "month" and "county," which controlled for seasonal and county-specific effects. With the estimation results, we calculated the predicted mortality rate for each month and county from 1998 to 2004. The differences between observed mortality rates and predicted mortality rates were standardized with the standard error of individual predicted values.

The data were managed with SAS software, version 9.1.3. All analyses were tested for a significance level by using a αvalue of 0.05. Because only secondary data are analyzed, no Institutional Review Board (IRB) approval is necessary.

Results

Figure 1 is adapted from Lee et al and shows the changes in childbirth services in hospitals of different levels.[17] Table 1 is adapted from Health and Vital Statistics of Taiwan 2004 and shows the number of neonatal and maternal deaths from 1998 to 2004. Neither the neonatal mortality rate nor the maternal mortality rate for the year 2003 was higher than for other sample years.

Table 3. The univariate statistics of standardized predicted errors of monthly county mortality rates

Panel A: Standardized predicted errors of monthly county mortality rates are based on the model based on the total sample during the years 1998–2004			
	SARS period (May-August 2003)	Pre-SARS period (January 1998-April 2003)	Post-SARS period (September 2003-December 2004)
Standardized predicted errors (95% CI)	-0.10 (-0.34–0.14)	-0.00 (-0.06–0.04)	-0.00 (-0.10–0.08)
Panel B: Standardized predicted errors of monthly county mortality rates are based on the model based on the sub-sample of areas with hospitals of more than 1,000 beds			
Standardized predicted errors (95% CI)	-0.42 (-0.74—0.11)	0.01 (-0.06–0.08)	-0.06 (-0.19–0.06)

To compare the mortality rates for the SARS period of May to August 2003 with the same months of other sample years, we aggregated the monthly mortality rates into a four month period. After the exclusion of the data from the three isolated islands, the number of childbirths from 1998 to 2004 was 1,798,369 and the number of neonatal mortality cases was 5,747. Table 2 shows a decrease in neonatal mortality rates over time, which did not increase during the SARS epidemic.

Using the analysis of a linear regression model based on pre-SARS observations, Table 3 summarizes the univariate statistics of predicted errors of monthly county mortality rates. We applied the standard error of an individual predicted value to obtain standardized predicted errors. The mean of standardized predicted errors of 22 counties during the SARS epidemic period (i.e., May-August 2003) is -0.10 (95% confidence interval: -0.34–0.14), which indicates that the predicted values are insignificantly different from the observed values during the SARS period. This result demonstrates that, despite an increased use of local community hospitals, neonatal mortality during the SARS epidemic was lower, even though the difference was insignificant.

We formed a sub-sample containing 12 counties where there were hospitals with more than 1,000 beds. The impact of shifting services would be greater in these areas because switching from one hospital level to another tends to occur more often there. The sub-sample presents a significantly negative mean of standardized predicted errors, (-0.42, CI (-0.74– -0.11)) during the SARS period. This evidence indicates that the neonatal mortality rate in areas with large hospitals was significantly lower than predicted, despite the shift of childbirth services to local community hospitals during the SARS epidemic.

With the aggregation of the county data from Year 1998 to Year 2002, we recalculated total neonatal mortality rates of the pooled data and estimated a linear regression model with "month" and "trend" variables. Table 4 presents the observed monthly mortality rates and predicted mortality rates of Year 2003, which provides the comparison of the predicted errors of four months before the SAS, of the SARS period and of four months after the SARS period. Similar to the results of monthly county mortality rates, the analysis of the aggregated data shows negative predicated errors during the SARS period of May 2003–August 2003. The aggregated data of counties with large hospitals demonstrates a significant predicted error in July 2003, which indicates that in counties with advanced hospitals of more than 1,000 beds, neonatal mortality was significantly reduced in July 2003, despite an increased use of childbirth services in local community hospitals.

Discussion

Normal birthweight or low-risk deliveries account for the majority of childbirth experiences. Although regionalized perinatal care is well-established for high-risk deliveries, it is crucial to examine the outcomes of normal birthweight deliveries in local community hospitals. The issue of whether high-technology hospitals provide better quality of care for normal birthweight deliveries than small maternity units has been examined extensively; however, the literature shows conflicting results regarding the outcome of normal birthweight infants in local community hospitals.[7-15] Due to these inconsistent results, the concern about quality of care as a result of the shifting of maternity services from advanced hospitals to local community hospitals associated with the SARS epidemic is understandable.[17] This study has shown that neonatal mortality during the SARS period did not increase. Hence, this evidence resolves the questions that Lee et al. raised about the impact of SARS on the shifting of childbirth services between hospitals of different levels.[17]

We assumed that the majority of the shifts in childbirth services during the SARS event involved low-risk deliveries. At present, the National Health Insurance (NHI) program of Taiwan provides ten free antenatal clinics, which help obstetricians in local community hospitals assess high-risk pregnancies that they are then required to refer to regional hospitals and medical centers. Furthermore, obstetricians in local community hospitals have also been referring these high-risk patients to medical centers more often, due to the legal concerns associated with the complications inherent in high-risk deliveries and the increased malpractice lawsuits in Taiwan. In addition, Lee et al.'s study of the impact of the SARS epidemic on childbirth shows a 2.2% increase in the cesarean section rate in medical centers, but no increase in the cesarean section rate in local community hospitals during the SARS period, which implies that the increased services provided by local community hospitals involved low-risk deliveries.[17] Therefore, our assumption that the majority of childbirth cases that shifted from high- to lower-level hospitals involved low-risk deliveries is reasonable.

Our results echo the results of similar studies that tracked the outcome of low-risk births,[7-10] but contradict predictions of a worse outcome for low-risk deliveries in local community or small hospitals.[11-15] A possible explanation for our findings of the similar outcome in both advanced and local community hospitals is that the analysis is based on the data of the most recent sample period, which is characterized by improved monitoring at local community hospitals. Frequent monitoring and quick detection thanks to more advanced technologies, such as bedside monitoring machines, have been allowing obstetricians

Table 4. Observed monthly mortality rates and predicted mortality rates based on the aggregated county data

Panel A: The aggregated monthly mortality rates of 22 counties

	Predicted mortality Rate (%) (95% CI)	Observed mortality rate (%)	Standardized predicted errors
Jan 2003	3.28 (2.11–4.45)	3.56	0.48
Feb 2003	3.04 (1.87–4.20)	2.86	-0.30
March 2003	3.01 (1.84–4.17)	2.09	-1.58
April 2003	2.79 (1.62–3.96)	2.45	-0.58
May 2003	3.39 (2.22–4.55)	2.97	-0.71
June 2003	3.54 (2.37–4.71)	3.45	-0.15
July 2003	3.23 (2.06–4.40)	2.24	-1.70
August 2003	2.86 (1.69–4.03)	2.70	-0.28
September 2003	3.28 (2.11–4.45)	2.60	-1.18
October 2003	2.97 (1.80–4.14)	2.98	0.01
November 2003	2.93 (1.76–4.10)	2.89	-0.07
December 2003	2.66 (1.49–3.83)	2.24	-0.72

Panel B: The aggregated mortality rate of 12 counties where contain hospitals with more than 1,000 beds

Jan 2003	3.04 (1.86–4.23)	3.31	0.45
Feb 2003	2.85 (1.67–4.03)	3.12	0.46
March 2003	2.95 (1.77–4.14)	2.14	-1.39
April 2003	2.70 (1.52–3.88)	2.41	-0.48
May 2003	3.34 (2.16–4.53)	3.25	-0.16
June 2003	3.70 (2.52–4.89)	3.13	-0.98
July 2003	3.25 (2.06–4.43)	1.82	-2.42
August 2003	2.98 (1.80–4.16)	2.50	-0.81
September 2003	3.26 (2.07–4.44)	2.43	-1.41
October 2003	2.98 (1.79–4.16)	2.64	-0.58
November 2003	2.87 (1.69–4.06)	2.42	-0.77
December 2003	2.55 (1.37–3.73)	1.97	-0.98

to take appropriate precautions and avoid complications. However, the results of studies concluding lower neonatal mortality rates in advanced or large hospitals than in local community hospitals sampled the birth data before 1999.[11-15] For example, using German data from 1990 to 1999, Heller et al found that birthweight-specific mortality rates were lowest in large delivery units and highest in smaller delivery units.[15] Similar findings were documented in the study with the Norwegian data from 1972 to 1995[14] and data from the United States in 1980.[13]

Research on birth settings for women with low-risk pregnancies often involves methodological challenges, such as small samples, non-random samples, differences between women who choose local community versus technology-advanced hospitals, confounding factors associated with inconsistencies in physician behavior, and data limitations.[18] This study applied a population-based approach to research the change in neonatal mortality during the increased use of local community hospitals associated with the SARS epidemic. The exogenous nature of the SARS event mitigates the problem of confounding factors as they relate to characteristics of expectant mothers and physician behavior among levels of hospitals. Issues surrounding non-random sampling are also moot because we used data on neonatal mortality for the entire newborn population in Taiwan between 1998 and 2004. Furthermore, this study's large sample size of 1,848 observations allows us to demonstrate clearly that the shifting of childbirth services among hospitals associated with the SARS epidemic did not increase the risk of neonatal deaths. In contrast, we found that the neonatal mortality rate decreased in areas that contained large hospitals which were more likely to incur the shifting of childbirth services. We acknowledge a limitation of this study that we did not directly measure neonatal mortality among hospitals because of data availability. Considering the small effect size associated with the impact of a 9.2% service shifting among hospitals, we recognize potential weak statistical power of our sample in concluding the outcomes of different hospitals. However, our result of the subsample with a larger shifting effect is robust against the concern of the impaired childbirth outcome associated with the shifting of childbirth services.

This study has important implications for public health policy; in addition to the improved outcome of perinatal care, regionalization of high- and low-risk deliveries leads to better allocation of health-care resources and cost savings for the health-care system. In response to the escalation of health expenditures, health planners can not only maintain quality of care, but also better allocate resources and minimize costs by encouraging the use of less expensive healthcare facilities for low-risk deliveries whenever possible. Regionalized perinatal care ensures that high-risk deliveries that require more sophisticated equipment and care are referred to technologically advanced hospitals. The concentration of high-risk deliveries in a smaller number of advanced hospitals increases patient volume in neonatal intensive care units (NICUs), and leads to better outcomes for high-risk infants.[19] Hence, regionalized perinatal care has efficiently allocated expensive resources of advanced hospitals to high-risk infants who are most in need of help and has provided better quality of care for these babies.

In acknowledging governmental budget constraints and the need for efficient allocation of health-care resources to enhance the quality of childbirth care, we emphasize the importance of routine antenatal screening services and a well-established referral system for high-risk pregnancies. This study shows that it is possible to successfully shift low-risk deliveries from advanced hospitals to local community hospitals without impairing childbirth outcomes. The shift allows for a more efficient use of resources because low-risk deliveries seldom need high-technological medical facilities, such as NICUs. In addition, the shifting of childbirth services to local community hospitals would likely reduce patient travel and wait times and, thereby, increase the accessibility of care. However, public perception that technologically advanced hospitals provide a safer environment in which to deliver can discourage low-risk expectant mothers from using local community hospitals. Policy makers should therefore encourage pregnant women to seek childbirth services in local community hospitals in combination with providing antenatal screening services and appropriate referrals.

Conclusions

Although it has not been documented conclusively whether or not advanced hospitals provide better care for normal birthweight deliveries than small maternity units,[7-15] this study has demonstrated that childbirth outcomes were not influenced by the shift in maternity services to local community hospitals

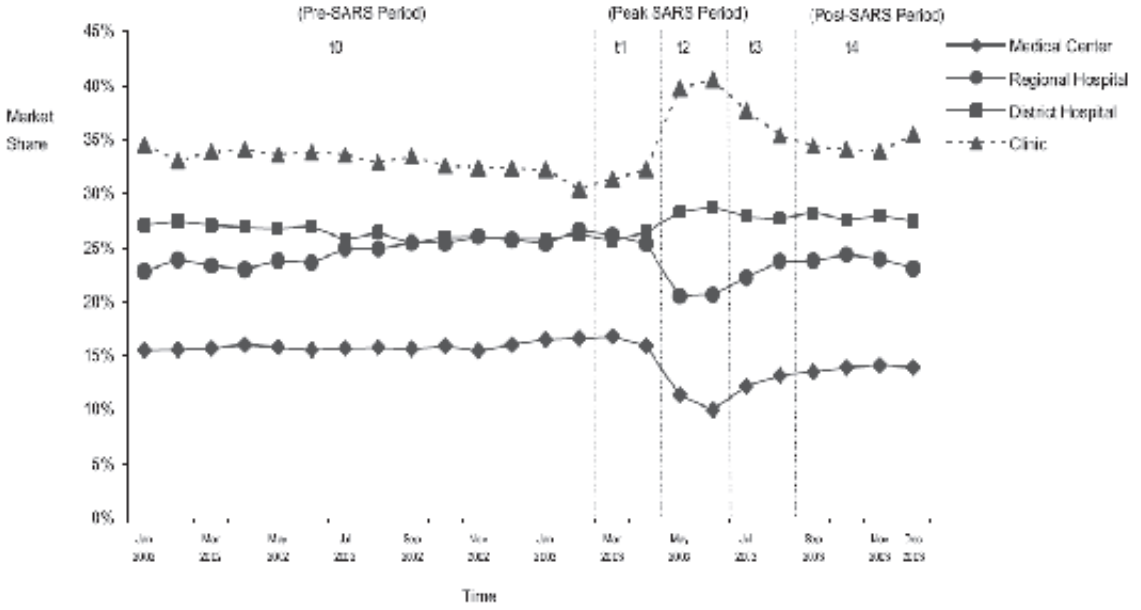

Figure 1. Trends in market shares of childbirth services in Taiwan by provider's level, January 2002-December 2003. Adapted from Lee et al. BMC Public Health 2005, 5:30-36.

during the SARS epidemic in Taiwan. There was no significant change in neonatal and maternity mortality associated with the increased services in clinics and community hospitals, implying that local community hospitals provide similar quality of maternity care for low-risk births as advanced hospitals. Therefore, this study offers a potentially cost-efficient strategy for public health planners by providing evidence that can be used to encourage low-risk expectant mothers to seek childbirth services in local community hospitals. The provision of antenatal screening services and the implementation of an effective referral system for high-risk deliveries must also be in place.

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Norovirus Infections in Preterm Infants: Wide Variety of Clinical Courses

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Abstract

Background: Norovirus is an important cause of nonbacterial acute gastroenteritis in all ages. Atypical courses are described. Clinical symptoms are diarrhea, vomiting, nausea, abdominal cramps, fever and malaise. Apart from three recent short reports we describe for the first time an outbreak of norovirus in a tertiary Neonatal Intensive Care Unit.

Findings: The typical symptoms of norovirus infection are in part also seen in premature born infants but with a different pattern and a huge variety of clinical courses. Vomiting is not the main symptom of norovirus infection in premature infants but distended abdomen and other symptoms such as apnea, gastric remainders or sepsis like appearance. The course in premature born patients could be explained by an immunocompromised mice model. Extensive hygienic measures were necessary to control the outbreak without closing the Neonatal Intensive Care Unit.

Conclusion: Norovirus infection in premature infants shows an impressive pattern of a wide variety of clinical courses. Only the consequent use of different hygienic pattern can lead to elimination of norovirus.

Background

Norovirus, belonging to the family of Caliciviridae, is a highly contagious virus and has been found to be one of the most important causes of nonbacterial acute gastroenteritis in all ages in developing as well as in developed countries.[1-3] While most of the outbreaks are known to have a seasonal pattern, sporadic cases of disease throughout the year are described.[4,5] Although outbreaks can occur in a variety of settings, semiclosed communities like hospitals are favoured.[6] Norovirus are transmitted through common sources such as food and water, person-to-person contact or airborne via aerosolized vomit whereas an extremely small dose of virus patricles (3-10) already can lead to infection.[7-9] Norovirus can be detected by ELISA as in this report, by RT-PCR or electron microscopy.

A lot of reports and studies about norovirus and its outbreaks exist covering a wide range of different areas and age groups with the few, typical clinical symptoms. Atypical courses of the disease are described in immunocompromised patients and persons under severe stress.[10,11]

Cause of this outbreak was a mother of a hospitalized preterm baby. She suffered from typical clinical signs of norovirus infection including acute diarrheal illness and was tested positive for norovirus shortly before the onset of clinical symptoms in our patients.

Apart from three recent reports dealing with norovirus outbreaks in premature infants we describe for the first time an outbreak of norovirus infections, its clinical course and control with extensive hygienic measures in a tertiary Neonatal Intensive Care Unit (NICU) affecting 11 infants over a period of two months showing an impressive pattern of a wide variety of clinical courses.[12,13]

Case Reports

Case 1

26 weeks of gestation, 760 g, on nasal CPAP, on day 14 acute severe worsening of the general condition, anemia, increasing oxygen demand, sepsis-like clinical appearance with increasing apnea followed by intubation and ventilation for 7 days, proof of norovirus for three weeks also in tracheal aspirate.

Case 2

26 weeks of gestation, 820 g, initial clinical course without complications, on day 34 sudden development of tachycardia, restlessness, distended abdomen and worsening of general condition, sepsis-like clinical appearance with tachypnea, thrombocytopenia and anemia, increasing oxygen demand. Proof of norovirus, later also rota- and astrovirus. Child developed necrotizing enterocolitis 2B° and underwent surgery with left sided hemicolectomy and ileostoma.

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Case 3
29 weeks of gestation, 1150 g, on day 5 acute worsening of the general condition, increasing gastric remainders, vomiting, distended abdomen, proof of norovirus.

Case 4
25 weeks of gestation, 740 g, increasing oxygen demand, recurrent severe apnea with bradycardia parallel to the detection of norovirus. Recurrent severe infection during a two month period with constant proof of norovirus shedding. No abdominal symptoms.

Case 5
32 weeks of gestation,
1. twin, 990 g, distended abdomen, on day 21 vomiting and distended abdomen, parenteral nutrition, proof of norovirus.
2. twin, 1900 g, distended abdomen, greenish—mucous stool with visible blood, norovirus suspected but not surely proven.

Case 6
29 weeks of gestation, 1170 g, distended abdomen, proof of norovirus.

Case 7
32 weeks of gestation,
1. triplet, 1780 g, on day 7 vomiting and distended abdomen for five days, proof of norovirus.
2. triplet, 1260 g, on day 8 acute worsening of the general condition, green gastric remainder, increasing oxygen demand, increasing apnea and respiratory insufficiency, then mucous stool with visible blood followed by colitis and coecostomy, capillary leak and multi organ failure, death on day 14. Norovirus not surely proven but proof of rotavirus.
3. triplet, 1480 g, on day 11 slight worsening of the general condition with pale marble like skin colour, gastric remainder, distended abdomen, stool with visible blood, no proof of norovirus.

Case 8
29 weeks of gestation, 1220 g, on day 4 slight gastric remainder with fresh blood, proof of norovirus infection

All different clinical symptoms are summarized in table 1.

Discussion

Norovirus has not been proven in all our patients but according to the case categories of the German Federal Health Office (Robert Koch Institute, Berlin) norovirus infection can be assumed in an outbreak with similar clinical courses, proof of norovirus and/or with an epidemiological connection.[14] Other similar definitions have been also used in defining norovirus outbreak.[15,16] Also the given sensitivity and specificity of ELISA tests can lead to negative results despite the presence of norovirus.[17] The test used at our laboratory was a commercial ELISA test kit (Ridascreen Norwalk like virus, R-Biopharm, Darmstadt, Germany).[18]

Two recent studies question the validity of enzyme immunoassays (ELISA) in norovirus infection and request RT-PCR instead.[12,13] It seems true that the currently available methods vary greatly in sensitivity, specificity and scope for the detection of norovirus.[17] RT-PCR was not available in our study but in a study by Duizer et al the sensitivity using ELISA increases with sufficient positive samples.[19] In another study by Rabenau et al. which compared ELISA, PCR and transmission electron microscopy it was shown that all three methods are useful.[20] The discrepancies seen can be explained by the different components each method detects. Even though PCR has the highest sensitivity a negative PCR would not necessarily exclude norovirus infection. Having a source with proven norovirus infection plus the typical clinical course in a mother of one of our hospitalised preterm babies and eight positive samples plus a much better sensitivity in our test kit we therefore see the results of our ELISA being sufficient to confirm norovirus outbreak in our patients.

General clinical symptoms of norovirus infection are described as diarrhea, vomiting, nausea, abdominal cramps, fever and malaise, whereas vomiting occurs more frequently in children and diarrhea more typically in adults.[14] The disease typically lasts one to four days, is self-limited and does not cause chronic infection. Shedding of human calicivirus can last for two weeks and younger children tend to shed for a longer period than older children.[21] Viruses can be detected in stool specimens of some children for a longer period without any signs for illness.[22]

Looking at the wide variety of clinical courses in our patients it becomes clear that gastrointestinal problems are the leading symptoms also in neonates (81.8%). According to Kaplan et al one should always consider norovirus infection in case of explosive vomiting in more than 50% of the patients, acute diarrhea for a period of 12 to 60 hours with an incubation period of 6 to 48 hours.[23] Given these criteria vomiting occurred in only 27% of our patients whereas 63% suffered from distended abdomen. None of our patients suffered from acute diarrhea and apart from abdominal distension only one third showed signs of a lower gastrointestinal tract involvement. A very recent study by Turcios-Ruiz et al described an outbreak of necrotizing enterocolitis caused by norovirus especially in small premature infants which supports our observation in case 2 and our assumption that case 7.2 suffered also from norovirus infection although the norovirus infection has not been confirmed in this case.[24]

During the outbreak all patients of the NICU received a regular screening for norovirus. We found no asymptomatic carriers in our patients.

In general pulmonary symptoms are often the first non specific sign for infection in premature born infants but interestingly these last longer in patients with norovirus infection. Given the immaturity of the immune system of the premature born organism it is surprising that in one case we nearly did not see any signs for infection whereas it is known that the susceptibility of human to norovirus infection is determined by allelic variation in human histo-blood group antigens (HBGA) as described by Huang and others.[25] Proof of norovirus in tracheal aspirate has not been described before (case 1 and 2) and was done in our cases as we initially could not explain the high increase of oxygen demand. Apart from a direct infection of respiratory mucosal cells it might be possible that external contamination could have led to a contamination of respiratory secretions and also microaspiration.

Currently norovirus is divided into 7 genogroups with more than 40 genetic clusters but many aspects of norovirus biology are not well understood.[26] The murine norovirus model system provides the first opportunity to understand the mechanism

Table 1: Clinical symptoms of all cases

	Case 1	Case 2	Case 3	Case 4	Case 5.1	Case 5.2	Case 6	Case 7.1	Case 7.2	Case 7.3	Case 8
Respiratory insufficiency	X								X		
Apnea/Tachypnea	X	X		X					X		
Additional oxygen	X	X		X					X		
Sepsis like	X	X									
Anemia	X	X									
Thrombocytopenia		X									
Tachycardia		X									
Gastric Remainders			X						X	X	X
Distended Abdomen		X	X		X	X	X	X		X	
NEC/colitis		X							X		
Vomiting			X		X			X			
Recurrent severe infections				X							
Blood stool						X			X	X	
Blood in Gastric Remainders											X
Skin colour										X	
Death									X		
Proof of Virus											
In stool	X	X	X	X	X	(?)	X	X	(?)		X
In tracheal aspirate	X	X									

and pathogenesis of the infection.[27] In this mouse model Karst et al. were able to show that severely immunocompromised mice lacking the signal tranducer and activator of transcription 1 (STAT1) had high levels of virus RNA in all organs examined. Also these mice had histopathological signs of pneumonia and loss of splenic architecture and severe liver inflammation after oral inoculation.[27] Seeing the premature infant as a "naturally" immunocompromised patient this observation might explain the wide variety of clinical courses.

One might only speculate whether a prolonged virus shedding and so related immune reaction may lead to a higher susceptibility to bacterial infection in premature born infants as seen in case 4 or whether it is only expression of an immunocompromised situation with an extended time for recovery.

A couple of problems are pathognomonic for NICUs worldwide: there is rarely a larger space between the incubators. The opening of a heated incubator is similar to an overpressurized chamber and will inevitabely lead to an airborne spread of particles. The frequent visit from parents and relatives and even smaller infants are highly supported to strengthen the bonding between the preterm infant and its family. This all can lead to a persistent and circulating infection especially in a semi-closed community as described earlier.[6]

Therefore only the consequent use of different hygienic pattern can lead to elimination of norovirus in such a setting. In our case it was wearing single use coats, gloves and surgical face mask whenever a patient was handled and increased use of norovirus active disinfectants as hand disinfection and on the ward (wiping of floor and surfaces especially around incubators). At the beginning we used a hand disinfectant which was recommend as highly effective on enveloped and non-enveloped viruses although not specifically tested against feline calicivirus (surrogate virus for norovirus) according to the Robert Koch Institute.[28] Its pharmaceutically active ingredients contain Ethanol 95.0 g (on 100 g, Sterillium Virugard, Bode Hamburg/ Germany). As we could not stop the outbreak herewith we changed to a new, ethanol reduced hand disinfectant: Manorapid Synergy (Antiseptica, Pulheim/Germany). Its pharmaceutically active ingredients contain 10 g 1-Propanol, 57,6 g Ethanol 96% with 0,7% phosphoric acid (on 100 g). This disinfectant produced a $\log_{10}$ reduction factor of 2.38 in testing against feline calicivirus compared to other disinfectants with increased ethanol content.[29] For floor disinfection Perform 1% (Schülke & Mayr, Norderstedt/Germany) was used which is an active oxygen based highly effective disinfectant containing 45 g Pentakalium bis(peroxymonosulfate)bis(sulfate) and has been tested as being effective against feline calicivirus.

All symptomatic patients underwent strict cohortation and care by dedicated nurses, who were not allowed to care for other patients and to leave that area during work. Relatives were

not allowed to get into personal contact with their babies or to perform "kangarooing" as long as we could prove shedding of virus.

With this hygienic management we were able to limit the disease and completely terminate it after two months (case 4).

Finally, although not in our case, it can be necessary to close a ward completely until the virus is eradicated. This "worst case scenario" leads to a loss of proceeds which was calculated by Lopman et al. as 1,01 million $ per 1000 hospitals beds.[30]

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Regional Perinatal Mortality Differences in the Netherlands—Care is the Question

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Abstract

Background: Perinatal mortality is an important indicator of health. European comparisons of perinatal mortality show an unfavourable position for the Netherlands. Our objective was to study regional variation in perinatal mortality within the Netherlands and to identify possible explanatory factors for the found differences.

Methods: Our study population comprised of all singleton births (904,003) derived from the Netherlands Perinatal Registry for the period 2000–2004. Perinatal mortality including stillbirth from 22 weeks gestation and early neonatal death (0–6 days) was our main outcome measure. Differences in perinatal mortality were calculated between 4 distinct geographical regions North-East-South-West. We tried to explain regional differences by adjustment for the demographic factors maternal age, parity and ethnicity and by socio-economic status and urbanisation degree using logistic modelling. In addition, regional differences in mode of delivery and risk selection were analysed as healthcare factors. Finally, perinatal mortality was analysed among five distinct clinical risk groups based on the mediating risk factors gestational age and congenital anomalies.

Results: Overall perinatal mortality was 10.1 per 1,000 total births over the period 2000–2004. Perinatal mortality was elevated in the northern region (11.2 per 1,000 total births). Perinatal mortality in the eastern, western and southern region was 10.2, 10.1 and 9.6 per 1,000 total births respectively. Adjustment for demographic factors increased the perinatal mortality risk in the northern region; subsequent adjustment for socio-economic status and urbanization explained a small part of the elevated risk. Risk group analysis showed that regional differences were absent among very preterm births (22 - 25 weeks gestation) and most prominent among births from 32gestation weeks onwards and among children with severe congenital anomalies. Among term births (≥ 37weeks) regional mortality differences were largest for births in women transferred from low to high risk during delivery.

Conclusion: Regional differences in perinatal mortality exist in the Netherlands. These differences could not be explained by demographic or socioeconomic factors, however clinical risk group analysis showed indications for a role of healthcare factors.

Background

Perinatal mortality is an important indicator of health and the quality of healthcare. Countries or regions are often compared using perinatal mortality rate. The position of the Netherlands in international comparative research is unfavourable. In 2003 the results of the PERISTAT study showed that Dutch perinatal mortality for the year 1999 was substantially higher compared to other European countries (stillbirth rate of 7.4 per 1,000 total births and early neonatal mortality of 3.5 per 1,000 live births).

The observed differences in perinatal mortality across Europe are difficult to explain unequivocally because of the many potential explanations like variation in registration practices, differences in definitions, and variation in demographic structure. On the national level, fair comparisons can be achieved more easily. Dutch public health policies aim to reduce national health inequalities if existent. It is unknown whether the current Dutch perinatal mortality is uniformly distributed across the country; differences have been reported based on civil data in the early eighties. Although the Netherlands is a small country, regional variation exists in the degree of urbanisation, the number of immigrants and to a lesser extent, in socio-economic status. Regional variation in mortality from other causes like cardio-vascular diseases and cancer has been reported before.

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Figure 1. Provinces and regions in the Netherlands.

Factors related to regional differences in perinatal outcome reported in other European countries after adjustment for demographic factors, include population density, access and use of health services, income level and social inequality and excess risk for certain conditions.

The objective of this study is to examine whether regional differences in perinatal mortality in the Netherlands exist for the period 2000–2004, and whether these differences persist after taking into account various risk factors that have been linked to regional variation in perinatal mortality.

Methods

Data from the Netherlands Perinatal Registry (PRN) 2000–2004 were used. The PRN is a database that contains the linked data from three registries: the national obstetric database by midwives, the national obstetric database by gynaecologists and the national neonatal/paediatric database. The PRN registry contains comprehensive data on pregnancy, provided care (interventions, referrals) and pregnancy outcomes. The coverage of the PRN is about 96% of all deliveries in the Netherlands. All variables are recorded by the caregiver during prenatal care, delivery and neonatal, lying-in period. The data are annually sent to the national registry office, where a number of range and consistency checks are conducted. Data on socio-economic status (SES) on the postal code level was obtained from The Netherlands Institute for Social Research (SCP).

The population for this study consisted of all singleton births born between 2000 and 2004 from 22.0 gestational weeks onwards. Gestational age was based on ultrasound or last menstrual period. If gestational age was unknown, children with a birth weight below 500 grams were excluded in accordance with the World Health Organization reporting criteria.

Perinatal mortality was our primary outcome measure. Perinatal mortality is defined as the sum of stillbirth (≥ 22.0 gestational weeks) and early neonatal mortality (deaths of live born children during the first week of life). Stillbirth rate and perinatal mortality rate were both calculated per 1,000 total births. Early neonatal mortality was calculated per 1,000 live births. Apart from mortality, the following mediating outcome measures were also analysed: preterm delivery (<32.0 weeks gestational age), low birth weight (<1500 gram) and low APGAR score after five minutes (APGAR score <4).

Regional differences in perinatal mortality were analyzed on a province level and on a regional level. The Netherlands is formally divided into 12 provinces, which form regional administrative units in between municipalities and the national government. The provinces were grouped into 4 regions based on their geographical position: Northern region, eastern region, western region, and southern region. The northern region is the most rural area in the Netherlands, while the western region is most urbanized. The province of each woman was based on her registered postal code (4 digits) in the registry. Women with an unknown or invalid postal code (0.2%) were removed from the analyses.

Demographic characteristics of included women were compared across regions including maternal age, parity and ethnicity. Maternal age was categorized into <20 years, 20–34 years and ≥35 years. Parity was categorized into 0 (first birth), 1 (second birth) and 2+ (third or higher birth). Ethnicity is ascribed by the woman's care provider. For this study, we differentiated between Western (native Dutch and other Westerners) and non-Western (including different ethnic groups like African/Surinamese Creole, Surinamese Hindustani, Moroccan and Turkish).

In addition, data on socioeconomic status (SES) were obtained from The Netherlands Institute for Social Research/SCP on postal code level. Using the woman's postal code, these data could be linked to the perinatal registry file. The SES score is based on mean income level, the percentage of households with a low income, the percentage of inhabitants without a paid job and the percentage of households with on average a low education in a postal code area. The continuous SES score was for our purpose categorised into a high, middle and low group based on percentile ranges (≤ 25th percentile, middle, > 75th percentile). The data on socioeconomic status were available for the year 2002. The categorized score was applied to the total population for the period 2000–2004 as large changes in SES score for a postal code area within two years are unlikely. By using the same postal code we could add the degree of urbanisation (number of addresses per square kilometre), a number which is routinely available. The degree of urbanization was categorised into three groups: very rural, rural to urban and very urbanised.

Besides population characteristics, we analyzed regional variation in healthcare services. We geographically compared the mode of delivery and risk selection at start of delivery. Risk selection is an important feature of the Dutch obstetric system. Healthy women with an uncomplicated obstetric history and/or pregnancy remain under the care of the primary level midwife and are selected as at low risk at start of delivery. In that case a woman can choose to deliver at home or at the hospital, both under supervision of the midwife. If complications occur the woman is selected as high risk and is referred to an obstetrician at the secondary or tertiary level. We analyzed the risk selection status at the start of delivery.

Table 1: Adverse outcomes by region and province for singletons in the period 2000–2004.

Region/Province	Total number of children		Perinatal mortality ≥22+0wks – 6 d	Still birth ≥22+0wks	Early neonatal mortality (0–6 d)	Preterm birth <32+0wks	Low birth weight <1500 gram	Low APGAR score <4
	#	%	‰	‰	‰	%	%	%
Region								
North (N)	87,857	9.7	11.2*	7.9	3.3	1.2*	1.2*	0.3
East (E)	200,158	22.1	10.2	7.3	2.9	1.1	1.1	0.3
West (W)	416,768	46.1	10.1	7.2	2.9	1.1	1.1	0.3
South (S)	199,220	22.0	9.6*	6.9	2.7	1.1	1.1	0.3
Province								
Groningen-N	30,200	3.3	11.5	8.4	3.1	1.4*	1.4*	0.4
Friesland-N	31,554	3.5	11.9*	8.1	3.9*	1.3*	1.3	0.3
Drenthe-N	26,103	2.9	9.9	7.1	2.8	1.1	1.0	0.2
Overijssel-E	65,980	7.3	10.2	7.3	2.8	1.1	1.1	0.3
Gelderland-E	113,496	12.6	10.1	7.2	2.9	1.1	1.1	0.3
Flevoland-E	20,682	2.3	10.9	7.9	3.1	1.2	1.3	0.3
Utrecht-W	73,645	8.1	10.2	6.7	3.5*	1.0	1.0*	0.3
Noord-Holland-W	149,009	16.5	9.8	7.1	2.8	1.2	1.1	0.3
Zuid-Holland-W	194,114	21.5	10.3	7.5	2.8	1.1	1.1	0.3
Zeeland-S	15,363	1.7	10.9	7.5	3.4	0.9	1.1	0.3
Noord-Brabant-S	130,973	14.5	9.5	6.8	2.7	1.1	1.1	0.3
Limburg-S	52,884	5.8	9.4	6.8	2.6	1.1	1.2	0.3
Total	**904,003**	**100**	**10.1**	**7.2**	**2.9**	**1.1**	**1.1**	**0.3**

* Significantly different ($p < 0.01$) from all other regions/provinces excluding the region/province itself.

Differences in adverse outcomes by region and province were tested by Chi-Square test using all other regions/provinces as the reference category. Differences in population characteristics by region were tested by Chi-Square test. After describing crude mortality, logistic regression modelling was used to estimate differences in perinatal mortality between regions after adjustment for socio-demographic factors. All previously described factors were added to the model in two successive steps. First we adjusted only for demographic factors parity, maternal age and ethnicity, parity and maternal age were included as categorical variables with the category with the lowest mortality risk as reference. In the second model we additionally adjusted for the degree of urbanization and SES. In both models we included the year of registration to incorporate changes in perinatal mortality over time. The strength of the association between potential predictors and perinatal mortality are expressed as odds ratios with 95% confidence intervals.

For further interpretation of possible regional differences in perinatal mortality, the perinatal mortality risk for five clinical relevant risk groups was examined by region. These groups represent distinct clinical entities with different patterns of

Table 2: Population characteristics by region for the period 2000–2004

	North		East		West		South		Chi-Square
	#	%	#	%	#	%	#	%	
Number of singleton pregnancies	87,857	100	200,158	100	416,768	100	199,220	100	
Maternal age									
<20 years	1,805	2.1	3,258	1.6	8,179	2.0	3,344	1.7	p < 0.0001
20–34 years	71,651	81.6	161,834	80.9	322,647	77.4	162,188	81.4	
>= 35 years	14,401	16.4	35,066	17.5	85,942	20.6	33,688	16.9	
Parity									
Nulliparous	40,459	46.1	89,976	45.0	197,514	47.4	93,654	47.0	p < 0.0001
Parity 1	32,160	36.6	72,213	36.1	143,731	34.5	72,746	36.5	
Parity 2+	15,238	17.3	37,969	19.0	75,523	18.1	32,820	16.5	
Ethnicity non-western	6,356	7.2	20,810	10.4	94,415	22.7	23,206	11.6	p < 0.0001
Heavy smoking	727	0.8	1,102	0.6	1,678	0.4	1,036	0.5	p < 0.0001
Urbanisation									
Very urban	6,332	7.2	6,107	3.1	152,444	36.6	10,505	5.3	p < 0.0001
Middle	44,806	51.0	149,537	74.7	232,546	55.8	138,893	69.7	
Very rural	36,719	41.8	44,514	22.2	31,778	7.6	49,822	25.0	
SES									
High	13,175	15.0	46,103	23.0	137,766	33.1	40,413	20.3	p < 0.0001
Middle	41,321	47.0	112,929	56.4	163,727	39.3	120,345	60.4	
Low	33,361	38.0	41,126	20.5	115,275	27.7	38,462	19.3	

Table 3: Perinatal mortality (22+0 weeks – 6 days) risk per region after adjustment for risk factors.

	Unadjusted		Adjusted Model I#		Adjusted Model II†	
	OR	95% CI	OR	95% CI	OR	95% CI
Region						
North	1.11	1.03–1.19	1.20	1.12–1.28	1.11	1.03–1.20
East	1.01	0.96–1.07	1.08	1.02–1.14	1.04	0.98–1.10
West*	1.00	reference	1.00	reference	1.00	reference
South	0.95	0.90–1.00	1.01	0.95–1.06	0.97	0.91–1.03
Maternal age						
< 20 years	1.68	1.49–1.91	1.38	1.22–1.57	1.36	1.20–1.54
20–34 years	1.00	reference	1.00	reference	1.00	reference
≥ 35 years	1.23	1.17–1.30	1.28	1.21–1.35	1.29	1.23–1.36
Parity						
Parity 0	1.40	1.33–1.47	1.42	1.35–1.49	1.42	1.35–1.49
Parity 1	1.00	reference	1.00	reference	1.00	reference
Parity 2+	1.44	1.36–1.53	1.32	1.24–1.41	1.31	1.23–1.40
Ethnicity						
Western	1.00	reference	1.00	reference	1.00	reference
Non-Western	1.42	1.35–1.50	1.43	1.36–1.50	1.37	1.29–1.45
Urbanization						
Very urban	1.10	1.05–1.16			0.92	0.86–0.98
Middle	1.00	reference			1.00	reference
Very rural	1.01	0.96–1.07			1.03	0.98–1.10
SES						
Low	1.23	1.18–1.30			1.15	1.09–1.21
Middle	1.00	reference			1.00	reference
High	0.90	0.85–0.95			0.91	0.86–0.96

* Region west was set as reference area as the perinatal mortality rate of this region was equal to the overall rate.
# Model I was adjusted for maternal age, parity and ethnicity.
† Model II was an extension of model I with additional adjustment for degree of urbanization and SES.

care based on mediating risk factors gestational age and severe congenital anomalies. Severe congenital anomalies were defined as anomalies which are either highly fatal or as anomalies potentially detectable by ultrasound and severe enough for optional late termination of pregnancy. The five groups are very preterm births (22-25weeks), severe congenital anomalies, preterm births (26^{+0}–31^{+6} weeks) without severe congenital anomalies, preterm births (32-36weeks) without severe congenital anomalies and term births (≥ 37weeks) without severe congenital anomalies. All analyses were performed using SAS for Windows (version 9.1, SAS Institute Inc, Cary, NC).

Results

During the period 2000–2004, there were 904,003 singletons births in the Netherlands. Nearly half of all births were in the urbanised western region (46.1%) and only 9.7% in the northern more rural region. The overall perinatal mortality in the Netherlands in the period 2000-2004 was 10.1 per 1,000 total

Table 4: Description of health care factors by region.

	North		East		West		South	
	#	%	#	%	#	%	#	%
Mode of delivery								
Spontaneous	64,010	72.9	151,816	75.8	315,282	75.6	149,366	75.0
Elective Caesarean Section	6,046	6.9	12,010	6.0	24,416	5.9	12,826	6.4
Instrumental vaginal delivery	10,680	12.2	22,019	11.0	45,538	10.9	21,018	10.6
Emergency Caesarean Section	7,121	8.1	14,313	7.2	31,532	7.6	16,010	8.0
Care at start of delivery								
low risk selection	37,506	42.7	103,069	51.5	209,376	50.2	92,418	46.4
low risk & home delivery	17,337	19.7	60,869	30.4	95,724	23.0	46,918	23.6
low risk & hospital delivery	10,349	11.8	18,157	9.1	60,656	14.6	20,250	10.2
from low to high risk during delivery	9,820	11.2	24,043	12.0	52,996	12.7	25,250	12.7
high risk selection	50,351	57.3	97,089	48.5	207,392	49.8	106,802	53.6
Number of hospitals	15		18		39		25	
Number of tertiary centres	1		2		5		2	
Total	**87,857**	**100**	**200,158**	**100**	**416,768**	**100**	**199,220**	**100**

Table 5: Prevalence and mortality risk for clinical risk groups by region.

Clinical risk groups	North Prev %	North Mortality risk ‰	East Prev %	East Mortality risk ‰	West Prev %	West Mortality risk ‰	South Prev %	South Mortality risk ‰
Very preterm births <26^{+0} weeks	0.27	937	0.28	947	0.31	928	0.32	951
Severe congenital anomalies	0.80	204	0.81	163	0.81	147	1.02	105
Premature 26^{+0}–31^{+6} weeks	0.89	233	0.74	248	0.76	237	0.72	214
Premature 32^{+0}–36^{+6} weeks	5.14	33.6	4.77	30.2	4.75	29.6	5.26	26.6
Term ≥ 37^{+0} weeks	92.89	3.4	93.40	3.2	93.38	3.1	92.69	2.8
Total	**100**	**11.2**	**100**	**10.2**	**100**	**10.1**	**100**	**9.6**

Prev = prevalence.

births. The northern region has the highest perinatal mortality rate with 11.5 and 11.9 per 1,000 total births in provinces Groningen and Friesland respectively. The southern region had the lowest perinatal mortality rate, with lowest rates in provinces Noord-Brabant and Limburg: 9.5 and 9.4 per 1,000 total births. The perinatal mortality rate in the northern region was significantly higher than in the other regions (Chi-square p-value < 0.01). Both stillbirth and early neonatal mortality were high in the northern provinces. The proportion of preterm births and children with a low birth weight was also significantly higher in the northern region (1.2% and 1.2% respectively).

The northern region had the largest proportion of women from rural areas (41.8%) and with a low SES score (38.0%) and the lowest proportion of non-western women (7.2%) (Table 2). The western region had the highest proportion of women aged above 35 years (20.6%), with non-western ethnicity (22.7%), with a high SES score (32.9%) and living in urban areas (36.4%). All these regional differences were statistically significant.

Table 3 shows that women from the northern region had a significantly higher perinatal mortality risk compared to the western region. The western region was set as reference area because the perinatal mortality risk was the same as the overall rate. After adjustment for demographic factors (maternal age, parity and ethnicity), the women in the northern region and eastern region had a significantly higher perinatal mortality risk compared to women in the western region. Living in a very urban area and having a low SES score were significant risk factors for perinatal mortality, while a high SES score lowered the risk. Subsequent adjustment for urbanisation degree and social-economic status explained a small part of the excess risk in the northern region. Living in an very urban area was no longer a risk factor in adjusted model II.

The health services patterns also exhibited regional differences. The northern region had the lowest number of spontaneous deliveries (72.9% versus 75.6% in the western region) and the lowest number of women selected as low risk at start of delivery (42.7% versus 50.2% in the western region). The percentage of home births was 19.7% in the northern region versus 23.0% in the western region and in the eastern region the percentage of home births was as high as 30.4%. There were only small variations in the percentage of women transferred from low risk to high risk during delivery (11.2% in the northern region and 12.7% in the western region). In the northern region most deliveries take place under supervision of an obstetrician (57%). The northern region has the lowest number of hospitals and only one tertiary hospital.

Among very preterm births (responsible for 28% of all perinatal deaths), the perinatal mortality risk was about the same in all regions . The perinatal mortality risk for children with severe congenital anomalies (responsible for 12% of perinatal deaths) was higher in the northern region (204 per 1,000 births) compared to the western region (147 per 1,000). The mortality risk among preterm births 26-31 weeks (responsible for 14% of perinatal deaths) in the northern region was lower than in the western region (233 versus 237 per 1,000). The mortality risk among preterm births 32-36 weeks (responsible for 18% of perinatal deaths) was higher in the northern region and lower in the southern region than in the western region. For the term births (responsible for 28% of all perinatal deaths) the mortality risk was about 11% higher in the northern region compared to the western region (3.4 per 1,000 versus 3.1 per 1,000 in region west). Within the term group (≥37 weeks), the regional mortality difference was the largest for the group of births from women transferred from low risk to high risk during delivery (4.0 per 1,000 in north versus 2.6 per 1,000 in west). The perinatal mortality risk for term births from women selected as high risk at start of delivery was similar; in both northern and western regions 5.0 per 1,000.

Discussion

The perinatal mortality in the Netherlands for the period 2000-2004 shows regional variation, with an increased perinatal mortality in the rural northern region. The regional variation was present in both stillbirth and early neonatal mortality. The elevated risk in the northern region could not be explained by regional variation in demographic risk factors like maternal age, parity and ethnicity. Socioeconomic status and urbanisation grade only explained a small part of the excess risk. Analyses focussed on clinical relevant subgroups showed regional differences were most prominent among births from 32 weeks gestation onwards and especially among term births from women transferred from low to high risk during delivery.

Data from a period of five years could be analyzed including 904,003 pregnancies in the Netherlands. The Netherlands Perinatal Registry contains the combined information on pregnancy, childbirth and the neonatal period derived from three separate registries that have recently been linked using probabilistic record linkage techniques. This enabled us to adjust for a combination of demographic, care related and socio-economic factors in relation to perinatal outcome.

Data from general practitioners providing obstetric care were not available from the Netherlands perinatal registry. General practitioners more often provide obstetric care in rural areas,

which are found in the northern region but also in the eastern and southern regions. Overall the proportion of deliveries that took place under supervision of a general practitioner is estimated at 4%. However over 99% of hospital deliveries were included and a woman is transferred to an obstetrician by the general practitioner in case of high risk. This is in accordance with the finding when the perinatal registry data were linked to civil registry data in a pilot study, more foetal deaths were registered in the perinatal registry, especially the very premature fetal deaths. Medical registries suffer from entry errors by professionals as any database. Limited entry options and data checks by professionals combined with validated linkage procedures have confined errors to a minimum. The current perinatal registry does not contain information on smoking (only reporting on heavy smoking with clear underestimation), food intake, folic acid intake, maternal education and body mass index (BMI), factors which may (partly) explain the regional differences in perinatal mortality. Additional adjustment for BMI and smoking on a province level for women in the reproductive age did not change the elevated perinatal mortality risk in the northern region. Risk factor behaviour in pregnancy is related to both socio-economic class and ethnicity. After adjustment for these factors the risk status of the northern region remained high; therefore we believe that regional variation in unmeasured risk factors is unlikely to explain the observed differences in mortality in our adjusted models. One could challenge the use of the SES score on a neighbourhood level rather than on the individual level. However, previous research on socioeconomic inequalities have demonstrated that this is a valid approach.

This is the first time that regional differences in perinatal mortality were studied in the Netherlands using the national linked perinatal registry data on 904,003 pregnancies. Previous regional analyses were based on aggregate data on 11 provinces for the period 1979–1982 and on 40 economic sub-regions for the period 1980–1984, rather than on individual data. Treffers et al. found differences in the percentage of hospital deliveries (versus home deliveries) per province, but could not relate this to regional perinatal mortality rate. We also found differences in hospital deliveries per region and found that the regional differences were most pronounced among term women transferred from low to high risk during delivery. Mackenbach et al reported perinatal mortality rate to depend on mean income, part of the population living in a large municipality and the presence of a level-two hospital. We applied individual demographic adjustment, and used more refined variables to account for SES and urbanisation. We had access to urbanization and SES on the neighbourhood level based on postal code, which showed large variation between regions. Social factors have been reported as explanatory factors for perinatal mortality differences, however adjustment for SES and urbanisation only explained a small part of the excess risk in the northern region in our study. The presence of fewer hospitals in the northern region may have played a role. The differences in regional perinatal mortality are sizable, and consistent with recently observed mortality differences for other causes (cardiovascular, cancer).

Regional variation in health outcomes can be caused by variation in incidence of complications and/or variation in prognosis. Health status of the women and preventive and obstetric care if applicable can influence incidence and prognosis. Both stillbirth and neonatal mortality were increased in the northern region, which indicates a role for factors common to both. Population composition factors and environmental risk factors, undetected by the direct and indirect adjustment factors can be present, but their presence is less likely given the adjustments. The analyses suggest that prevention and care factors may have played a role. Potential candidates are the following.

The uptake of prevention (general—smoking, specific—folic acid, screening) may be less or the intensity or effectiveness of health services may be lower. As differential access will have been partly covered by the adjustment factor urbanisation, explanations at the care level are more likely. The number of clinical facilities in the northern region is smaller, and only 1 tertiary centre is available. Perhaps intensity and quality of preventive and delivery care is less in areas with low population density. The elevated mortality risk for children with congenital anomalies in the northern region (while prevalence was similar) might also point to differences in care shortly after birth. Late neonatal mortality (7–27 days) showed the same regional pattern, excluding mortality differences by different care management during the first week and subsequent delay of mortality. As an increased mortality risk in the northern region is present in both preterm and term births also differences in hospital supply services (obstetrical, neonatal) has to be considered, and delay due to the on average larger travelling distances in case of intended home births with an emerging risk requiring hospital admission. The group transferred from low to high risk during delivery is at higher risk for perinatal mortality than women who deliver under care of a midwife completely. For term births the regional mortality differences were most pronounced in the group transferred from low to high risk during delivery, possibly indicating a role for travel distance. Further exploring the role of care factors rests on more detailed analysis of clinical risk groups for perinatal mortality and of stillbirth and neonatal mortality separately, but also on audit studies. Audit studies could also provide information on causes of death, which is not registered in the current PRN registry. Against the background mortality observed in the other regions, the observed mortality in the northern region of 11.2 per 1,000 births and about 17,500 deliveries annually, this excess risk in the northern region accounts for about 19 deaths a year.

Conclusion

In conclusion, our study revealed persistent adverse perinatal outcome in the northern part of the Netherlands even after adjustment for demographic and socio-economic factors. Analysis of clinical risk groups showed perinatal mortality differences were most pronounced among children with severe congenital anomalies and among term births from women transferred from low to high risk during delivery. The results provide an incentive to explore the role of healthcare factors, both at the prenatal and delivery stage of care.

Hemodynamic Management and Regional Hemoglobin Oxygen Saturation (rSO_2) of the Brain, Kidney and Gut

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Abstract

Cerebral oximetry is used widely in adult and pediatric cardiovascular surgery and intensive care to monitor and manage cerebral, regional hemoglobin oxygen saturation (rSO_2). It is also used to monitor rSO_2 in somatic tissues under the sensor. This report details the rSO_2 response to occlusion of arterial flow to the brain, kidney and gut in newborn piglets.

Following stable induction of anesthesia, there was an immediate and significant drop in cerebral rSO_2 when the internal carotid artery was occluded in five piglets, limiting flow to the brain. The correlation of cerebral rSO_2 with internal jugular vein hemoglobin saturation was highly significant with an r^2=0.90. Further, there was an immediate and significant drop in rSO_2 (31 ± 7% mean ± SD, n=9, expressed as % of baseline rSO_2) from sensors placed transversely over the kidney on the dorsal abdominal wall when the renal artery was occluded. Occlusion of the superior mesenteric artery caused an immediate and significant drop in rSO_2 (45 ± 9% mean ± SD, n=6, expressed as % of baseline rSO_2) from sensors placed vertically over the gut on the ventral abdominal wall.

Animal weight and abdominal wall thickness as well as age limited the somatic response, with piglets weighing 5 to 7 kg having a diminished response to occlusion of the respective arterial flow in kidney (3 ± 3% mean ± SD) and gut (9 ± 3% mean ± SD). There was no rSO_2 change seen from sensors placed over reference tissues in response to arterial occlusion of brain, kidney or gut, regardless of age or weight.

Introduction

Near-infrared spectroscopy (NIRS) is used extensively to noninvasively monitor hemoglobin oxygen saturation in arteries (SpO_2) and tissue. Pulse oximetry was the first major application of the technology in medicine to achieve widespread adoption and provides information on the oxygenation status of arterial blood. Cerebral/somatic oximetry utilizes NIRS to monitor venous-weighted regional hemoglobin oxygen saturation (rSO_2) in the brain and other tissues beneath the sensors.

The INVOS System was the first cerebral oximeter to be marketed in the United States over ten years ago. It is intended for use on all patients at risk of ischemia, and has shown a high correlation (r=0.93) with internal jugular vein hemoglobin oxygen saturation in pediatric patients as reflected in independent, peer reviewed publications.[1,2]

While hemoglobin oxygen saturation on the arterial side is well defined, venous hemoglobin saturation levels are more variable and reflect oxygen delivery to the tissues versus tissue demand, the arteriovenous balance. There are misconceptions in the marketing of some NIRS devices that confuse the term "absolute" with the long accepted concept in analytical chemistry of accuracy. An example of the inherent variability of arteriovenous balance is reflected in mixed venous oxygen saturation (SvO_2). Unlike arterial saturation (SpO_2) that has defined target levels that are acceptable, venous saturation depends on the delivery of oxygen to the tissues and tissue consumption of the oxygen and varies with the oxygen-carrying capacity of the blood.

The INVOS System provides real-time data accuracy in patients above 2.5 kg, meaning studies have found both its single-point and cumulative rSO_2 readings to be clinically significant.[1,2] Its use has also been shown to improve outcomes in randomized clinical trials in surgical patients.[3,4] Studies in infants and children have shown that rSO_2 changes in the peripheral circulatory system are useful in predicting the presence of anaerobic metabolism.[5] It is the only cerebral/somatic oximeter available for use in patients below 2.5 kg as a monitor of continuous changes in oxygen delivery and tissue viability. The experiments reported here demonstrate that, in piglets, the cerebral rSO_2 is highly specific and accurate and that reduction of flow to the brain, kidney or gut results in a rapid and significant response in rSO_2 from the sensors placed over the organs.

Disturbances in oxygen delivery are observed in a number of clinical situations such as congenital heart disease, necrotizing enterocolitis, renal failure, uncompensated shock, loss of autoregulation in the brain, and tissue-specific effects of pressors and inotropes. The ability to monitor oxygen delivery to the organs is of critical importance since organ blood flow abnormalities are associated with a range of morbidities, perhaps most notably shock and the attendant multiple organ failure that can lead to death.

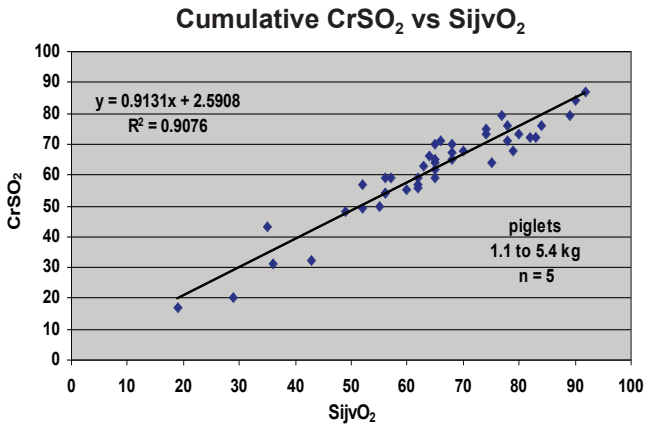

Figure 1. Regression analysis of cerebral rSO_2 vs hemoglobin oxygen saturation of blood samples taken from the internal jugular vein following change of the cerebral rSO_2 by either bilateral carotid occlusion or CO_2 manipulation.

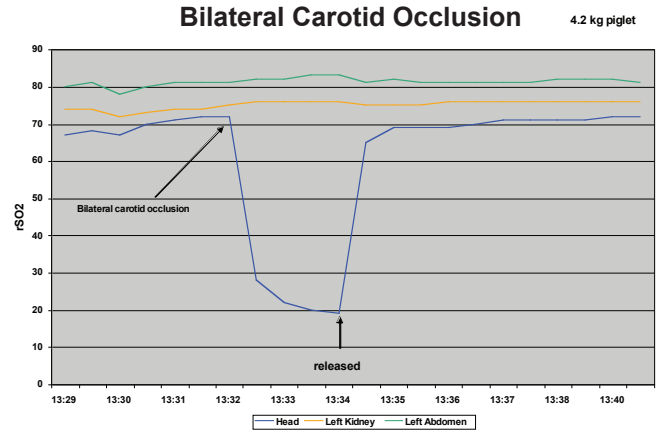

Figure 2. Cerebral rSO_2 response to bilateral internal carotid occlusion.

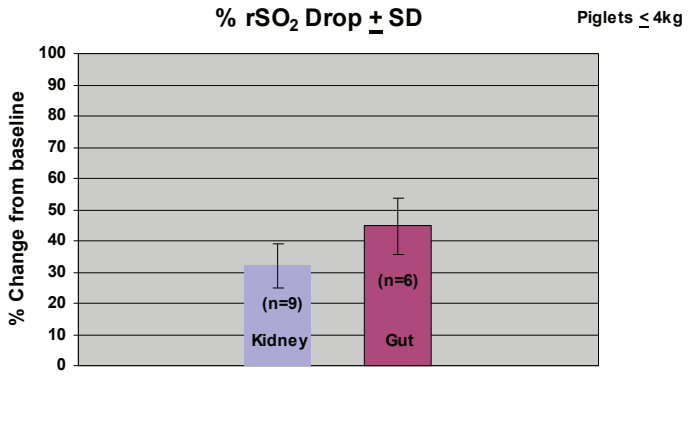

Figure 3. Mean ± SD of maximum relative % change from baseline rSO_2 resulting from complete arterial occlusion of kidney and gut.

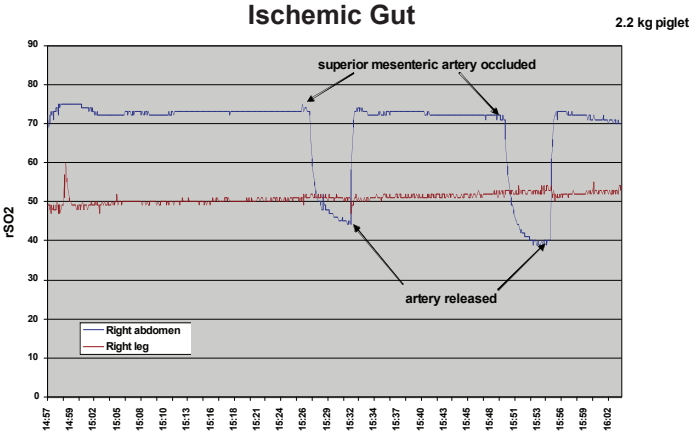

Figure 4. Example graph of rSO_2 response to occlusion of the superior mesenteric artery. The 29 point change in rSO_2 equals a 40% maximum relative change from baseline.

Blood pressure and ultrasound (US) velocity estimates of blood flow can give insight into vascular resistance and tissue perfusion. However, there are numerous situations where blood pressure does not give a true picture of peripheral hemodynamics and US is expensive, intermittent, and does not reflect micro vascular perfusion or tissue oxygen consumption.

The challenge of managing proper hemodynamic balance in infants and neonates is exacerbated by the limited technology available to monitor arteriovenous oxygen difference (A/V difference) and impending physiologic changes, preventing proactive interventions. An awareness of deteriorating oxygen delivery to the periphery can alert the clinician to alterations in the hemodynamic status that are not apparent from SpO_2 or arterial pressure.

While pulse oximetry and mean arterial pressure provide information on cardiopulmonary performance, these metrics only reflect systemic/global adequacy of perfusion. The only measure of A/V difference currently available is mixed venous oxygen saturation which is global and can be a poor reflection of regional oxygen delivery and tissue viability. Further, venous blood sampling for analysis is invasive, intermittent and can contribute to anemia.

To better understand the ability of the INVOS System to noninvasively detect total cessation of blood flow to individual organs, we designed a study where the organ's major feeder artery was ligated and recorded the resultant changes in rSO_2 from sensors placed over the organs. The animal procedure described here demonstrated that, in piglets, cerebral/somatic oximetry via the INVOS System is capable of detecting low oxygen saturation associated with organ ischemia during reduced-flow and no-flow states.

Materials and Methods

All studies were reviewed and approved by the Providence Hospital, Institutional Animal Care and Use Committee (IACUC) and the Research Committee for compliance with animal care guidelines. Yorkshire—Duroc blend piglets weighing 1.7 to 7.0 kg were premedicated with ketamine (22 mg/kg) and atropine (0.05 mg/kg), intubated and placed on a volume-cycled respirator and ventilated with 3 l/min of 100% O_2. Anesthesia was maintained with isoflurane 1.5-2.5%.

A warming mat and hot air fan were used to maintain intraoperative normal body core temperature. Body temperature and pulse oximetry were continuously monitored. The skin was shaved in areas where sensors would be placed, a depilatory applied to remove remaining hair and the skin wiped clean with alcohol.

Catheters were inserted into the femoral artery and vein and advanced into the abdomen, flushed with heparinized saline

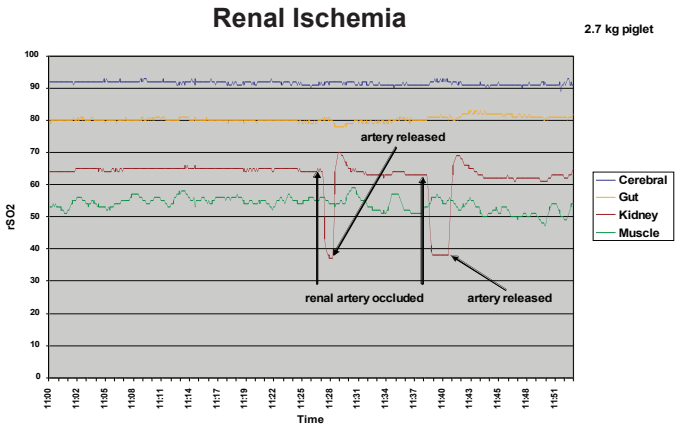

Figure 5. Example graph of rSO_2 response to occlusion of the renal artery. The 27 point change in rSO_2 equals a 42% maximum relative change from baseline.

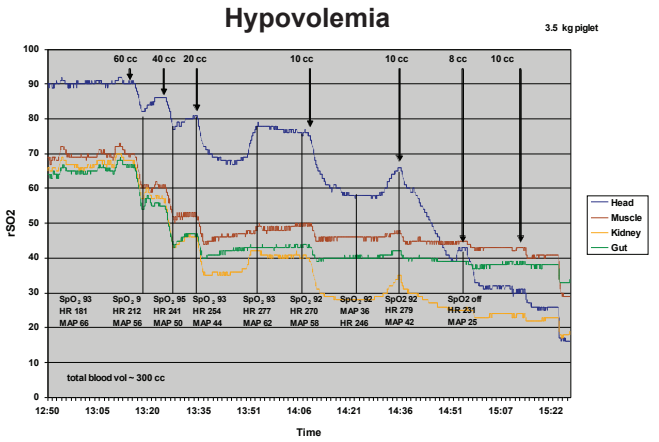

Figure 6. Impact of the sequential removal of blood from the femoral vein (volume of blood removed indicated at top of graph) on cerebral and somatic rSO_2.

and secured with ligatures. Heparin 200 U/kg was given IV with additional boluses hourly. Intravenous lactated Ringer's solution was given at a rate of 10 cc/kg/hr.

There were 3 separate groups of animals used to examine the rSO_2 response to ischemia of brain, kidney and gut. In the first group, the internal carotid arteries were exposed through incisions in the left and right lateral cervical regions of the neck and ligatures placed around the arteries. A catheter was inserted in the right, internal jugular vein for blood sampling. The ligatures were exteriorized and the incision closed with staples.

A second group of piglets had a midline incision made in the ventral abdominal wall and a ligature placed around the right renal artery. The third group had ligatures placed around the superior mesenteric artery through a midline incision. The ligatures in all animals were exteriorized and the incisions closed with staples.

INVOS System Pediatric SomaSensors (model SPFB) were placed over the gluteus muscle on the right leg and over the right kidney extending transversely from the midline just under the costal margin on the dorsal abdomen or over the gut vertically just lateral of the umbilicus on the left ventral abdomen.

The animal was allowed to equilibrate for 30 minutes at which time 0.5 cc blood samples were taken from the femoral arterial and venous catheters and analyzed by co-oximetry for hemoglobin concentration and oxygen saturation to insure that the animal was properly ventilated and hydrated. Tension was then applied to the externalized ligatures around the internal carotid arteries, renal artery or mesenteric artery and maintained for approximately 5 minutes.

Cerebral rSO_2 was manipulated either by occlusion of the internal carotid arteries or by ventilatory changes to increase or decrease the end tidal CO_2 levels at which time the rSO_2 was recorded and a blood sample taken from the internal jugular vein catheter and analyzed by co-oximetry ($SijvO_2$). Tension on the ligature was released and the animal allowed to equilibrate for 20 minutes at which time the procedure was repeated.

In a final experiment, piglets were prepared as described above but without placing ligatures around any vessels. Aliquots of blood were withdrawn at various time intervals from the femoral vein to demonstrate the sensitivity to change in oxygen delivery produced by hypovolemia.

Data was downloaded from the INVOS System (Somanetics, Troy, MI), graphed and analyzed for the relative % change from baseline caused by occlusion of the arterial supply to the respective organ and to systemic blood loss.

Results

Cerebral Response

Cerebral rSO_2 varied reliably during changes in pCO_2 or blood flow associated with ventilator changes or carotid occlusion in 5 piglets weighing 1.7 to 5.4 kg. Regression analysis of the cerebral rSO_2 compared to the $SijvO_2$ from internal jugular vein blood samples demonstrated a close correlation ($R^2 = 0.91$) of the INVOS System reading with the blood oxygen saturation as shown in Figure 1. Bilateral occlusion of the internal carotid arteries caused a rapid and significant drop in cerebral rSO_2 as shown in Figure 2.

Somatic Response

Baseline readings for 2 minutes prior to occlusion of the artery were averaged in each experiment and used to calculate the peak relative % change from baseline rSO_2. Complete occlusion of arterial blood supply to the kidney or gut caused a rapid and significant drop in the regional hemoglobin oxygen saturation (rSO_2) in all cases, as shown in Figure 3.

Mesenteric Response

The first occlusion of arterial blood flow to the gut in 6 animals weighing 4 kg or less resulted in an average maximum relative % change from baseline rSO_2 of 45 ± 9% (mean ± SD, n=6) from the sensor placed on the ventral abdominal wall. There was no change in the rSO_2 from the sensor placed over left leg as a reference tissue.

The response was rapid and tissue-specific, as demonstrated by the fact that the leg muscle did not change despite the marked change in the mesenteric rSO_2, as can be seen in the example graph shown in Figure 4.

Renal Response

The first occlusion of arterial blood flow to the kidney in 9 animals weighing 4 kg or less resulted in an average maximum

relative change from baseline rSO_2 of 31 ± 7% (mean ± SD, n=9) from the sensor placed transversely on the dorsal abdominal wall over the kidney. There was no change in the rSO_2 from the sensor placed on the left leg, ventral abdomen or head as reference tissues.

The response was rapid and tissue-specific, as demonstrated by the fact that the other sensors did not change despite the marked change in the renal rSO_2, as can be seen in the example graph shown in Figure 5.

Hypovolemia Response

Following removal of approximately 40% (120 cc) of the calculated blood volume the SpO_2 had not changed and the mean arterial pressure was still within acceptable limits of 44 to 58. Heart rate increased to 254. Somatic rSO_2 decreased rapidly and significantly from the high 60s down to the 40s from renal, mesenteric and muscle sensors. Cerebral rSO_2 decreased with each blood draw but recovered to within 11 points of the initial rSO_2. Removal of another 6% of the blood volume (2 X 10 cc) caused a rapid drop in cerebral rSO_2 as shown in Figure 6.

Limitations

Reductions in magnitude of the rSO_2 response to total organ ischemia were observed in animals over 4 kg. The average maximum rSO_2 change from the sensor placed over the kidney when the left renal artery was occluded in piglets weighing between 5 and 7 kg was 3 ± 3% (mean ± SD, n=2). The maximum change observed from the ventral abdominal sensor placed over the gut in piglets weighing 5 to 6 kg was 9 ± 3% (mean ± SD, n=2). These limitations were associated with greater thickness of the animal's abdominal wall over the respective organ corresponding to 1.4 cm or greater.

Discussion

The INVOS System is widely used to monitor hemoglobin oxygen saturation in the brain and tissues which, along with other diagnostic information, can help guide peripheral and cerebral perfusion balancing to reduce tissue damage from ischemia. Results from these experiments demonstrate that, in these piglets, the INVOS System is highly accurate and sensitive in reflecting $SijvO_2$ and highly specific in detecting flow-induced changes in regional oxygen saturation in tissue under the sensor when placed over brain, kidney and gut.

The response of the sensor to ischemia in gut and kidney of the smaller piglets was immediate. The use of multiple sensors on different tissues allowed detection of focal regional organ ischemia. For example, when the signal from a sensor placed over the ischemic kidney dropped but the signal from another somatic sensor placed elsewhere did not, it was clear that the change reflected a localized reduction in oxygen saturation.

The removal of 40% of the blood volume of piglets induced a dramatic reduction in the rSO_2 of the kidney, gut and muscle while the brain was able to maintain acceptable saturation levels presumably through autoregulatory mechanisms. The response of somatic rSO_2 to hypovolemia demonstrated the sensitivity of the sensor to changes in oxygen delivery independent of blood pressure and SpO_2. Removal of a critical volume of blood caused a dramatic drop in the rSO_2 of the brain and a parallel drop in somatic rSO_2.

This procedure showed that, in piglets, somatic rSO_2 levels can detect the critical limit of oxygen delivery (DO_2), indicating changes in flow to the organs and the arteriovenous oxygen gradient. Reduction of the blood volume causing reduced oxygen delivery was reflected in early reduction in somatic saturation ahead of other indicators such as SpO_2 and blood pressure and prior to major changes in cerebral oxygenation. As such, tissue rSO_2 combined with other diagnostic parameters such as SpO_2, mean arterial pressure, heart rate, CO_2, respiratory rate and blood chemistries, can contribute significantly to managing hemodynamic balance and provides an early warning of potential hemodynamic instability.

Conclusion

Cerebral/somatic oximetry via the INVOS System can provide a window into oxygen delivery to, and consumption by, the brain and body, to help manage perfusion and avoid site-specific oxygen deprivation. The studies reported here demonstrate the sensitivity, specificity and accuracy of the INVOS Cerebral/Somatic Oximeter in detecting changes in organ-bed regional hemoglobin oxygen saturation in piglets under 4 kg. While these findings in piglets cannot be replicated in humans due to the direct manipulation and occlusion of critical arteries, the ability to detect organ ischemia and perfusion distribution changes along with other diagnostic parameters has the potential to enhance the management of perfusion-related morbidities and may lead to better diagnostics and early warning signs to direct therapeutic intervention.

The noninvasive INVOS 5100C is intended for use as an adjunct monitor of regional hemoglobin oxygen saturation of blood in the brain or in other tissue beneath the sensor. It is intended for use in individuals greater than 2.5 kg at risk for reduced-flow or no-flow ischemic states. It is also intended for use as an adjunct trend monitor of regional hemoglobin oxygen saturation of blood in the brain or in other tissue beneath the sensor in any individual.

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Evidence-Based Practice in Neonatal Health: Knowledge Among Primary Healthcare Staff in Northern Viet Nam

Leif Eriksson, Nguyen Thu Nga, Mats Målqvist, Lars-Åke Persson, Uwe Ewald and Lars Wallin

Abstract

Background: An estimated four million deaths occur each year among children in the neonatal period. Current evidence-based interventions could prevent a large proportion of these deaths. However, healthcare workers involved in neonatal care need to have knowledge regarding such practices before being able to put them into action.

The aim of this survey was to assess the knowledge of primary healthcare practitioners regarding basic, evidence-based procedures in neonatal care in a Vietnamese province. A further aim was to investigate whether differences in level of knowledge were linked to certain characteristics of community health centres, such as access to national guidelines in reproductive healthcare, number of assisted deliveries and geographical location.

Methods: This cross-sectional survey was completed within a baseline study preparing for an intervention study on knowledge translation. Sixteen multiple-choice questions from five basic areas of evidence-based practice in neonatal care were distributed to 155 community health centres in 12 districts in a Vietnamese province, reaching 412 primary healthcare workers.

Results: All healthcare workers approached for the survey responded. Overall, they achieved 60% of the maximum score of the questionnaire. Staff level of knowledge on evidence-based practice was linked to the geographical location of the CHC, but not to access to the national guidelines or the number of deliveries at the community level. Two separated geographical areas were identified with differences in staff level of knowledge and concurrent differences in neonatal survival, antenatal care and postnatal home visits.

Conclusion: We have identified a complex pattern of associations between knowledge, geography, demographic factors and neonatal outcomes. Primary healthcare staff knowledge regarding neonatal health is scarce. This is a factor that is possible to influence and should be considered in future efforts for improving the neonatal health situation in Viet Nam.

Background

The former executive director of UNICEF, James Grant, said: "The most urgent task before us is to get medical and health knowledge to those most in need of that knowledge. Of the approximately 50 million people who were dying each year in the late 1980s, fully two thirds could have been saved through the application of that knowledge." Many years after Grant's statement, the use of appropriate knowledge remains a global problem, particularly in the area of child healthcare. Every year almost 10 million children die in the world, of whom around four million die during the neonatal period. This tragedy continues to unfold despite the existence of cheap, evidence-based interventions that could prevent a large proportion of these deaths.

Evidence-based practice (EBP) is a term increasingly used to describe the application of empirically acquired knowledge in practice. In the neonatal period more than 70% of the current deaths could be prevented through evidence-based procedures (eg by exclusive breastfeeding and hypothermia management). However, healthcare workers involved in neonatal care need to have adequate knowledge about the different procedures before they can implement and use them. Educational programmes targeting healthcare staff in developing contexts have shown improvements in both staff knowledge and healthcare outcomes. Thus, a primary issue is whether staff has the required knowledge or not. Understanding the level of knowledge is of interest for deciding what implementation strategy

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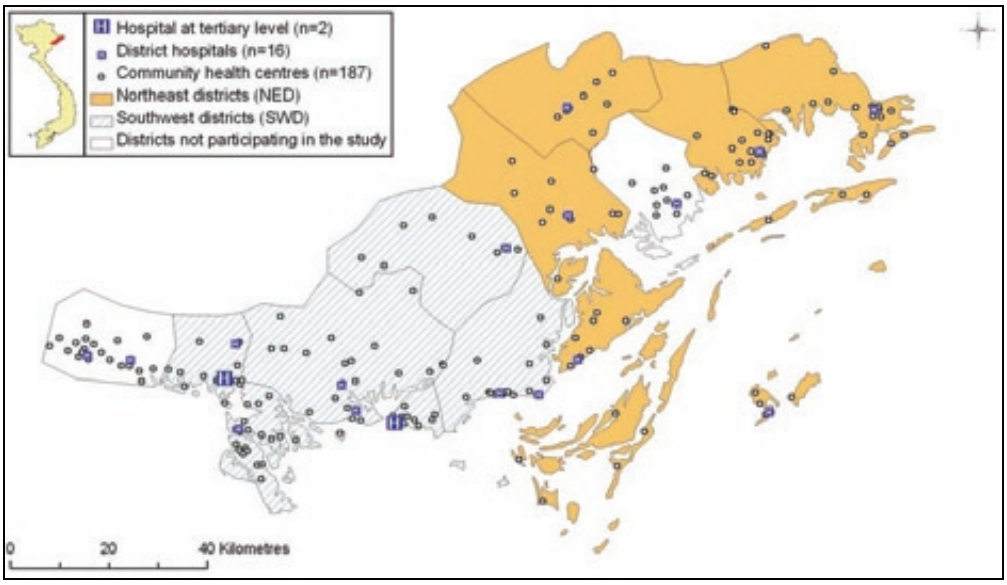

Figure 1
Map over survey area. Map over Quang Ninh province in northern Viet Nam indicating the location of hospitals and community health centres. Knowledge survey results indicated two areas of clustered districts: the northeast districts and the southwest districts.

might be effective. Unfortunately, effective and sustainable implementation of knowledge into practice is not a trivial task, and only a few studies have evaluated strategies for knowledge translation in low-income countries.

Staff knowledge regarding evidence-based practice is key, but also a number of contextual factors are highly influential for a well-functioning healthcare system, such as adequate geographical coverage of healthcare, sufficiency of material resources (eg equipment and drugs) and a certain level of activity (eg number of assisted deliveries) at the healthcare units. Although the impact of contextual factors in relation to knowledge translation has been given a great deal of attention over the years, this has primarily been from the perspective of the local work context (eg leadership and workplace culture). Factors such as geographical location of healthcare units and level of activity have received less attention in relation to knowledge translation.

Viet Nam has achieved substantial improvements in child and infant survival, reporting a level of infant mortality corresponding to middle-income countries. However, neonatal mortality has remained unchanged over the past three decades, currently constituting nearly three quarters of all infant deaths. In 2003, the Ministry of Health in Viet Nam adopted a groundbreaking initiative to improve neonatal healthcare by launching practice guidelines for reproductive healthcare (here called the National Guidelines). These guidelines were disseminated to all public healthcare units providing antenatal, intrapartum and postnatal care, but were not accompanied by specific implementation activities.

In Quang Ninh province, our research group has set up the Neonatal Knowledge Into Practice project. NeoKIP entails collaboration between Uppsala University in Sweden, the Ministry of Health in Viet Nam and the Viet Nam-Sweden hospital in Uong Bi, Viet Nam. The aim of NeoKIP is to evaluate facilitation; a knowledge translation intervention that we hypothesize will speed up identification of local healthcare-related problems at community level, increase primary healthcare staff knowledge and use of evidence-based knowledge and subsequently achieve improvement of neonatal outcomes.

In 2006, we performed a baseline study that identified an overall neonatal mortality rate (NMR) of 16 deaths per 1000 live births, with districts within the province ranging in NMR from 10 to 45 per 1000. The higher rates were noted in remote and mountainous districts, which are known to have a higher prevalence of poverty and people belonging to ethnic minority groups. The existence of inequities in child survival is a well-known problem throughout the world and one on which more studies are needed to assess specific approaches to overcome these inequities. Knowledge regarding evidence-based practice and use of this knowledge are central components for changing the severe situation. In the NeoKIP project, assessing knowledge will be helpful for planning and evaluating the coming intervention.

The aim of this survey was to assess the knowledge of primary healthcare practitioners regarding basic, evidence-based procedures in the neonatal care field in a Vietnamese province. Further aims were to assess the availability of material resources at the community health centres (CHCs) and to investigate whether differences in knowledge level were linked to (CHCs): (1) access to National Guidelines, (2) number of assisted deliveries and (3) geographical location.

Methods

A questionnaire for assessing staff knowledge was developed by the research team. It consisted of 16 multiple-choice questions covering basic aspects of EBP in neonatal care. The following five areas were included in the knowledge survey: breastfeeding, immediate postnatal care, infection management, low birth weight management and postnatal home visits.

A maximum of 48 points could be obtained in the knowledge survey. Each of the 16 questions could generate three points;

Table 1: Availability of equipment and drugs at all hospitals and all community health centres in Quang Ninh province, Viet Nam

Items	18 Hospitals % (n)	187 CHCs % (n)
Guidelines		
The National Guidelines[a]	*67 (12)*	*70 (131)*
Hygiene and infections		
Soap	*100 (18)*	*94 (175)*
Clean gloves	*100 (18)*	*97 (181)*
Clean water	*100 (18)*	*81 (151)*[1]
Alcohol for disinfection	*94 (17)*	*95 (178)*
Iodine for disinfection	*100 (18)*	*92 (172)*
Antibiotics	*100 (18)*	*99 (185)*
Safe delivery		
Foetus stethoscope	*94 (17)*	*99 (185)*
Forceps	*44 (8)*	*2 (3)*[1]
Vacuum extraction equipment	*28 (5)*	*1 (2)*[1]
Vitamin K_1	*67 (12)*	*11 (21)*[1]
Temperature control		
Radiant heater	*89 (16)*	*11 (21)*[1]
Towels for newborn	*78 (14)*	*38 (71)*[1]
Thermometer	*100 (18)*	*99 (185)*
Resuscitation		
Face mask and ambo for newborns	*89 (16)*	*10 (18)*[1]
Face mask and ambo for adults	*50 (9)*	*22 (41)*[1]
Manual suction	*17 (3)*	*16 (30)*
Suction machine	*94 (17)*	*76 (143)*
Tube for suction machine	*94 (17)*	*49 (92)*[1]

[a]*Guidelines of reproductive health* (2003) by the Ministry of Health in Viet Nam
[1]Difference ($p < 0.05$) in availability of an item compared with hospitals as derived from the χ^2 test.

for a maximum score, the respondent had to fill in the correct alternative(s) required for each question. A scoring system was developed for calculation of points.

Results

Data collection was performed in all (n = 205) healthcare units (Fig 1) providing neonatal care in Quang Ninh province. At tertiary level there were two hospitals and at district level 16 hospitals. The community level had 779 healthcare staff working in the 187 CHCs, including at least one midwife or one assistant doctor responsible for neonatal care at each CHC. The findings of the visual audit of 19 items for neonatal care revealed that most hospitals were well-equipped, whereas the CHCs generally were lacking in equipment and drugs for safe delivery, temperature control and neonatal resuscitation (Table 1).

The questionnaire was completed by all (n = 412) primary healthcare workers on duty at the time of the knowledge survey,

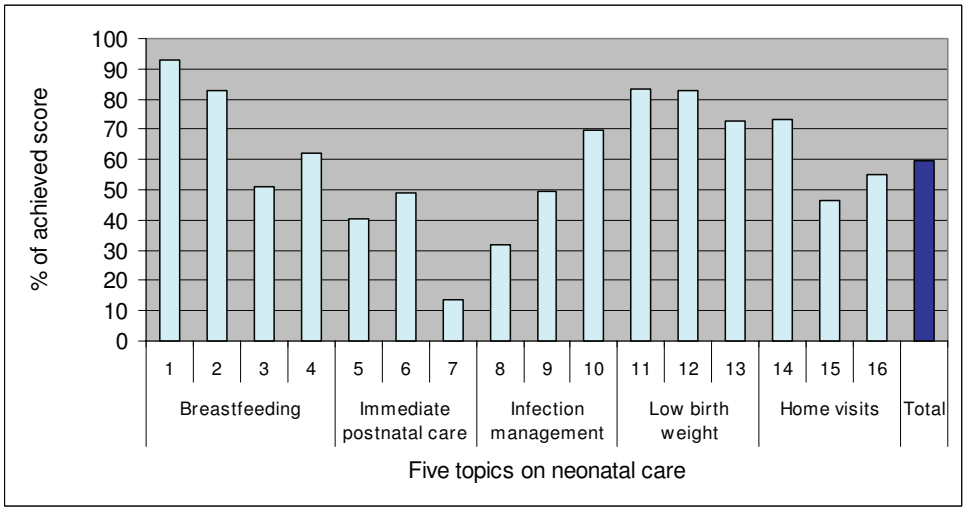

Figure 2
Knowledge survey results. Results of the knowledge survey among primary health care staff on five topics of neonatal health care (n = 412).

which was 63% (412/657) of the total number of staff in the 12 participating districts. Among the respondents, 8% (33/412) were doctors, 37% (151/412) assistant doctors, 24% (98/412) midwives and 31% (130/412) nurses. The mean age of the respondents was 37 years; 77% (316/412) were female and 80% (331/412) belonged to the Kinh ethnic group. In total, survey participants achieved 60% of the potential points (11 817 points out of 19 776) (Fig 2), resulting in a mean score of 28.7 (SD ± 6.1) (11 817 points/412 participants). Individual results ranged from 3 to 44, and mean scores at the district level varied from 26.7 to 31.5. Midwives (30.4), medical doctors (29.2), nurses (28.7) and assistant doctors (27.4) differed in mean scores ($p < 0.01$).

The availability of the National Guidelines was similar at CHCs and hospitals (Table 1). Among the 155 CHCs participating in the knowledge survey, 74% had a copy of the National Guidelines. There was a similar mean score in the knowledge survey among staff having access to the National Guidelines at their CHC (28.7) and those not having such access (28.6), ($p = 0.96$). During 2005, 32% (131/412) of the knowledge survey respondents worked at a CHC where staff had not assisted in any deliveries, 49% (202/412) worked at a CHC where staff had assisted in 1 to 24 deliveries and 19% (79/412) worked at a CHC where the staff assisted in 25 to 92 deliveries. There was no association between the staff's level of knowledge and the number of deliveries at the corresponding CHC ($p = 0.44$).

Based on the results from the knowledge survey, the 12 districts were divided into two groups (the districts with the six highest and six lowest mean scores), resulting in two distinct geographical areas, designated here as the northeast districts (NED) and the southwest districts (SWD) (Fig 1). NED consisted of 68 CHCs where staff had a mean score of 27.1 on the survey, while staff in the 87 CHCs in SWD achieved a mean score of 29.9 ($p < 0.01$). This distinct geographical division led us to analyse whether the use of healthcare services, neonatal death and other factors related to neonatal health also differed between the two areas. The two areas were different in all assessed healthcare outcomes. The NED had fewer pregnant women who attended three or more ANC visits, fewer families receiving a postnatal home visit, higher NMR and lower accessibility of National Guidelines than the CHCs in the SWD (Table 2). The two tertiary level hospitals in the province were both situated in the SWD (Fig 1). Patients and healthcare personnel in the NED were, on average, three times farther from the tertiary hospitals than patients and personnel in the SWD (Table 2).

Table 2: Characteristics of the northeast districts (NED) and the southwest districts (SWD) of Quang Ninh province, Viet Nam, 2005

Variable	NED	SWD	P-value
Average distance to regional hospital (kilometres)	95	31	<0.01[1]
Average distance to provincial hospital (kilometres)	75	24	<0.01[1]
Neonatal mortality rate[a]	21.9	14.2	<0.01[2]
Percentage of pregnant women with at least three antenatal care visits	45.6	70.6	<0.01[2]
Percentage of live births receiving a postnatal home visit	48.5	56.7	<0.01[2]
Percentage of community health centres having the National Guidelines[b]	64.7	79.3	<0.05[2]

[a] Number of deaths during the first 28 days of life per 1000 live births
[b] *Guidelines of reproductive health* (2003) by the Ministry of Health in Viet Nam
[1] P-value derived from independent sample t-test comparing NED and SWD
[2] P-value derived from the χ^2 test comparing the NED and the SWD

Discussion

Only 60% of the potential points in the knowledge survey were achieved, indicating that primary healthcare staff in the current province appears to have deficient knowledge regarding basic, evidence-based neonatal care. Geographical location was identified as a factor linked to staff knowledge on EBP. The level of knowledge was not associated with access to the National Guidelines or the volume of deliveries at community level, however. By targeting the primary healthcare practitioners on duty at the time of data collection in the 12 districts, an acceptable coverage was reached (ie 63% of all staff individuals). The survey questions were based on recommendations in general guidelines and further supported by the findings in a recently published systematic review of community-based interventions for perinatal health. These sources emphasize the importance of the five neonatal topics targeted in our knowledge survey.

Assessing the level of neonatal knowledge in this survey has helped us to understand if practitioners' awareness of current knowledge is an issue that needs to be addressed in the coming intervention. The staff performed well on some questions, but the overall findings must be judged as relatively poor, as the questions were limited to a basic level. The poor results on the questions about umbilical cord management indicate that CHCs lack a common strategy, despite concordant recommendations for cord care in the literature. Furthermore, the respondents had higher scores on questions about initiating breastfeeding than duration of breastfeeding. This corresponds to how women in a previous study in Viet Nam responded to questions about breastfeeding and might indicate a general lack of knowledge among healthcare workers on WHO's recommendations about duration of breastfeeding. Another area assessed in the knowledge survey was immediate postnatal care. The results clearly demonstrate a lack of knowledge on the particular questions on this topic.

There was no difference in knowledge between staff at CHCs with access to the National Guidelines and staff at CHCs lacking the guidelines. Despite availability of guidelines in three out of four CHCs, the recommendations do not seem to be fully known by the healthcare workers who participated in this study. This finding, which is consistent with previous research, suggests that access alone to the National Guidelines does not imply enhanced knowledge, indicating that passive dissemination of guidelines has limited impact. Additional methods reinforcing the implementation of these guidelines appear to be necessary.

The two geographical areas that had different levels of knowledge among healthcare staff were also found to differ in quality of care (ANC and postnatal home visits) and neonatal survival. Generally there was uncertainty among survey respondents as to why, when and by whom a home visit should be conducted, even though this is clearly described in the National Guidelines and stated in other literature. More than half of all families with a newborn child did not receive a home visit and, in accordance with the knowledge survey, staff members working in the NED were conducting fewer home visits than staff in the SWD. If home visits are neglected, there is an increased risk that severe infections that might arise a few days after birth are not detected. Such infections, in most cases, will need the attention of professional healthcare personnel, and the absence of home visits might therefore have severe consequences for the families. This is especially true for those families with a woman delivering at home, since a home visit of a midwife could be the family's only link to the healthcare system. Moreover, there was a 50% higher NMR in the NED than in the SWD, which strongly points to an inequity in neonatal survival, probably primarily because of differences in socioeconomic factors and distance to health facilities. The difference in knowledge among healthcare staff might also contribute to the difference in neonatal mortality: the area with the lowest level of knowledge had the highest NMR. Evidently the difference in knowledge alone cannot explain the difference in NMR. Rather, this identified link between knowledge and neonatal mortality might provide one ingredient in a complex picture of potentially casual associations. Globally, the underuse of EBP is described as a major reason for high neonatal mortality. Further, recent studies demonstrate that increased use of EBP resulted in improved neonatal care and reduced neonatal mortality. Whether staff level of knowledge is a contributing cause to the inequities in quality of care and neonatal survival or an effect of differences in socioeconomic factors is open for further investigation and discussion. Tugwell and co-workers suggest an evidence-based framework for equity-oriented knowledge translation to incorporate issues on health equity. This framework underlines the importance of identifying and prioritizing barriers as a base for choosing effective knowledge translation strategies for individuals belonging to different socioeconomic groups.

Conclusion

Overall, the findings point to a rather low level of knowledge in neonatal care among the primary healthcare workers in a Vietnamese province. We also found that geographical location of a community health centre was associated with the level of knowledge. Two distinct geographical areas not only differed in staff knowledge but also proved to have major inequities in neonatal mortality and quality of neonatal care. These inequities were probably linked to socioeconomic differences. Although the findings indicate a complex web of associations involving knowledge, geography, demographic factors and neonatal outcomes, we believe staff knowledge and use of knowledge to be important and feasible factors to work on for improving the neonatal health situation in Viet Nam.

Executive Profile…continued from page 24
more types of therapy from a single device. The system streamlines the ventilation process with interchangeable active and passive exhalation ports and the flexibility to choose the best available circuit and patient interface. Trilogy100 can accommodate a mask, mouthpiece or tracheostomy. The portable ventilator also can eliminate cumbersome valves and tubing by utilizing the passive circuit with Whisper Swivel II for invasive ventilation. For patient mobility, the compact design includes detachable, internal, and external power options, with up to 6 hours of battery capacity. Patients can be as active as possible while using the ventilator to support their breathing. The Trilogy100 ventilator's intuitive design allows for quick access to device settings and patient information. The easy-to-read, easy-to-navigate screens and clear, concise directions offer simplified patient views. In addition, optional DirectView patient data management software allows clinicians to more efficiently manage ventilation therapy with access to full patient information, including waveforms, trends, usage patterns, and summary statistics. The Trilogy100 life-support ventilator is backed by Philips Respironics service and support programs, including a 24/7 call center staffed with clinical and technical specialists, in-depth ventilation workshops, and educational training resources.

EXECUTIVE PROFILE

An interview with Carol Zilm of CareFusion Corporation

CareFusion Corporation is a new company resulting from the "spin-off" of the Clinical Medical Products group from Cardinal Health. The name is new, however the brands should be familiar to most readers. Medical dispensing and infusion brands such as Pyxis and Alaris have been around for several years. Today, we will focus on the Respiratory Care business unit, where some brands have been in the marketplace for over fifty years—names like Bird, Bear, SensorMedics, Pulmonetic Systems, VIASYS, Jaeger and AirLife. The CareFusion name is new, but the brands and products are very familiar.

Leading the Respiratory Care business is Carol Zilm.

Carol, who is CareFusion?
CareFusion is a global company that is focused on improving the safety and quality of healthcare. The depth and breadth of our products has made us an industry leader and widely recognized around the world. CareFusion employs about 15,000 people and our products are used in over 120 countries. Two of the biggest issues facing healthcare today are medical errors and infection control. Medical errors cost $6.5 billion dollars in the US and Europe. In the US, hospital acquired infections affect more than 1.5 million people and result in a reported 271 fatalities per day. As an industry we must face this challenge, and as a company we are.

What makes CareFusion different?
What makes us unique is how we "fuse" all of our core technologies. We are not just a device, diagnostic or heath information technology company. We combine our innovative core technologies with actionable intelligence to deliver measurable improvements to patient care.

We are also unique in that just about everything we do is driven by our customers. We put extensive effort into building close relationships with our customers and providing them with opportunities to offer feedback and direction to our innovation efforts. We work closely with trade organizations, customer focus groups, advisory boards, key opinion leaders, and our individual customers as we explore new opportunities, develop new products and evaluate new technologies. It is our customers that guide our efforts and this often differentiates us from other companies.

Can you give us an example of CareFusion innovation?
Our new ICU product the EnVe Ventilator, is a full featured, critical care ventilator that weighs about 9½ pounds. That's one tenth the weight of comparable ventilators. A typical ICU patient on a ventilator makes about two off-unit trips while he is in the hospital. Right now it's very difficult, if not impossible, to move that 90 pound ventilator with the patient. The healthcare team must place the patient on another ventilator for the trip. It makes much more sense to provide the same high standard of care by allowing patients to remain on their current ventilator. This helps reduce the stress on the patient, helps reduce the risk associated with changing ventilators and may reduce the risk of hospital acquired pneumonia. Essentially, you can provide ICU care anywhere you need.

What are some of the measureable improvements to patient care you spoke of?
From our infusion and dispensing business, we help prevent a harmful medication error every 2.6 days and protect 1.5 million patients annually from medication errors. Our data/analytics group is projecting an annual savings of 6,800 lives and $1 billon in healthcare costs by helping to reduce hospital acquired infections in member hospitals. We also help improve the bottom line. One hospital doubled its charge capture, while halving its inventory costs with our supply automation technologies.

What products are in your Respiratory Care portfolio?
Our Respiratory offerings are unsurpassed by any other company in the world. We are a market leader in mechanical ventilation with the Avea, Vela, 3100 series HFOV, LTV series, Infant Flow Nasal CPAP and the soon to be released EnVe and ReVel ventilators. In sleep diagnostics and therapy, our offerings include the SomnoStar and T-3 brands for sleep diagnostics and PureSom and Orion nasal CPAP devices. We are the market leader in pulmonary diagnostics with the SensorMedics and Jaeger families. Products include the VMax Encore, MasterScreen, MasterScope and FlowScreen devices. We are also a leader in respiratory consumable products. Our AirLife brand of products include a wide variety of disposable devices for use with invasive and non-invasive ventilation, oxygen therapy and medication delivery.

What is on the horizon for CareFusion?
With rising healthcare costs, declining reimbursement, personnel shortages and a global demand for quality, we have clear drivers for growth and innovation. Over the next couple of years we estimate that we will have about 40 new products available to further provide safety and value for our customers. We plan to meet our goals by increasing our R&D efforts, and further development of our core technologies.

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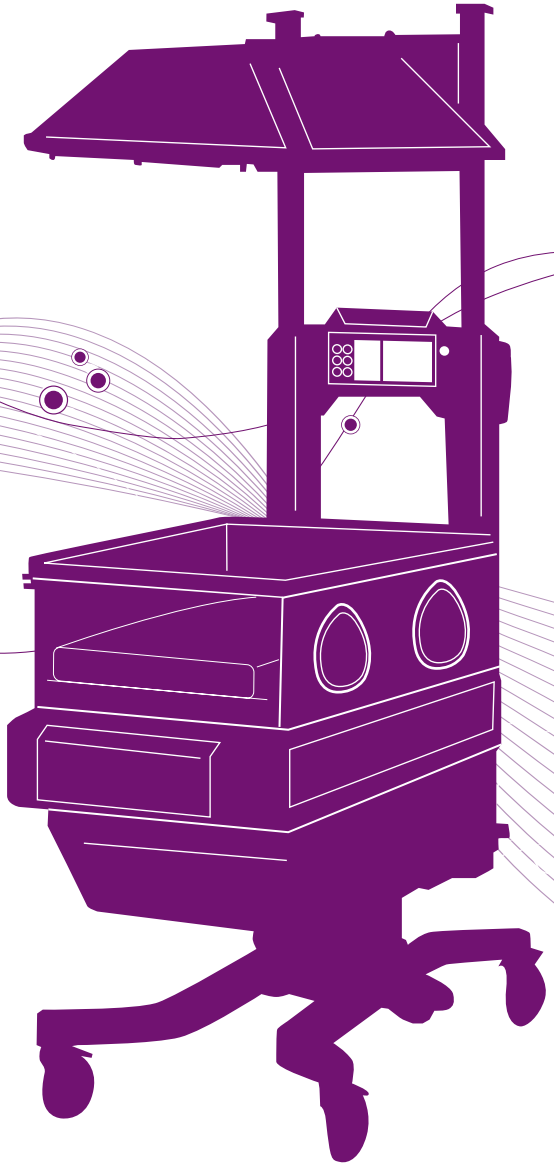

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