Vol. 23 No. 5
September 2010

neonatal INTENSIVE CARE

The Journal of Perinatology-Neonatology

NANN PREVIEW
CO2 REACTIVITY
EDI CATHETER
C-SECTIONS
PULSE OXIMETRY
BILIRUBIN EVALUATION
VLBW AND MORTALITY

Continued innovation in NIRS data...via Vital Sync.™ Enhance patient assessment by having all critical patient data at your fingertips, in a format you define. Whether for bedside care or research data aggregation, let Vital Sync technology cut through the complexity.

Revealing Perfusion Imbalance

My gut ischemia was discovered early with the help of rSO_2.

Enhanced Detection for Rapid Response.

Every patient has unknown clinical variables. Let the INVOS® System help you reveal them. This gentle cerebral/somatic oximeter noninvasively monitors regional oxygen saturation (rSO_2) changes in the brain, renal area, abdomen and other specific sites. Its real-time data enhances detection and response to oxygen threats such as those related to low cardiac output[1], renal dysfunction[2], neurologic damage[3], shock[4], gut ischemia[4] and seizures[5]. It also reflects the impact of interventions, so you can assess efficacy and next steps before problems escalate.

Reveal new insights with the INVOS System.

CEREBRAL/SOMATIC INVOS® OXIMETER
REFLECTING THE COLOR OF LIFE®

1. Hoffman GM, et al. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu. 2005, pp 12-21. 2. Hoffman GM, et al. Anesthesiology 2005; 103:A1327 3. Dent CL, et al. J Thorac Cardiovasc Surg 2005; 130: 1523-30. 4. Kaufman et al. J Ped Crit Care Med 2008; 9:62-8. 5. Diaz GA, et al. Eur J Paediatr Neurol 2006; 10:19-21

SOMANETICS®

www.somanetics.com | 800.359.7662

The last step in bereavement care…

Presentation & Handling

The **Preshand System™** offers caregivers a dignified and practical approach to Presenting and Handling an infant loss.

The **Presentation** offers parents a softer, less clinical setting for good-byes in the hospital and helps create a comforting memory and a lasting image of their baby resting peacefully in a baby basket.

At this time, staff or parents may consider taking photos of the baby in the Presentation Basket to preserve this image.

For **Handling**, in a staff work area, the caregiver makes final preparations for the baby and securely closes the Insert by tying the ribbons. Serving as both a respectful means of storing the baby, and providing the baby's final resting place, the Preshand Insert is placed inside the Handling Carrier, where transporting to the morgue or pathology throughout any public area in the hospital can now be done with confidence and discretion.

The **Preshand System** provides the needed tools to complete the last step in bereavement care and considers the dignity and respect for *both* the baby *and* the caregiver.


Present Baby In Preshand Basket


Away From Family, Remove Insert From Basket


Fold Coverlet Over Baby


Secure Lid W/ Ribbons, Fill Out Insert ID Card


Place Insert Into Carrier


Transport Baby Confidently

To View A Product Demonstration
visit www.memoriesunlimited.com/fern
enter password: basket

They came to you for care…and left knowing that you do.™

memories UNLIMITED

tel: (360) 491-9819
fax: (360) 491-9827
email: info@memoriesunlimited.com

neonatal
INTENSIVE CARE

Vol. 23 No. 5
September 2010

Table of Contents

DEPARTMENTS

ARTICLES

Editorial

Blast From The Past

What haven't we said about neonatal care? Instead, here's a report on neonatal care from 1848, by R. Annan, published in Medical Times 18:109. This article has been slightly edited, and is from Neonatology on the Web, a terrific site for neonatal caregivers and the parents of preemies. I would especially draw your attention to its fine collection of historical articles, photographs and monographs. Copyright © 1998 Neonatology on the Web.

Case of a Child Born Betwixt the End of the Sixth and Middle of the Seventh Month and Brought Up, by R. Annan.

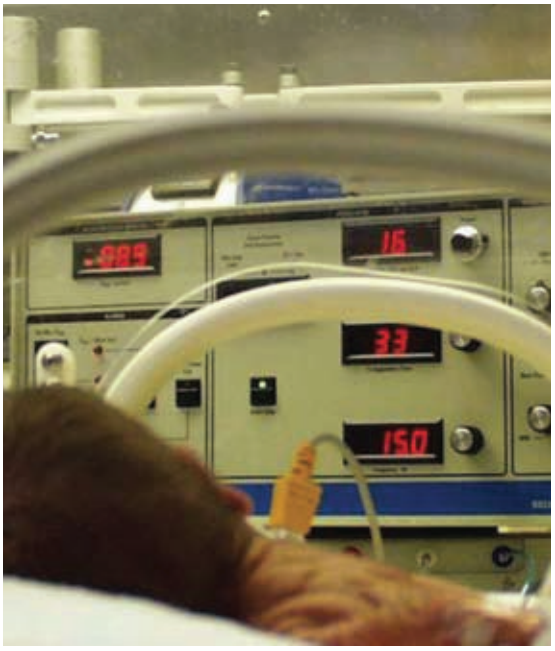
On the 5th of April 1848, at 26 weeks of gestation, the pains of labor came on rather unexpectedly, and in less than two hours [Mrs R, age 38] gave birth to a female child, which I found very carefully wrapped up and placed so as to receive the gentle warmth of a fire. Unloosening the cloths to enable me properly to tie the cord, which had been hastily cut through and tied about six inches from the navel, I found a tiny infant, the proportions of which I did not think it proper then to take time to ascertain. As it was not expected to survive long it was placed on a cushion in an easy-chair, so as to be sheltered from draughts of air, and at the same time so as to receive benefit from the fire, being previously wrapped up in folds of cotton wool and covered over with flannel. An earthenware bottle, filled with warm water, which has been pretty constantly continued, was placed behind the cushion. To attempt otherwise to dress the infant was never once thought of. This was about 10 AM. As the infant showed more signs of vitality, the lips and mouth were gently moistened with a mixture of one part of cream, three parts of warm water, and sweetened with sugar. At first it was not observed to swallow, but in the evening, when I returned, there could be little doubt that this had been the case from the minute quantities of the mixture, given from time to time, not having been rejected. On the following day, to this mixture from three to four drops of sherry wine were added, and continued to be used as yesterday. On the third day the deglutition was very perceptible. Of this advantage was taken, and under the eye of a most careful female relative from three to four drops of wine were given every six hours, in as much of the mixture as the infant was found able to swallow.

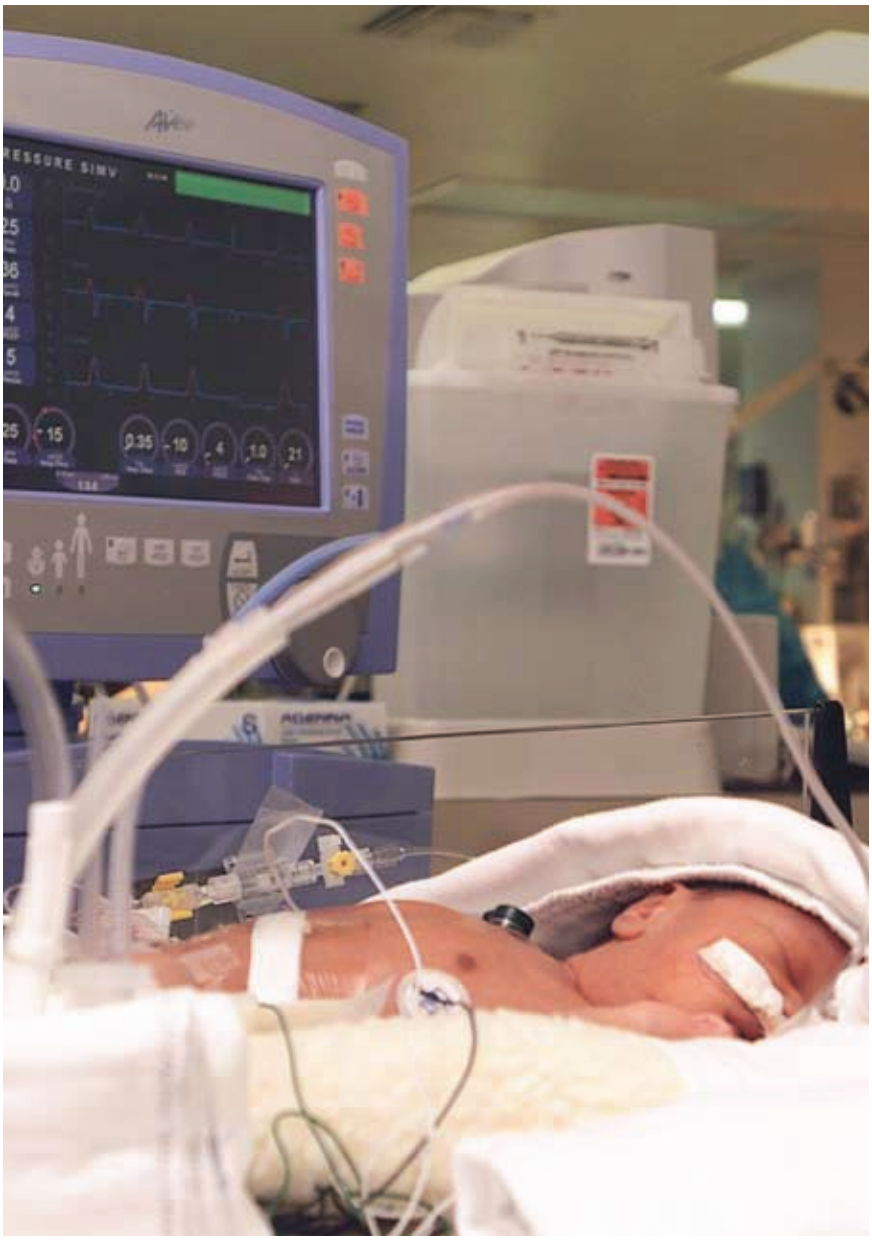
On the seventh day the child was weighed and found, including a small flannel roller, to be twenty-four ounces. The roller was under one ounce in weight. At this period the length of the child was not taken, but was supposed to be from twelve to thirteen inches. As the feelings of the mother were most acute, and as, indeed she was considered to be in a dying state, and as it was not expected that the infant could suck, an occasional wet nurse was not got till the ninth day; the other nourishment being supplemented nearly as above. At first the nurse merely milked a proportion into the mouth, but in less than eight days it was found that the child could draw a little, which gradually improved. Occasionally a small portion of magnesiausta or castor oil was given, so as to ensure regularity in the bowels. About the end of the third week very fine oatmeal gruel, sweetened with sugar, was alternated with the cream and water, the quantity of wine being gradually increased; and latterly the quantity given during twenty-four hours has been from one to one and a half teaspoonful.

When six weeks and one day old, the weight was accurately ascertained to be thirty-nine ounces; the length, as nearly as a tape applied to the child would enable, showed sixteen and a half inches; and on the 30th of May the weight was forty-three ounces, having gained four ounces since last weighing. At the last period the circumference, by the forehead and occiput, was barely eleven and a half inches.

During the last four weeks the child has been regularly bathed in water, at first tepid, but latterly of the temperature of from 65° to 70° of Fahrenheit; and occasionally, according to the testimony of the very careful female relative, who has hitherto so creditably and successfully super-intended the nursing, sometimes considerably

Continued on page 48…





Our biggest concern is your **smallest patient.**

The name may be new, but CareFusion products have helped redefine the care of infants with measureable improvements in outcomes. From non-invasive support to conventional and high frequency ventilators CareFusion has the specialized tools you need to treat your most fragile patients.

AVEA® **3100A** **Infant Flow SiPAP** **Air*Life*™ nCPAP**

carefusion.com

CareFusion

neonatal INTENSIVE CARE

ISSN 1062-2454
Published seven times each year by
Goldstein and Associates, Inc.
10940 Wilshire Blvd., Suite 600
Los Angeles CA 90024
Phone: 310-443-4109
Fax: 310-443-4110
E-mail: s.gold4@verizon.net
Web: www.nicmag.ca

Publisher
Steve Goldstein

Editor
Les Plesko

Senior Editor
Carol Brass

Associate Editor
Laszlo Sandor

Design, Typography, Prepress and Production Management
http://accugraphics.net

Circulation, Coverage, Advertising Rates: Complete details regarding circulation, coverage, advertising rates, space sizes, and similar information are available to prospective advertisers. Closing date is 45 days preceding date of issue.

Change of Address notices should be sent promptly to Circulation Department: provide old mailing label as well as new address: include zip code or postal code. Allow two months for change.

Editorial Contributions may be sent by e-mail and will be handled with reasonable care: however, publishers assume no responsibility for safety of art work, photographs, or manuscripts. Every precaution is taken to ensure accuracy, but the publishers cannot accept responsibility for the correctness or accuracy of information supplied herein or for any opinion expressed. Editorial closing date is the first day of the month preceding month of issue.

Editorial Advisory Board

Fully automated critical care testing. The revolution is at your fingertips.

Unmatched quality assurance, total remote management and the most accurate results—in a single touch. The GEM Premier 4000 brings complete automation to the most labor- and skill-intensive tasks in critical care testing. At the touch of a button, the GEM Premier 4000 *automates:* **quality management** through Intelligent Quality Management (iQM), **instrument maintenance** with its multi-use disposable cartridge PAK, and **information management** with GEMweb Plus connectivity software and automated operator certification. The GEM Premier 4000—it's advanced, simple, revolutionary—and leading the automation revolution in critical care.

Measured Parameters:

- **Blood Gas:** pH, pCO_2, pO_2
- **Electrolytes:** Na^+, K^+, Ca^{++}, Cl^-
- **Metabolites:** Glucose, Lactate
- **Hematocrit**
- **Liver Function:** Total Bilirubin*
- **CO-Oximetry:** tHb, O_2Hb, COHb, MetHb, HHb, sO_2
- **Renal Function:** BUN/Creatinine**

* CE marked. Not currently saleable in US and Canada.
** In development

Werfen Group | Instrumentation Laboratory

IL is a company of Werfen Group.

Visit **www.ilus.com/GOGEM** or contact your local IL sales representative today.

GEM® PREMIER 4000 *with* iQM®

Focus on patient care, not the device.

Bubble CPAP therapy is easy to implement with the new Babi.Plus™ Bubble PAP Valve 0–10 cm H_2O.

Precise, versatile and FDA cleared for use with infants weighing <10 kg.

Now you're free to focus on your patient.

Safe and effective
Clearly marked settings for precise CPAP pressure adjustment

Versatile applications
Ready for immediate set up in the NICU

Convenient packaging
Eliminates time consuming tasks associated with assembly and maintenance of hospital assembled bubble CPAP devices

Cost effective solutions
Adjustable from 1 to 10 cm H_2O
Accepts 15 mm OD and 22 mm ID circuits

BABI.PLUS™ PACIFIER ADAPTOR
Fits onto pacifier to rapidly deliver therapy

SIL.FLEX™ STOMA PAD
Comfort for tracheostomy patients; extended use 28 days

B&B MEDICAL TECHNOLOGIES

A **world** of PRODUCTS for **better breathing**

Toll-free: +1.800.242.8778
Tel: +1.760.929.9972 • Fax: +1.760.929.9953
2734 Loker Avenue West, Suite M • Carlsbad, CA 92010 USA

www.BandB-Medical.com

When treating infants for respiratory distress syndrome (RDS)

EXPERIENCE FAST RDS SUCCESS[1-4]

The benefits of CUROSURF® add up to rapid success

- Delivers more surfactant with less volume at initial dose[1,5,6]
- Rapid onset of action with sustained FiO_2 reduction[2-4]
- Single-dose success in 73% of treated infants[2]
- Facilitates transition from mechanical ventilation[7-10]

CUROSURF®
(poractant alfa) Intratracheal Suspension

Clinical studies have not established that fewer doses or lower volume result in superior safety or efficacy based on clinically relevant end points

Physiological end points (eg, faster reduction in FiO_2) have not been proven to impact key clinical outcomes such as mortality due to RDS

Indication

CUROSURF (poractant alfa) Intratracheal Suspension is indicated for the treatment (rescue) of Respiratory Distress Syndrome (RDS) in premature infants. CUROSURF reduces mortality and pneumothoraces associated with RDS.

Important Safety Information

CUROSURF is intended for intratracheal use only. THE ADMINISTRATION OF EXOGENOUS SURFACTANTS, INCLUDING CUROSURF, CAN RAPIDLY AFFECT OXYGENATION AND LUNG COMPLIANCE. Therefore, infants receiving CUROSURF should receive frequent clinical and laboratory assessments so that oxygen and ventilatory support can be modified in response to respiratory changes. CUROSURF should only be administered by those trained and experienced in the care, resuscitation, and stabilization of preterm infants. TRANSIENT ADVERSE EFFECTS SEEN WITH THE ADMINISTRATION OF CUROSURF INCLUDE BRADYCARDIA, HYPOTENSION, ENDOTRACHEAL TUBE BLOCKAGE, AND OXYGEN DESATURATION. These events require stopping CUROSURF administration and taking appropriate measures to alleviate the condition. After the patient is stable, dosing may proceed with appropriate monitoring.

Please see brief summary of prescribing information on reverse.

References: 1. CUROSURF® (poractant alfa) Intratracheal Suspension prescribing information, Cornerstone Therapeutics Inc, April 2010. **2.** Ramanathan R, Rasmussen MR, Gerstmann DR, Finer N, Sekar K; and The North American Study Group. *Am J Perinatol.* 2004;21:109-119. **3.** Speer CP, Gefeller O, Groneck P, et al. *Arch Dis Child.* 1995;72:F8-F13. **4.** Malloy CA, Nicoski P, Muraskas JK. *Acta Paediatr.* 2005;94:779-784. **5.** Survanta® (beractant) Intratracheal Suspension prescribing information, Abbott Laboratories, Inc, May 2008. **6.** Infasurf® (calfactant) Intratracheal Suspension prescribing information, ONY, Inc, June 2009. **7.** Verder H, Robertson B, Greisen G, et al; for The Danish-Swedish Multicenter Study Group. *N Engl J Med.* 1994;331:1051-1055. **8.** Verder H, Albertsen P, Ebbesen F, et al. *Pediatrics.* 1999;103:1-6. **9.** Dani C, Bertini G, Pezzati M, Cecchi A, Caviglioli C, Rubaltelli FF. *Pediatrics.* 2004;113:e560-e563. **10.** Bohlin K, Gudmundsdottir T, Katz-Salamon M, Jonsson B, Blennow M. *J Perinatol.* 2007;27:422-427.

Under license of:

Chiesi
People and ideas for innovation in healthcare

CORNERSTONE THERAPEUTICS INC.®

CUROSURF®
(poractant alfa) Intratracheal Suspension

Brief Summary of Prescribing Information

SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATION AND USAGE
CUROSURF is indicated for the treatment (rescue) of Respiratory Distress Syndrome (RDS) in premature infants. CUROSURF reduces mortality and pneumothoraces associated with RDS.

WARNINGS
CUROSURF is intended for intratracheal use only.

THE ADMINISTRATION OF EXOGENOUS SURFACTANTS, INCLUDING CUROSURF, CAN RAPIDLY AFFECT OXYGENATION AND LUNG COMPLIANCE. Therefore, infants receiving CUROSURF should receive frequent clinical and laboratory assessments so that oxygen and ventilatory support can be modified to respond to respiratory changes. CUROSURF should only be administered by those trained and experienced in the care, resuscitation, and stabilization of pre-term infants.

TRANSIENT ADVERSE EFFECTS SEEN WITH THE ADMINISTRATION OF CUROSURF INCLUDE BRADYCARDIA, HYPOTENSION, ENDOTRACHEAL TUBE BLOCKAGE, AND OXYGEN DESATURATION. These events require stopping Curosurf administration and taking appropriate measures to alleviate the condition. After the patient is stable, dosing may proceed with appropriate monitoring.

PRECAUTIONS
General
Correction of acidosis, hypotension, anemia, hypoglycemia, and hypothermia is recommended prior to CUROSURF administration. Surfactant administration can be expected to reduce the severity of RDS but will not eliminate the mortality and morbidity associated with other complications of prematurity. Sufficient information is not available on the effects of administering initial doses of CUROSURF other than 2.5 mL/kg (200 mg/kg), subsequent doses other than 1.25 mL/kg (100 mg/kg), administration of more than three total doses, dosing more frequently than every 12 hours, or initiating therapy with CUROSURF more than 15 hours after diagnosing RDS. Adequate data are not available on the use of CUROSURF in conjunction with experimental therapies of RDS, e.g., high-frequency ventilation.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Studies to assess potential carcinogenic and reproductive effects of CUROSURF, or other surfactants, have not been conducted. Mutagenicity studies of CUROSURF, which included the Ames test, gene mutation assay in Chinese hamster V79 cells, chromosomal aberration assay in Chinese hamster ovarian cells, unscheduled DNA synthesis in HELA S3 cells, and in vivo mouse nuclear test, were negative.

ADVERSE REACTIONS
Transient adverse effects seen with the administration of CUROSURF include bradycardia, hypotension, endotracheal tube blockage, and oxygen desaturation. Pulmonary Hemorrhage is a known complication of premature birth and very low birth-weight and has been reported both in clinical trials with Curosurf and in post-marketing adverse event reports in infants who had received Curosurf. The rates of common complications of prematurity observed in Study 1 are shown below.

COMPLICATIONS OF PREMATURITY

	Curosurf 2.5 mL/kg (200 mg/kg) n=78 %	CONTROL* n=66 %
Acquired Pneumonia	17	21
Acquired Septicemia	14	18
Bronchopulmonary Dysplasia	18	22
Intracranial hemorrhage	51	64
Patent Ductus Arteriosus	60	48
Pneumothorax	21	36
Pulmonary Interstitial Emphysema	21	38

*Control patients were disconnected from the ventilator and manually ventilated for 2 minutes. No surfactant was instilled.

Immunological studies have not demonstrated differences in levels of surfactant-anti-surfactant immune complexes and anti-CUROSURF antibodies between patients treated with CUROSURF and patients who received control treatment.

FOLLOW-UP EVALUATIONS
Seventy-six infants (45 treated with CUROSURF) were evaluated at 1 year of age and 73 infants (44 treated with CUROSURF) at 2 years of age. Data from follow-up evaluations for weight and length, persistent respiratory symptoms, incidence of cerebral palsy, visual impairment, or auditory impairment was similar between treatment groups. In 16 patients (10 treated with CUROSURF and 6 controls) evaluated at 5.5 years of age, the developmental quotient, derived using the Griffiths Mental Developmental Scales, was similar between groups.

OVERDOSAGE
There have been no reports of overdosage following the administration of CUROSURF. In the event of accidental overdosage, and only if there are clear clinical effects on the infant's respiration, ventilation, or oxygenation, as much of the suspension as possible should be aspirated and the infant should be managed with supportive treatment, with particular attention to fluid and electrolyte balance.

How Supplied
CUROSURF (poractant alfa) Intratracheal Suspension (NDC Numbers: 10122-510-01 [1.5 mL]; 10122-510-03 [3 mL]) is available in sterile, ready-to-use rubber-stoppered clear glass vials containing 1.5 mL [120 mg surfactant (extract) or 3 mL (240 mg surfactant (extract)] of suspension. One vial per carton.

Store CUROSURF Intratracheal Suspension in a refrigerator at +2 to +8°C (36-46°F). Unopened vials of CUROSURF may be warmed to room temperature for up to 24 hours prior to use.

CUROSURF should not be warmed to room temperature and returned to the refrigerator more than once. PROTECT FROM LIGHT. Do not shake. Vials are for single use only. After opening the vial discard the unused portion of the drug.
Rx only.

CORNERSTONE THERAPEUTICS INC.®

Manufactured for:
Cornerstone Therapeutics Inc.
Cary, NC 27518

Manufactured by and licensed from:

Chiesi
People and ideas for innovation in healthcare

Chiesi Farmaceutici, S.p.A.
Parma, Italy 43100

CTC1485A0710

F&P Neopuff™

Infant T-Piece Resuscitator

Continuing to raise the standard of care in infant resuscitation

Fisher & Paykel Healthcare is dedicated to improving patient care and outcomes. With over 20 years of worldwide use and acceptance involving millions of safe and effective resuscitations, the F&P Neopuff Infant T-Piece Resuscitator has recently been updated to further enhance functionality and usability while providing optimal resuscitation.

To experience the enhanced F&P Neopuff please visit us at the NANN 2010 Conference in Las Vegas. **Or call us on (800) 446-3908 and we'll gladly come and visit you.**

(800) 446-3908
experienceneopuff@fphcare.com

F&P INFANT RESPIRATORY CARE CONTINUUM™

T-PIECE RESUSCITATION | INVASIVE VENTILATION | CPAP THERAPY | NASAL HIGH FLOW | LOW FLOW OXYGEN

Fisher & Paykel Healthcare 15365 Barranca Parkway, Irvine, CA 92618 USA.
Tel - 800 446 3908 **or** +1 949 453 4000 Fax - +1 949 453 4001

Fisher & Paykel HEALTHCARE

You Know the Answer:

Which Practice is Safer

Introducing the First and Only Waterless Milk Warmer™ Designed for NICUs.

Medela's Waterless Milk Warmer

The Safer, Easier Way to Warm Human Milk

- Eliminates risk associated with warming with water.
- Consistently warms milk to temperatures consistent with expressed human milk.
- Safely thaws human milk in less than 30 minutes.
- Accommodates all Medela breastmilk bottles and syringes 1ml - 60ml.

OR

medela

Call or email your local Medela Representative for a demonstration.

Medela, Inc., P.O. Box 660, 1101 Corporate Drive, McHenry, IL 60051-0660 • Phone: (800) 435-8316 or (815) 363-1166 Fax: (815) 363-1246 Email: customer.service@medela.com

Are You Modeling Safe Sleep Practices?

Help Reduce the Risk of SIDS by Modeling Safe Sleep Practices In-Hospital

Are you telling new parents how to reduce the risk of SIDS and then swaddling their newborn with a loose blanket? Your nursery practices could actually be sending the wrong message to parents. The American Academy of Pediatrics suggests the use of a wearable blanket to replace loose blankets in the crib. Designed by Bill Schmid, who lost his first born to SIDS, the HALO® SleepSack® wearable blanket is the #1 trusted choice of hospitals. It's the perfect solution for modeling safe sleep practices in-hospital and as gifts for new parents.

"The babies love them and the nurses do as well… we wrap the babies in SleepSack Swaddles while they are here, then provide SIDS prevention literature for parents when they are discharged. We think it makes a difference."

– Cathy Anderson, North Memorial Hospital Newborn Intensive Care Nurse Manager

FREE TRIAL

Request a FREE HALO® SleepSack® wearable blanket and join the more than 400 hospitals that have implemented the HALO® Safer Way to Sleep initiative.

Call 888-999-HALO or visit HaloSleep.com/Hospitals

FIGHTING SIDS SINCE 1994 #1 CHOICE OF HOSPITALS HALO™

The First Candle GIFTS that GIVE FOUNDING PARTNER SIDS Alliance

Canadian Foundation For the Study of Infant Deaths — RECOMMENDED HALO® SleepSack™ wearable blanket & Swaddle

HALO® the safer way to sleep®

Aeroneb® Pro Aeroneb® Solo

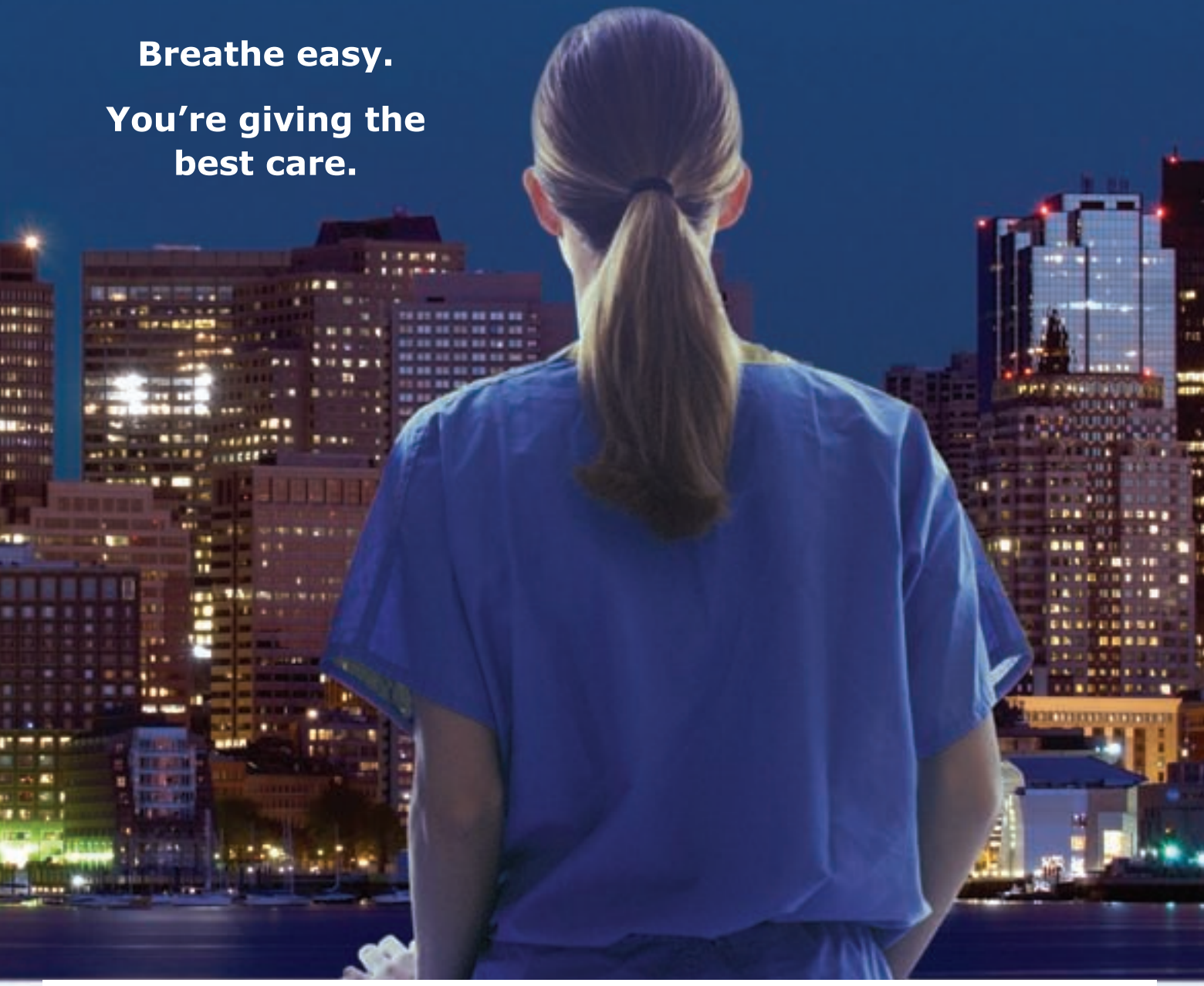
Aerogen nebulizers deliver an incredible four times more medication than traditional jet nebulizers, offering you unsurpassed efficiency and allowing you to give your patients the very best care available. They work independently to the ventilator settings meaning there's no added flow, no nuisance alarms, no loss of PEEP when opened for refill and no drug wastage. Aerogen truly sets a new standard.

Aerogen

We deliver best

Breathe easy.

You're giving the best care.



www.aerogen.com Phone USA (866) 423-7643 (toll free)

News

☐ September 2010

GET SOME SLEEP

The common practice of successive 12-hour shifts for US hospital nurses leaves many with serious sleep deprivation, higher risk of health problems, and more odds of making patient errors, according to a University of Maryland, Baltimore (UMB) study. The 12-hour shift trend started in the 1970s and 1980s when there were nursing shortages. The study involved 80 registered nurses, working three successive 12-hour shifts, either day or night. Researchers were surprised at the short duration of sleep that nurses achieve between 12-hour shifts. Over 50% of shifts were longer than 12.5 hours, and with long commutes and family responsibilities, nurses were found to have very little opportunity to rest between shifts. The study also found that the average total sleep time between 12-hours shifts was only 5.5 hours. Night-shift nurses averaged only about 5.2 hours of sleep, and the quality of their sleep was extremely fragmented. People who are sleep deprived experience microsleep periods, little lapses in attention, and intershift fatigue, meaning that on the next shift you don't fully recover from the previous one. The researchers noted that few hospitals offered alternatives to the pattern. In 10 previously published studies on the effects of 12-hour shifts, none showed positive effects, while four showed negative effects on performance. One study of 393 nurses on 5,317 shifts found that the odds of making errors by those who reported working more than 12 hours in shifts was three times greater than nurses who reported working 8.5 hour shifts. The most common problems were needle-stick injuries, musculoskeletal disorders, drowsy driving, and other health breakdowns related to sleep deprivation.

DON'T INTERRUPT

Nurses who are interrupted while administering medication appear to have an increased risk of making medication errors, according to researchers at the University of Sydney. As a result, medication errors occur as often as once per patient per day in some settings, and approximately one-third of harmful medication errors are thought to occur during medication administration. Researchers studied nurses preparing and administering medications in six wards of two major teaching hospitals. Interruptions were noted and two types of errors were tracked: procedural failures, including failure to read labels, check patient identification or record administration on medication chart; and clinical errors, including wrong drug, dose, formulation or strength. Ninety-eight nurses were observed while preparing and administering 4,271 medications to 720 patients over 505 hours from September 2006 through March 2008. Only 19.8% of these administrations were free of both kinds of errors. At least one procedural failure occurred in 74.4% of administrations and at least one clinical failure in 25%. Interruptions occurred during 53.1% of administrations. Each interruption was associated with a 12.1% increase in procedural failures and a 12.7% increase in clinical errors. When nurses were not interrupted, procedural failure rates were 69.6% and clinical error rates were 25.3%, compared with procedural failure rates of 84.6% and clinical error rates of 38.9% if they were interrupted three times. Errors became more severe as the number of interruptions increased. Without interruption, the estimated risk of major error was 2.3%; with four interruptions this risk doubled to 4.7% percent. The researchers suggested that nurses might wear vests with signs that said "Do Not Interrupt."

PARTNERSHIP

The Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN) announced a partnership with University of Virginia Health System. The UVA Health System will implement AWHONN's EDGE Benchmarking Database, a new technology that extracts data directly from electronic health records. These data will be used by UVA nurses to make staffing, clinical, and quality decisions specific to women and infant's health. The system allows nurses to compare their unit to that of other institutions, and the database has the ability to track birth patterns. The information helps nurse administrators make staffing decisions and deploy resources wisely. For example, users can see the peak times for births, inductions and c-sections, and staff accordingly.

AT RISK

The risk of autism and/or special educational needs were 1.16 times greater for babies born at 37 to 39 weeks of gestation, compared to those born at the full 40 weeks, according to researchers at the University of Glasgow, who analyzed the birth history of 400,000 schoolchildren. Babies born at 37-39 weeks of gestation were 1.16 times as likely to have a SEN as babies born at 40 weeks.

NO HELP

A lack of skilled attendants at birth accounts for two million preventable maternal deaths, stillbirths and newborn deaths each year, according to the newly released Countdown to 2015 Decade Report (2000-2010). Nearly 50% of women in the 68 countries tracked in the Countdown report, mostly in Sub-Saharan Africa and South Asia, still give birth without the aid of a trained midwife, nurse, doctor, or other skilled birth attendant. Only 10 of the 68 Countdown countries have increased the rate of skilled care at childbirth by at least 10% since 1990. Eleven countries made no progress. The global shortage of midwives is especially severe: an estimated 700,000 new midwives and other trained providers are needed in order to provide skilled childbirth care to all women who need it. On the plus side, a skilled provider attends more than 75% of births in Azerbaijan, Tajikistan, Iraq, Egypt and Indonesia. Almost 100% of births are attended in Turkmenistan and China. Angola, Bhutan, Laos, Nepal, Peru, Burkina Faso, Pakistan, and Rwanda have also shown gains. Among the countries making negative progress are Bolivia, Cote d'Ivoire, Liberia, Malawi, Nigeria, Somalia, Swaziland, and Zimbabwe.

INDUCTED

Between 1992 and 2003, the rate of labor inductions in the US nearly doubled, causing earlier births, according to a study at McGill University. Researchers examined US government vital

statistics, finding that labor inductions increased from 14% of full-term births in 1992 to 27% in 2003. During the same period, the proportion of births occurring at the 37th or 38th week of pregnancy increased from 19% to 30%. About 42% of births occurred before week 40 in 1992, compared with more than 60% of full-term births in 2003. The above info is copyright 2010 National Partnership for Women & Families. All rights reserved.

GOOD NEWS

The rate of premature births in the US fell to 12.3% in 2008, following a decrease in 2007 and marking the first two-year decrease in nearly three decades, according to the National Center for Health Statistics. The preterm birth rate was 12.7% in 2007 and 12.8% in 2006. The late preterm birth rate, for infants born at 34 to 36 weeks gestation, declined from 9.1% in 2006 to 8.8% in 2008. The rate of infants born earlier than 34 weeks also fell slightly, from 3.7% in 2006 to 3.6% in 2008. The report also found that the rate of preterm infants delivered via cesarean section dropped from 17.8% in 2006 to 17.1% in 2008. Preterm birth rates dropped in all states except Hawaii, and women younger than age 40 experienced decreases in preterm births. The preterm birth rate among non-Hispanic black infants was 17.5%, compared with 12.1% among Hispanic infants and 11.1% among white infants. Information copyright 2010 National Partnership for Women & Families. All rights reserved.

BLOCKED

Dietary supplement CDP-choline, under study for stroke and traumatic brain injury, may block skull and brain damage that can result from alcohol consumption early in pregnancy, according to researchers at the Medical College of Georgia. Alcohol consumption in early pregnancy increases levels of the lipid ceramide and results in neural crest damage. Researchers said there's a window of about four weeks after conception when neural crest cells emerge for a few days before morphing into other cell types that help form numerous organs. This is often before a woman knows she is pregnant. Researchers found that 25% of mouse embryos exposed to alcohol during the formation of the neural crest had defects in the fibrous joints that connect the skull. If the crest is damaged, the meninges doesn't develop properly and tissue like bone and brain that are regulated by the meninges don't develop properly either. When the researchers added ceramide-neutralizing CDP-choline to the mouse cells, cell death and ceramide levels were reduced. CDP-choline results in the production of less ceramide, preventing damage, providing the drinking stops.

MALE SHOCK

The general stress caused by psychological shock from the 9/11 terrorist attacks may have led to an increased number of male children being miscarried in the US, according to researchers at UC Berkeley and Irvine. The fetal death rate for boys spiked in September 2001, and significantly fewer boys than expected were born in December of that year. According to the researchers, the theory of "communal bereavement" holds that societies may react adversely to unsettling national events. Another study found that women in California miscarried more male babies in the year after 9/11 than they did in other years from 1995 to 2002. Researchers said that an evolutionary adaptation is likely to blame for the increase, in that male fetuses are more sensitive to female stress hormones. When a pregnant woman experiences some sort of crisis her male baby is more vulnerable to be miscarried. Researchers conjectured that female fetuses are hardier than males because women have adapted to

Introducing the First Disposable

Infant T-Piece Resuscitator

Neo-Tee™

flow-controlled, pressure limited with built-in manometer

- Provides consistent PIP and PEEP Pressure
- Reliable Built-in manometer verifies pressures
- Disposable feature eliminates bulky capital equipment
- Lightweight portable, space-saving
- Cost-Efficient, clinicians can now afford to implement consistent T-piece resuscitation at every NICU bedside

Adjustable PIP Controller
(with internal pressure relief)

Mercury Medical®

Your need... Our innovation

Mercury Medical • Clearwater, Florida 33762-4807 • (800) 237-6418 • 727-573-0088 • www.mercurymed.com

Please visit us at the Mercury Medical Booth #720 for the NANN 2010 Annual Conference, Paris Hotel, Las Vegas, Nevada

produce the alpha male. In times of prosperity and security, male fetuses are more likely to be brought to term, because there's a greater chance that they'll be healthy and robust. During periods of scarcity or instability, however, male miscarriages are much more common: A woman's body faces an evolutionary decision of whether to carry her male baby to term, or abort the fetus. In other words, if you're pregnant in a time of low resources, there's less impetus for your body to bear that child. Researchers also noted that the phenomenon has been observed during other instances of national stress, like economic recessions or natural disasters. Reported in Medical News Today and by AOL.

MARKED FOR LIFE

A study in mice at Yale University reveals that prenatal exposure to endocrine-disrupting chemicals like BPA and diethylstilbestrol (DES) may program a fetus for life and as such, adult women who were exposed prenatally to BPA or DES could be at increased risk of breast cancer. Endocrine-disrupting chemicals in the environment interfere with hormone biosynthesis and result in adverse developmental, reproductive, neurological and immune effects in both humans and wildlife. These chemicals are designed, produced and marketed largely for specific industrial purposes. Both have a profound effect on gene expression in the mammary gland throughout life. Researchers treated pregnant mice with BPA or DES and then looked at the offspring as adults. When the offspring reached adulthood, their mammary glands still produced higher levels of EZH2, a protein that plays a role in the regulation of all genes. Higher EZH2 levels are associated with an increased risk of breast cancer in humans. Information copyright Medical News Today.

SAD DADS

Ten percent of dads experience prenatal or postpartum depression, with rates being highest in the 3 to 6 month postpartum period, according to researchers at Eastern Virginia Medical School. Researchers conducted a meta-analysis to determine estimates and variability in rates of paternal prenatal and postpartum depression and its association with maternal depression. The authors included studies that documented depression in fathers between the first trimester and the first postpartum year, and identified 43 studies involving 28,004 participants for inclusion in the analysis. The overall estimate of paternal depression was 10.4% percent, compared to 4.8% in the non-dad population. The 3 to 6 month postpartum period showed the highest rate (25.6%) and the first 3 postpartum months showed the lowest (7.7%). Significantly higher rates were recorded in the US as opposed to internationally. There was a moderate correlation between depression in fathers and mothers.

STOP A MINUTE

The timing of umbilical cord clamping at birth should be delayed just a few minutes longer, suggest researchers at the University of South Florida, because delaying clamping the umbilical cord for a slightly longer period of time allows more umbilical cord blood volume to transfer from mother to infant and, with that critical period extended, many good physiological gifts are transferred through nature's first stem cell transplant. Several clinical studies have shown that delaying clamping the umbilical cord not only allows more blood to be transferred. Once the blood equilibrates, the cord's pulse ceases and blood flow from mother to newborn stops. In recent Western medical practice, early clamping, from 30 seconds to one minute after birth, remains the most common practice among obstetricians and midwives, perhaps because the benefits of delaying clamping have not been clear. Throughout human history and in cultures and areas where delivering mothers squat to deliver, gravity helps speed the stem cell transfer. Today, the cord may be clamped early for a number of reasons, including the medical resuscitation and stabilizing of infants or the notion that delaying clamping might lead to adverse effects or, more recently, to quickly facilitate umbilical cord banking. Several randomized, controlled trials, systematic reviews and meta-analyses have compared the effects of late versus early cord clamping. In preterm infants, delaying clamping the cord for at least 30 seconds reduced incidences of intraventricular hemorrhage, late on-set sepsis, anemia, and decreased the need for blood transfusions. Another potential benefit of delayed cord clamping is to ensure that the baby can receive the complete retinue of clotting factors. While there is disagreement about early vs later clamping, the researchers said that many common disorders in newborns related to the immaturity of organ systems may receive benefits from delayed clamping, including respiratory distress, anemia, sepsis, intraventricular hemorrhage and periventricular leukomalacia. They also speculate that other health problems, such as chronic lung disease, prematurity apneas and retinopathy of prematurity, may also be affected by a delay in cord blood clamping. The researchers said that delaying cord clamping should appropriately be delayed for preterm babies and babies born where there is no effort to bank umbilical cords, and for babies born where there is limited access to health care and where nutrition may be poor.

JOINT EFFORT

The Children's Hospital and the University of Colorado Hospital (UCH) have finalized an agreement to jointly establish a center for advanced maternal fetal medicine offering state-of-the-art care for high-risk pregnant women and their babies. The new center will focus on babies needing highly-specialized surgical care within 72 hours of birth, and both mother and baby will be cared for at The Children's Hospital. This center will offer personalized support services to families that are unique to this region, including a Perinatal Mental Health Program to support mothers with post partum depression and a Fetal Concerns Program to provide support and education to families who have learned their unborn baby has a medical condition. Children's is regularly named as one of the top children's hospitals in the nation by U.S. News & World Report, which recently named the Children's neonatal department as one of the top ten in the nation.

NEONATAL ISSUES

The March 2010 issue of Clinics in Perinatology, published by Elsevier, provides neonatologists and maternal-fetal-medicine specialists with the tools and concepts necessary to understand Quality Improvement methodology and to initiate QI projects within their own practices and NICUs. The issue includes articles on topics such as: "Crossing the Quality Chasm" in neonatal and perinatal care, QI methodologies and measurement, human factors related to QI, using evidence-based medicine, and the role of data collection, as well as info on quality-assurance procedures, pay for performance, and collaboration between obstetricians and neonatologists. See Volume 37, Issue 1, Pages 1-10 (March 2010).

HOME OR HOSP?

A study at Maine Medical Center, Portland reported that home birth is associated with a tripling of the neonatal mortality rate

compared to planned hospital deliveries, and results in more deaths due to respiratory distress and failed resuscitation. The message is, however, mixed, and needs to be considered in light of the very few (.5%) births achieved this way. According to the researchers, low-risk women choosing home birth who have given birth before are mostly successful and give birth with less morbidity and medical intervention than those having a hospital birth. But these benefits are associated with a doubling of the neonatal mortality rate and a near tripling for infants with congenital defects. Other studies have expressed results that home birthed babies had significantly more 5-minute Apgar scores <7 as compared to low-risk term hospital births, with the inference that lack of neonatal resuscitation equipment during home births contributed to that method's mortality rate. Researchers investigated data on more than 340,000 home births and 200,000 hospital deliveries. Perinatal mortality rates for both types of birth were about the same. Home birth moms needed fewer medical interventions including epidurals and FHR monitoring, and gave birth to fewer preemies and LBW babies. Information for the above is from Elsevier, published in Medical News Today, written by Christian Nordqvist, copyright Medical News Today.

SIMPLE TEST

Researchers at Maastrich University Med Centre in The Netherlands have come up with a simple molecular genetic probe test on DNA that could reveal fetal chromosomal abnormalities, and the test has identified Duchenne's muscular dystrophy and hemophilia. The technique, called Multiplex Ligation-dependent Probe Amplification, detects fetal DNA in the blood of women who have been pregnant for six to eight weeks. The MLPA test is part of an already used kit that's cheap and fast, with results in 2 to 3 days. Previously, the test has been used only on samples taken during invasive procedures. MLPA test results obtained in 2009 were compared with the results of amniocentesis, chorionic villus sampling and pregnancy outcome. All but one sample correlated with the non-invasive MLPA test results.

SEMENSHIP

Pregnant drinkers' sons may wind up with less semen, according to researchers at Aarhus University Hospital, Denmark. Researchers measured the sperm concentration of 20-year old guys whose moms had about 5 or more drinks while pregnant and found that their sperm count was a third lower than non-drinking-mom guys. Researchers cautioned that the observational study, as such, couldn't explicitly establish that alcohol was the cause of the lower sperm concentrations. Researchers studied 347 sons of 11,980 women. Their sons were studied at between age 18 and 21. Sons of mothers drinking 4.5 or more alcoholic drinks a week had average sperm concentrations of 25 million/ml, while the sons who were least exposed to alcohol had sperm concentrations of 40 million/ml. The sons most exposed to alcohol had the lowest sperm counts. Paternal alcohol consumptions had no effect on subsequent sperm count.

HOSPITAL PERFORMANCE

Complication rates for vaginal and C-section deliveries vary between best and worst-performing hospitals, according to a study by HealthGrades, a healthcare rating company. The best hospitals had 51% fewer maternal complications for vaginal births and 74% fewer for c-sections. The top hospitals had a 57.1% less neonatal mortality than poor-performing hospitals, and a 35.2% lower mortality than average-performing hospitals. Top hospitals had the highest episiotomy rates and vacuum-assisted delivery rates and the lowest forceps-assisted delivery rates. The best hospitals handled more deliveries, more than 7,000 over three years, vs 1,700 at the worst-rated hospitals. Fourteen million hospital records from 19 states were examined.

ART AND FAT

Being overweight leads to a greater risk of miscarriage for patients undergoing assisted reproductive technology, according to researchers at Guy's and St Thomas Hospital. Increased BMI was associated with a higher miscarriage rate after IVF or ICSI treatment. Researchers analyzed all pregnancies from embryo transfer at their facility for four years. The miscarriage rate was significantly lower in women with normal weight (22%) compared to women who were overweight (33%). After adjusting for other variables, researchers demonstrated that being overweight or obese more than doubled the risk of miscarriage. The researchers said their study was more definitive than previous ones because it was limited to single-embryo transfers.

DRUGS AND DEFECTS

A study at the University of Copenhagen showed that use of psychotropic drugs during pregnancy increases the probability of birth defects. Over a ten-year period, psychotropic medications were associated with 429 adverse drug reactions in Danish children under the age of 17. Researchers concluded that more than half of the 429 cases were serious and several involved birth defects, such as birth deformities and severe withdrawal syndromes. They found that 42% of adverse reactions were reported for psychostimulants such as Ritalin, 31% for antidepressants, like Prozac, and 24% for antipsychotics like as Haldol. The researchers concluded: a range of serious side effects such as birth deformities, low birth weight, premature birth, and development of neonatal withdrawal syndrome were reported in children under two years of age, most likely because of the mother's intake of psychotropic medication during pregnancy.

NANN PREVIEW

The companies below invite you to visit them at the NANN convention. Information was provided by the companies.

B&B Medical Technologies

Booth 616

What Products do you plan to exhibit?

B&B Medical Technologies will be showcasing our new Babi. Plus product line, which includes the Bubble PAP Valve 0-10 cm H_20 for noninvasive ventilatory support of neonates and premature infants, Silicone Infant Nasal CPAP Cannula (prongs) for delivery of comfortable nCPAP, and a single or dual pole clamp for both the Bubble PAP Valve and humidifier system. For post CPAP babies, B&B Medical Technologies will introduce the new Babi.Plus Pacifier Adaptor for nebulized medication delivery via a baby's own personal pacifier. In addition, B&B will present the new preemie-sized Sil.Flex Stoma Pad for advanced tracheostomy stoma care for the very smallest infants. B&B Medical Technologies is the first and only company to offer an FDA-cleared, professional Bubble CPAP system specifically designed to deliver precise CPAP pressure in the premature infant population. The Babi.Plus Bubble Pap Valve and Infant Nasal CPAP Cannula eliminates the need for hospital personnel

to invest time and money manufacturing and maintaining the "homemade" bubble devices previously used for nasal CPAP application.

What educational materials will be available at the convention?
B&B Medical Technologies will have complete product brochures and clinical application guides to assist the clinician in the introduction and education of the new Babi.Plus product line.

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

Bunnell Incorporated
Booth 116

What products do you plan to exhibit?
Bunnell Incorporated is celebrating 25 years in the ventilator industry. The Life Pulse High-Frequency Jet ventilator has passed the test of time. Its therapeutic flexibility makes it an indispensable tool in many NICUs. Jet pulse technology, passive exhalation, and an adjustable I:E ratio makes this high-frequency uniquely effective. The most recent improvement has lowered the sound output from 56 to 41 dB.

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

Why should our readers stop by your booth?
The number one reason NICU nurses should stop by the Bunnell booth is to hear how quiet HFV can be, just 41 dB. Noise in the NICU has become an important topic of research and debate. Bunnell is committed to continuous improvement and our new "WhisperJet" proves it. Stop by Booth 116; hearing is believing. Whether you currently use HFV or not our clinical specialists can answer all your HFV questions. Stop by and give us a try.

CORPAK Medsystems
Booth 609

What products do you plan to exhibit?
CORPAK MedSystems, based in Wheeling, IL, is a leading developer, manufacturer and marketer of innovative medical devices focused on the enteral feeding and bedside location technology markets. The company has established the leading market position in premium branded, adult, long-term nasogastric ("NG") feeding tubes and offers a broad portfolio of other high quality, branded enteral products, including gastrostomy feeding tubes, gastric relief devices and enteral feeding safety devices. CORPAK MedSystems proudly presents the CORFLO Anti-IV Enteral Feeding System, the FARRELL Valve with CORFLO Anti-IV Connectors as well as the NAVIGATØR BioNavigation System. These products offer safer enteral and vascular access. **The CORFLO Anti-IV Enteral Feeding System** is compliant to the Joint Commission recommendations on enteral feeding (Issue 36, April 3, 2006). It has been engineered to be compatible only with oral-tip syringes and therefore, prevents the inadvertent feeding into intravenous lines. The **FARRELL Valve** with CORFLO Anti-IV Connectors is the only closed system that offers passive gastric venting. Patients who have suffered from pain, feeding intolerance or bloating due to gastric distension can use the FARRELL Valve which prevents loss of calories and exposure to caregivers while offering the benefits of an Anti-IV (oral only) system. The **NAVIGATØR BioNavigation System** confirms PICC/UVC catheter tip location during placement. It uses electromagnetic waves and a sensor stylet to assist in central catheter tip location during the initial sterile procedure; thereby minimizing additional x-rays, time and cost for the PICC/UVC placement procedure.

CUROSURF
Booth 405

What products do you plan to exhibit?
CUROSURF (poractant alfa) Intratracheal Suspension.

What educational materials will be available at the convention?
Get the latest information in RDS and surfactant-reviews on RDS and reviews on available surfactants.

What in-booth promotions will you be offering?
A $5 donation will be provided to the March of Dimes for each registered visitor.

Why should our readers stop by your booth?
We're eager to hear your experience with CUROSURF. Come in, discuss and register—Cornerstone will donate $5 to the March of Dimes NICU Family Support Program.

Dräger
Booth 305

What products do you plan to exhibit?
Dräger will demonstrate its newest product in the field of neonatal ventilation. Visitors will get a first-hand look at the **Babylog VN500** neonatal ventilator, a technologically advanced device with a comprehensive array of therapy options designed to support infant ventilation. Conventional and non-invasive ventilation gives the caregiver the entire spectrum of modern neonatal ventilation therapy in a single device. Designed with the clinician in mind, its versatility and range of operation make it well suited for neonatal care and pediatric intensive care units. We will also display a diverse product portfolio of advanced neonatal care and **thermoregulation solutions** in the areas of warming therapy, jaundice management, and transport. These therapeutic solutions, combined with patient monitoring and ventilation for newborns, enable a comprehensive, connected approach from delivery to discharge.

What educational materials will be available at the convention?
Dräger will offer a selection of new educational materials to include an interactive website for neonatal doctors, nurses, and parents of premature babies; a continuing education supplement on the topic of thermoregulation; and a booklet on ventilation modes for Dräger ventilators. Launched in 2010, **BabyFirst.com** is an innovative single destination where neonatal doctors and nurses can exchange information and experiences online across a range of neonatal care specialties. With content populated by clinicians and renowned experts, the website also offers parents and families of premature babies a trusted resource to gain a better understanding of neonatal care. They learn what to expect in the Neonatal Intensive Care Unit (NICU) with insights into common terms, procedures, equipment, post-hospital care, and more. We will also release a **CE supplement on thermoregulation**. The supplement includes several important published papers that address the overall environment within the NICU. It also looks at principles and guidelines around resuscitation and interventions to prevent heat loss and cold stress. **"Ventilation Modes in Intensive Care"** is the latest educational booklet designed to improve the understanding of contemporary modes of mechanical ventilation. The revised nomenclature is an effort in standardizing common understandings of pressure, volume, and spontaneous ventilation modes.

Why should our readers stop by your booth?
We invite you to stop by the Dräger NANN 2010 booth to see how our therapeutic solutions work together for a new level of simplicity, connectivity, efficiency, and synergy. Ask to see a demonstration of our new dedicated infant ventilator, designed specifically for clinicians to provide maximal effectiveness at the bedside for the special needs of neonates and infants. We also encourage you to take a tour of our new **interactive website** focused exclusively on neonatal care and supported by Dräger and NICUniversity, a Web-based medical education center for clinical professionals.

Fisher & Paykel Healthcare
Booth 520

Fisher & Paykel Healthcare, Inc (F&P) understands and appreciates the critical role neonatal nurses undertake in infant care. This is the reason F&P is dedicated to improving patient care and outcomes. With over 20 years of worldwide use and acceptance involving millions of safe and effective resuscitations, the F&P Neopuff Infant T-Piece Resuscitator has recently been updated to further enhance functionality and usability while providing optimal resuscitation and continuing to raise the standard of care for infant resuscitation.

What products do you plan to exhibit?
In addition to the launch of the newly enhanced Neopuff Infant T-Piece Resuscitator, F&P is excited to announce that attendees at the NANN Conference will be the first to see the launch of our new family of resuscitation circuits. Among the many benefits of the new resuscitation circuits, is the ability for the clinician to provide suction and deliver surfactant during resuscitation. This is another reason to visit our booth.

An integral component of the Neopuff Infant T-Resuscitator and family of circuits is the unique line of resuscitation masks, including the first ever micro-preemie mask for very low birth weight patients. The masks are specifically designed to conform comfortably to the infant's face, facilitating a seal for optimum resuscitation. The masks come in five sizes ranging from micro-preemie to pediatric size.

F&P will also be exhibiting the first humidified infant resuscitation system using the MR850 respiratory humidifier. The Neopuff Infant T-Piece Resuscitator facilitates the delivery of warm humidified gas to help protect the pulmonary epithelium and reduce heat and moisture loss especially during prolonged resuscitation. Conditioning cold, dry gas to body temperature and saturated with water vapor can help reduce the risk of an inflammatory response occurring in the infant's airway.

What educational materials will be available at the conference?
We look forward to discussing and demonstrating the F&P Infant Respiratory Care Continuum and sharing CNE opportunities with you.

Why should our readers stop by your booth?
Attendees are invited to experience all of the above-mentioned demonstrations and hands-on stations, including the opportunity to test their resuscitation skills on our simulator. Please join us at the NANN Conference in Las Vegas at booth 520 for a complete review and demonstration of all Fisher & Paykel Healthcare products that include our newly enhanced Neopuff Infant T-Piece Resuscitator and new family of circuits.

GE Healthcare Maternal-Infant Care
Booth 204

What products do you plan to exhibit?
The Giraffe Family of Products, Panda Infant Warmer, CARESCAPE Neonatal Monitoring Solutions, BiliSoft LED Phototherapy, Centricity Perinatal, Single Family Room NICU Resource Website, Engstrom Carestation Ventilator and GE Healthcare Clinical Education Programs.

Why should our readers stop by your booth?
GE Healthcare Maternal-Infant Care is dedicated to the clinical needs of the NICU and Labor & Delivery, and to the mothers and babies they serve. We are continuing to create leading technologies and innovations that support developmental care, seeking the best possible environment for patients and caregivers. We're committed to helping hospitals deliver the special care these most fragile patients need and to improve outcomes and reduce stress for babies, families and clinicians. Visit our booth to see our latest innovations for the NICU and visit us online at gehealthcare.com/perinatal. (See also "Taking Care" in this issue's products section, page 26.)

HALO
Booth 125

What products do you plan to exhibit?
HALO SleepSack Swaddle wearable blankets for modeling Safe Sleep practices in the NICU.

What educational materials will be available at the convention?
Our mission at HALO is to keep babies sleeping safely. That's why we've been educating parents on how to help reduce the risk of SIDS for over 15 years. We are providing Free SIDS risk reduction materials to help hospital professionals educate parents on safe sleep practices for babies.

What in-booth promotions will you be offering?
Through HALO's Safer Way to Sleep Initiative, HALO can now help your institution implement an In-Hospital Safe-Sleep Modeling Program FREE for ONE FULL YEAR. Our Safe-Sleep Modeling Program has been shown to effectively influence how parent's place their babies to sleep (supine) and create a safe sleep environment.

Why should our readers stop by your booth?
Attendees should be sure to stop at the HALO Innovations booth for ideas on how to educate parents through modeling of safe sleep practices to ensure a successful transition from NICU to home. At our booth we will provide product demonstrations of the HALO SleepSack Swaddle, free SIDS risk reduction materials and details on our special trial offer: free one year In-Hospital Safe Sleep Modeling Program.

Maico Diagnostics
Booth 614

What products do you plan to exhibit?
MB11 Newborn Hearing Screener

What educational materials will be available at the convention?
Product brochure

Why should our readers stop by your booth?
To learn about a newborn hearing screening system that can save their organizations thousands of dollars a year in costly disposables.

Medela
Booth 411

Products
Medela's system of innovative, evidence-based products, services and education helps you deliver more milk to your vulnerable patients every step of the way. Our system will help you improve outcomes, reduce costs, and improve patient satisfaction. Visit our booth and learn more about the research showing that higher doses of human milk can help NICU professionals achieve better outcomes for their patients. Learn about the clear dose-response effect between the dose of human milk and a reduction in risk for several disabling morbidities such as necrotizing enterocolitis, late onset sepsis and enteral feed intolerance. Medela's Symphony Preemie+ is the first pumping program clinically shown to produce more milk for NICU moms. Medela's new Waterless Milk Warmer is the safer, easier way to warm human milk. The Waterless Milk Warmer eliminates risk associated with warming in water, consistently warms milk to temperatures of expressed human milk, and safely thaws human milk.

Show special
Warmer Summer Special: Deadline Extended Through NANN Convention: Purchase 10 Waterless Milk Warmers through September 21, 2010 and get a great deal on disposable inserts. For every 5 cases of disposable inserts purchased you'll get 1 case free through December 31, 2011. If you purchase 20 Waterless Milk Warmers, in addition to the disposable insert special you'll also get a free online education course for your staff, available through 2010, that provides detailed information on the dose response relationship of human milk and its impact on serious morbidities, a review of water contamination sources and its impact on sepsis and nosocomial infection and the effect of temperature on enteral feeding tolerance with very low birthweight babies.

NeoMed, Inc
Booth 410

What Products do you plan to exhibit?
NeoMed, Inc is proud to present a unique line of products specifically designed to enhance the safety and outcome of the neonatal patient. Our products include: Enteral Safety System (Extension Sets, Feeding Tubes, and Oral Dispensers), Urinary Drainage Kits/Catheters, Lumbar Puncture Products, Specialty Kits, NeoDrape, and the SafeBaby Breast Milk Tracking System. Our product line features the latest clinical innovations that meet or exceed enteral safety recommendations set forth by the Joint Commission and ASPEN (American Society of Parenteral and Enteral Nutrition).

What educational materials will be available at the convention?
NeoMed will provide clinical documentation from ASPEN, the Joint Commission, ISMP and various case studies that highlight the importance of neonatal patient safety and how our products eliminate or mitigate misconnections, mis-feeds, enteral contamination, and patient misidentifications. NeoMed will also have our full line of products and product information sheets available to all attendees at NANN.

What speakers will your company be featuring?
Ms Robin Bissinger, NNP is the creator and instructor at The Golden Hour Symposia. Ms Bissinger is an Associate Professor at the Medical University of South Carolina and directs the Neonatal Nurse Practitioner Program. During the presentation, Ms Bissinger will discuss the importance of The Golden Hour and how industry led products help the first hour of life be a success. With her expertise in neonatal care, a preview of the latest clinical practice and products will be a focal point. NeoMed manufactures the NeoDrape which plays a vital role in maintaining thermo regulations of very low birth weight babies during delivery and invasive procedures.

What in-booth promotions will you be offering?
NeoMed will be providing a hotel room drop including a tote bag with our NeoDrape and an oral/enteral NeoMed syringe. These bags will also be available at our booth. All attendees will be eligible to register for a chance to win prizes such as Apple iPods and an iPad, plus much more.

Why should our readers stop by your booth?
NeoMed is committed to providing clinicians with the highest quality and most cost effective neonatal products on the market

delivering patient safety, protection against misidentifications, misconnections, and improved clinical outcome of the patient. Please visit our website: neomedinc.com, for more details.

ONY, Inc

Booth 618

Featured Products

Infasurf (calfactant) Intratracheal Suspension: ONY Inc is the manufacture of Infasurf a newborn lung surfactant. Among the lung surfactants available in the USA, Infasurf, is the only lung surfactant derived from pure natural surfactant, not from a minced whole lung. This natural origin provides the composition for Infasurf contributing to its positive characteristics.

Educational materials

Infasurf representatives will have available for your review educational and scientific materials on:

- How lung surfactant compositions determine activities
- Clinical use of lung surfactant
- Clinical trial comparisons of lung surfactants.

Staffing the Infasurf booth

Infasurf representatives available at our booth have an extensive background as neonatal practitioners. These clinicians have an understanding of both the science of surfactant replacement therapy, as well as the clinical application of surfactant as it applies to today's NICU patients. Infasurf's representatives are available to discuss with you:

- What makes your surfactant work effectively?
- How soon should your surfactant be administered?
- Instillation procedures for delivery of surfactant.
- Complications associated with surfactant replacement therapy.
- Patient response to surfactant replacement therapy
- Any other surfactant related issues you may have.

Paragon Data Systems

Booth 412

What products do you plan to exhibit?

SafeBaby, a secure feeding and milk management system that was developed to ensure that every baby in the NICU receives the right breast milk, donor milk or formula, risk free, at the bedside by way of 2-dimensional (2-D) bar coding technology driven by our SafeBaby proprietary software. Our system starts with a bar code label printer and mobile hand held computer with a bar code scanner and PC based software. This user friendly system allows you to immediately identify and record the receipts of each milk container, locate it, use it before expiration and make sure it is validated before used for a feeding. The SafeBaby system also has the ability to track volume of feeds, additives, fortifiers, donor milk, and is HL7 compatible with hospital EMR systems. SafeBaby will be exhibiting in the same booth/vendor space as NeoMed Inc.

What educational materials will be available at the convention?

SafeBaby system software live demo version; handheld and thermal printers; various literature on the benefits of bar coding and positive patient identification in the NICU; fresh breast milk versus frozen and work flow analysis using bar coding for patient safety in the NICU.

What in-booth promotions will you be offering?

SafeBaby system software live-demo version, handheld computers, thermal printers, SafeBaby labels.

Why should our readers stop by your booth?

Readers should stop by our booth to learn about the benefits of breast milk tracking, positive patient identification using bar coding; patient safety in the NICU using a breast milk tracking system, benefits of bar code systems and inventorying breast milk; SafeBaby software in work flow efficiencies; SafeBaby and EMR charting, and SafeBaby's newest display features using hospital monitors. In addition, there will be an opportunity for the attendee to review and use the software and handheld equipment in a live setting.

Philips Children's Medical Ventures

Booth 205

Philips Children's Medical Ventures (PChMV) is committed to improving the quality of care and developmental outcomes of hospitalized infants. In collaboration with leading clinical experts, we develop and offer a broad array of innovative products, process improvement programs and consulting services that support developmental care across the NICU and well-baby nursery. To learn more, visit us at NANN, booth 205.

What products do you plan to exhibit?

We will introduce a new line of specialty-use oral/enteral syringes designed to help reduce feeding errors and to help clinicians avoid potential tubing misconnections. For use in the neonatal and pediatric intensive care units, these syringes are available in seven sizes (1 ml, 3 ml, 5 ml, 10 ml, 20 ml, 30 ml and 60 ml) and include highly visible text on the barrel that reads "ORAL/ENTERAL ONLY." An oral only tip distinguishes it from medication syringes and will not attach to a standard luer lock connector. Because standard 1 ml syringes are commonly used to administer medication in the hospital setting, PChMV's 1 ml oral/enteral syringe is a highly noticeable orange color. A one-piece design eliminates tip separation during filling, and an airtight, brightly colored cap does not allow air or water in, or breast milk to leak out, during prep, storage and warming.

What educational materials will be available at the convention? What speakers will your company be featuring?

We will present a preview of our soon-to-be-released Late Preterm Infant education program as part of our continuing commitment to establish developmental care practices throughout neonatal units worldwide. During a pre-conference seminar, Sharyn Gibbins, NNP, PhD, a clinical consultant for PChMV, and our own Kay Johnson, will present a preview of the four-hour workshop on how to support the baby during admission to the NICU, care strategies that involve positioning and feeding, and techniques on how to transition home after the hospital stay. Participants will also learn about possible long-term medical complications, costs associated with caring for these special infants, and techniques for involving and supporting the family.

Why should our readers stop by your booth?

We will also provide an opportunity for you to experiment with developmentally supportive products such as Frederick T. Frog,

the SnuggleUp, and other positioning products from the Bendy Bumper and Prone Plus families. Or you can meet with one of our clinical education consultants to discuss how our one-day education workshops or comprehensive process improvement programs can help to provide a standardized approach to care delivery in your unit. Visit us at booth 205.

Salter Labs

Booth 531

What products do you plan to exhibit?
Salter Labs will be featuring a number of new and exciting respiratory care products at the NANN meeting that were developed and designed specifically for premature, neonate, infant and pediatric patients. Also at this year's meeting, we will be showing our extensive line of premature, neonate, infant, and pediatric sized Salter-Style Cannulas—the "worldwide standard for clinical comfort and efficacy." These small, lightweight cannulas are manufactured using unique designs, manufacturing processes and materials that ensure an anatomically correct fit that is very gentle to delicate skin. We will also be featuring Salter Labs' - • Innovative infant and newborn Tender Grip skin fixation systems that gently and safely hold tubes in place on baby's tender skin; • The aptly named "Comfort Care pediatric and infant headband cannulas for your active or restless "little patients"; • Special aerosol or oxygen delivery solutions for pediatrics or infants; • The pediatric I-Guard aerosol delivery system that diminishes the possibility of aerosolized medication entering a patient's eyes; • Infant Salter-Style end-tidal ($ETCO_2$) monitoring cannulas for O_2 delivery and simultaneous sampling; and • Sleep diagnostic cannulas and sensors that can be utilized on infant and pediatric patients.

What educational materials will be available at the convention?
We will be providing product demonstrations at our NANN Booth (531) and visitors will have access to the most recent clinical studies and educational materials regarding Salter Labs' products.

What in-booth promotions will you be offering?
All visitors to the Salter Labs' Booth (531) are eligible to enter an American Express Gift Card drawing.

Why should our readers stop by your booth?
• To learn about the wide range of Salter products designed specifically for your "little patients." • Explore how Salter's products can help you meet the various NANN guidelines for patient care and improve patient outcomes. • To be the first to see several new, innovative products such as new skin fixation offerings. • To obtain a unique and useful small gift (while supplies last) to use when you get home • And enter the drawing to win a $50 American Express Gift Card at Booth 531.

Teleflex Medical

Booth 221

What products do you plan to exhibit?
Concha Therm Neptune, Hudson RCI Infant Nasal CPAP line, and Comfort Flo high flow nasal cannula. Our mission at Teleflex Medical is to provide respiratory products that help you simply and safely address the complex needs of the intensive care infant. From the ConchaTherm Neptune Heated Humidifier to the Hudson RCI Infant Nasal CPAP line, these products offer effective solutions to the challenging clinical requirements of the NICU and PICU. These products will be featured at our booth, in addition to the Clinical Foundations Newsletter focused on neonates.

What educational materials will be available at the convention?
Clinical Foundations Newsletter focused on neonates.

Why should our readers stop by your booth?
We offer the latest technology for Infant Nasal CPAP, heated humidification, and high flow nasal cannula therapy for neonates.

PRODUCTS

CHECK PLEASE

Royal Philips Electronics announced that its BiliChek noninvasive bilirubin assessment tool has received a Gold award in the Medical, Laboratory and Test Equipment category in appliance DESIGN magazine's 23rd Annual Excellence in Design Awards Competition. An independent panel of three industrial design experts performed judging of the entries based on appearance, human factors, innovation and technical merits as well as the product's ability to make technology more accessible to the user. Contact philips.com.

OPEN HOUSE

Philips Respironics recently held an open house in its Pennsylvania facility. Opened in 2009, the state-of-the-art facility is devoted to high volume production of sleep therapy systems. Events included guided plant tours, product demonstrations, a mock production line where children and adults alike could build a CPAP device, face painting and balloon art, X-Box Beatles Guitar Hero, giveaways and a picnic lunch. More than 60 employees volunteered their time and talents for the day. Attendees also participated in an auction which raised $570 for Operation Troop Appreciation. The non-profit works with military units to provide "wish list" items for deployed troops. Contact philips.com.

CLOSED LOOP

CareFusion announced the launch of its Closed Loop Controller of Inspired Oxygen system, or $CLiO_2$, the first automatic oxygen controller of its kind designed to keep the oxygen level in the blood within a safe range for newborns needing mechanical ventilation. This new software algorithm is an enhancement to the CareFusion AVEA ventilator. The $CLiO_2$ system noninvasively and continuously measures the oxygen level in a newborn's blood using Masimo SET Measure-Through Motion and Low Perfusion pulse oximetry technology to provide accurate and reliable oxygen saturation (SpO_2) measurements, even under challenging clinical conditions. The $CLiO_2$ system processes blood oxygen saturation levels by a computer algorithm that then anticipates trends and modifies the amount of oxygen delivered. If necessary, adjustments can be made on a second to second basis, something not currently possible with manual control. The $CLiO_2$ system is currently available in most Western Europe and Asian countries through CareFusion and its authorized distributors, with future availability in the US and Canada. Contact carefusion.com.

FLOWING

The Infant Flow SiPAP System from CareFusion is clinically proven* to safely deliver noninvasive ventilatory support to thousands of infants worldwide. The Infant Flow SiPAP is the only dedicated nCPAP device to offer both nasal CPAP and Biphasic modes with apnea and low breath rate detection. The Infant Flow generator delivers stable pressure in harmony with the infant's respiratory efforts by using Coanda Effect and Fluidic Flip technology. This empowers clinicians with lung protective strategies to treat the smallest of patients. [*Gianluca L, et al, Nasal CPAP vs. Bi-level Nasal CPAP in Preterms With RDS: a randomized control study. Arch Dis Child Fetal Neonatal Ed. Published on-line Nov 29, 2009.] Contact carefusion.com.

VITAMINS

Upsher-Smith Laboratories, Inc announced the availability of a new formulation of PreNexa Rx prenatal vitamins with changes to the amounts of folic acid and iron. PreNexa's newest formulation contains 1.25 mg of folic acid and 27 mg of iron. PreNexa also contains essential vitamins and minerals including calcium, vitamins B6, C, D3 and 300 mg of plant-based DHA in one single gel capsule taken once a day. The NDC number for the new formulation of PreNexa is 0245-0178-30. Key product features remain the same. Contact upsher-smith.com.

PREMIER PERFORMER

Hamilton Medical, Inc announced that it is a winner of the Supplier Performance Award, presented by the Premier healthcare alliance. Premier contracts with more than 800 suppliers and Hamilton Medical is one of 65 contracted suppliers to receive the Performance Award. Premier is a performance improvement alliance of more than 2,300 US hospitals and 67,000-plus other healthcare sites working together to achieve high quality, cost-effective care. Owned by not-for-profit hospitals, Premier maintains a comprehensive repository of clinical, financial and outcomes information and operates a leading healthcare purchasing network. For more information, contact hamilton-medical.com, (800) 426-6331.

UPSCALE

DETECTO's model 8450 digital baby scale with DLM digital length measuring features all-digital weighing and length measurement, ensuring speed and accuracy in your patient measurements. The scale base, length measuring device, and padded carrying handles of this lightweight unit are incorporated together, making it easy to transport from one patient room to another as a portable measuring device. Padded side rails and handle covers are slightly contoured ensuring the baby will be cradled comfortably. This versatile baby scale features battery or AC power, large easy-to-read 1 inch/25 mm high LCD display on the scale, lightweight durable construction, and MEMORY/HOLD feature which retains measurements for active babies. Detecto's 8450DLM features digital length measuring in your choice of units: ft/in, in, or cm. Weight may be displayed in lb, oz, or kg. An optional black carrying case with handle protects the scale for easy transport. The DLM digital length measuring device is also sold separately and may be used stand-alone on an exam table for baby measurement. It runs on (2) AAA batteries which are included. Rubber feet ensure stable footing while measuring. The scale was recently featured on the TV show "How It's Made" on the Science Channel. Contact detecto.com.

TELEFLEX

The **Comfort Flo Humidification System** is designed to comfortably deliver flow rates of 1-40 lpm of heated, humidified oxygen through a nasal cannula interface to a broad range of patients. A completely disposable delivery system and line of specialty cannula, the Comfort Flo Humidification System allows clinicians to maximize patient comfort, improve therapy compliance, and avoid more invasive and often more expensive therapies. The **Comfort Flo Nasal Cannula** is available in premature, infant, pediatric, and adult sizes… The quest for optimal humidification in the NICU/PICU 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 Heated Humidifier**. Adjustable airway temperature and gradient control features allow you to customize therapy—maximizing humidity delivered while minimizing circuit condensation. The Neptune can be used across the continuum of care, eliminating the need to change equipment as treatment advances (HFV, IMV, CPAP, and Oxygen Therapy)… Infant Nasal CPAP has been proven to benefit premature infants of very low birth weight. The **Hudson RCI Infant Nasal Prong CPAP System** is designed to reduce trauma associated with the delivery of infant nasal CPAP. The Hudson RCI Infant Nasal CPAP Prong System was specifically designed to minimize the problems associated with more invasive therapies. The soft, anatomically curved prongs enhance fit and minimize nasal septal necrosis. Additionally, the luer fitting on the expiratory connector allows proximal airway pressure monitoring. Available in six prong sizes to allow greater choice for appropriate sizing of each infant, the Hudson RCI Infant Nasal CPAP offering can help improve clinical outcomes for the critical care infant… The **Rüsch Infant TruView EVO** is an innovative optical view laryngoscope blade designed to provide indirect laryngoscopy with continuous oxygen insufflation more safely, clearly and easily. Indicated for use in both standard and difficult intubations, the Rüsch Infant TruView EVO illuminates and expands angular view of the larynx and adjacent structures, thereby facilitating endotracheal intubation. The Rüsch Infant TruView EVO uses an optical system within the viewtube which consists of prisms and lenses that extend vision beyond the distal end of the blade. It is designed to decrease laceration and bleeding of the pharyngeal-laryngeal mucosal tissue in addition to reducing the amount of force needed to successfully intubate a patient by greater than 30%. This innovative approach protects patients and minimizes risk of esophageal intubation… **Sheridan Endotracheal Tubes**, part of the Hudson RCI line of products, includes a wide range of clinical solutions for adult and pediatric use. The Sheridan Ped-Soft line of uncuffed endotracheal tubes is made out of a soft PVC formulation which enhances the tube's compliance to a child's anatomy and makes it an ideal choice for short or long term pediatric intubation. The specially designed distinct black tip incorporated on the Ped-Soft endotracheal tubes aide in visualization during intubation. Additional depth markings are also included to assist in placement during nasal intubation. Contact teleflex.com.

SINGULAR

GE Healthcare has unveiled a new online resource to help empower professionals in the development of Single Family Room (SFR) Neonatal Intensive Care Units. The website, singlefamilyroom.gehealthcare.com, created by GE Healthcare's Maternal Infant Care division, is a compilation of vendor-neutral information, insights and experiences from US hospitals that have launched SFR NICUs. Subjects range from planning, budgeting and design through construction and workflow,

providing healthcare professionals with advice, successes and lessons learned in the development of SFR NICUs. Contact gehealthcare.com.

FERTILE

Circle + Bloom has announced the release of two new mind-body and relaxation programs for women's health and reproduction. Circle + Bloom's latest programs are designed for women to use while pregnant, as well as with its special program for In-Vitro Fertilization and Intrauterine Insemination. The IVF/IUI Program tracks to the specific regimen and timing of advanced fertility treatments, and includes 18 different sessions. The company has also released its program designed for use during pregnancy. The Pregnancy Program allows women to reduce their levels of stress. Contact circlebloom.com.

TAKING CARE

New innovations to the Engström Carestation from GE Healthcare are tailored to the needs of neonatal patients in the ICU. The Neonatal Proximal Flow Sensor is now optional, so hospitals can select the ventilator configuration that best matches its protocols and preferences regarding flow sensor equipment at the patient's airway. A new Volume Guarantee Pressure Support (VG-PS) mode is now available with the Carestation. Designed for the specific needs of neonatal patients, the VG-PS mode continuously adjusts the level of support in response to the patient's changing needs. It provides precise volume regulation during spontaneous and mechanical ventilation, breath-to-breath adjustment of the inspiratory pressure delivered, synchrony of both the inspiratory and expiratory phase of a breath, and the ability to control the point at which mandatory mechanical ventilation is initiated. The clinician can also use the Neonatal Proximal Flow Sensor to increase the accuracy of monitoring and delivery of each breath delivered. The "minimum rate setting" of the VG-PS mode provides safety and can also be set to stimulate a child who becomes apneic. In this case a breath would be delivered to stimulate spontaneous breathing. The point at which breaths are initiated is regulated by a combination of the minimum rate set by the clinician and the baby's own spontaneous respiratory rate. In other words, mechanical ventilation begins only when needed, and continues only as long as it's needed. In short, the VG-PS mode offers consistency in volume regardless of the type of breath delivered, and it provides synchrony of both the inspiratory and expiratory phases of a breath. The "Up O_2" button is now adjustable in smaller increments. This ease-of-use feature is now more flexible than ever, allowing the therapist to increase the O_2 level by 25 percent or less for neonatal patients, based on the hospital's specific protocols. These new innovations for neonatal intensive care will be on display at the GE Healthcare booth at the NANN Convention, along with a variety of educational materials and in-booth promotions. Contact gehealthcare.com.

NEXT LEVEL

Featuring advanced clinical applications that bring ob/gyn imaging to the next level, Siemens Healthcare showcased its exclusive syngo.fourSight Workplace image management software at the 58th Annual ACOG meeting in San Francisco. With Siemens' new syngo.fourSight Workplace, volume imaging takes on a whole new dimension with true stereoscopic views of 3D images delivering a 3D imaging experience more immersive, detailed and real-to-life than ever before. Siemens also showcased the new 2.0 release of the Acuson S2000T ultrasound system. The latest acoustic technologies deliver a powerful system optimized with 2D, Doppler and 3D/4D imaging for the most demanding requirements in maternal-fetal medicine. Unique industry applications, such as Skeletal Rendering further enhance the clinical excellence of the system. This Siemens-proprietary 3D/4D rendering technique results in true volumetric imaging, with accurate spatial resolution for enhanced visualization of the fetal skeleton. Compact, portable, and easy to use, the Acuson X300T PE - Women's Imaging offers a complete ob/gyn imaging solution for the clinical routine. The system is scalable to meet a wide variety of clinical and economic needs. A highlight of both the ACUSON S2000 system - Women's Imaging and the ACUSON X300 system PE - Women's Imaging is syngo Auto OB measurements, an advanced clinical tool that automates routine biometry measurements of the fetus. Contact medical.siemens.com.

HEAR HERE

The Maico MB11 newborn hearing screening system incorporates the latest technological advances based on years of research. Using fast rate ABR technology with a unique, CE chirp acoustic stimulus, MB11 stimulates an ABR that is almost two times larger than the response from a traditional click stimulus. This can translate into faster test times. MB11's "green technology" features an integrated, reusable earphone and electrodes, avoiding the exorbitantly high costs and medical waste associated with use of disposable electrodes and ear couplers. The cost for the supplies to perform an MB11 screening is approximately $.25 compared to $9-$12/screening with competitive systems. For more information on the MB11 please call (952) 941-4201, or email info@maico-diagnostics.com or visit maico-diagnostics.com.

SPOTLIGHT ON VENTILATION

TOP SCORER

Hamilton Medical, Inc has earned the top composite score for ventilator manufacturers from MDBuyline. Hamilton Medical has earned this rating for the past nine quarters. Hamilton not only rates the highest in the top composite score, it also holds the top score in every rating category, which includes system performance and reliability, installation/implementation, applications training, service response time and service repair quality. Robert Hamilton, President said, "We realize that the hospitals that choose to purchase our equipment are not just our customers but are our partners and we try to conduct our business as such." Contact hamliton-medical.com.

TEST OF TIME

Bunnell Incorporated is celebrating 25 years in the ventilator industry. The Life Pulse High-Frequency Jet ventilator has passed the test of time. Its therapeutic flexibility makes it an indispensable tool in many NICUs and PICUs. Jet pulse technology, passive exhalation, and an adjustable I:E ratio make this high-frequency uniquely effective. The most recent improvement has lowered the sound output from 56 to 41 dB. Constant improvement—Continued success! For more information or to arrange a free trial contact Bunnell at (800) 800-4358, bunl.com.

COMMITMENT

After over two decades of experiences and working with clinicians using the Babylog 8000 plus, Dräger continues its

commitment to Respiratory Care with the newest technology for infant ventilation – the Babylog VN500. Designed to meet the specific needs of the patient and the neonatal care team, the VN500 offers a comprehensive and dedicated mechanical ventilation platform for the special care nursery as well as the pediatric intensive care areas. Call (800) 437-2437 or contact draeger.com.

SOPHISTICATED YET EASY

In today's NICU and delivery rooms, intubation leads to a higher risk of airway trauma and infections. Stand-alone nasal CPAP machines with proprietary interfaces may mean higher costs… not better care. Sophisticated yet easy to use, the Inspiration LS Infant ventilator from eVent Medical is a fully featured, highly capable neonatal ventilator. Now available with NCPAP+ mode-built upon the exceptional performance of its original NCPAP mode-the ventilator allows clinicians to use approved nasal interfaces to provide customized, noninvasive treatment to their smallest patients. Contact (888) 454-VENT, event-medical.com.

PERFORMANCE AND MORE

MAQUET SERVO ventilators are known worldwide for performance, reliability, and adaptability. Neonatal to adult, the SERVO-i can be used for transport, Heliox administration, and conditionally in the MR environment. New for 2010, software enhancements for neonatal alarm management help reduce the incidence of unwanted alarms. Updates to non-invasive (NIV) functionality include improved leak compensation in addition to a new portfolio of NIV interfaces. The NAVA mode (Neurally Adjusted Ventilatory Assist), as of 2010, can be used in non-invasive ventilation (NIV NAVA) to provide assist levels capable of matching the patient's neural demands regardless of leakage or user interface. For more information visit maquetusa.com, criticalcarenews.com, or call (888) 627-8383.

EXECUTIVE PROFILE

Dräger

Describe your neonatal/perinatal product(s) and their features.

Dräger offers a total neonatal care solution with a full range of products that provide a new level of connectivity, efficiency, and synergy. Beginning in the Labor and Delivery Room, Dräger's open warmers provide an effective thermoregulation platform, along with the components needed for clinical resuscitation and stabilization. From a compact, mobile, and freestanding warmer to a fully integrated intensive care system, Dräger's incubators and warmers are clinically proven thermoregulation devices that can support the most compromised infants with a full range of integrated accessories for the Neonatal Intensive Care Unit (NICU). For transport within the hospital or for external transport between hospitals, Dräger provides high-performance transport incubators with integrated neonatal ventilation capability. A range of resuscitation products meet the rigorous demands of the delivery room and the NICU. Our hand-held jaundice screening meter is non-invasive and offers a gentle, pain free alternative to traditional screening. Caregivers have instant access to accurate information for clinical decision-making. As one of the worldwide leaders in mechanical ventilation, Dräger recently introduced the new Babylog VN500 for neonatal ventilation. The most advanced product on the market today, Babylog VN500 offers the latest technology in mechanical ventilation specifically designed for the special needs of neonates and infants.

Discuss your R&D process, including clinician and nurse input.

Our research and development programs are driven by the input and requirements of our customers—the clinicians and nurses who use our products. Our shared goal with our customers is to improve patient outcomes and to facilitate efficiencies for healthcare professionals. We constantly invest in research and development to improve technology and to spur innovation in the medical arena. Part of our R&D process is Dräger's ability to understand how new technologies will impact healthcare one year, five years, and ten years from now—sometimes even further into the future. While providing practical solutions for today, we consider the long-term impact of new technologies.

Tell us about the educational services you offer for neonatal caregivers.

Dräger supports neonatal workshops at key congresses and events around the world. Dräger's commitment to clinicians worldwide is to share clinical knowledge around the globe for the NICU community. As a testament to this belief, Dräger created an internet educational platform to support caregivers and parents of premature babies at www.babyfirst.com. Although only recently launched, to date, this website has been a remarkable success. Through internet platforms and web-based seminars, we are using technology to advance educational services for the healthcare community worldwide.

Discuss your technical support and services.

At Dräger, we provide all customers with clinical and biomedical support, along with the highest standards of service. Dräger has a team of neonatal consultants in the field that provide product servicing and training on its thermoregulation and jaundice management products including incubators, open warmers, transport incubators, jaundice screening devices and phototherapy devices. Our neonatal consultants and technicians go through a stringent training program with a focus on continuous education and learning. Dräger also maintains a relationship with Intensive Care On-Line Network, which provides consultation services 24 hours a day, 7 days a week which customers can access by calling (800) 554-1312.

Tell us about the latest neonatal advances germane to your product.

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

CO_2 Reactivity and Cerebral Oximetry

Erin Booth, PhD; Christopher Dukatz, BS; Michael Wider, PhD

Introduction

Brain injury is common in very low birth weight (VLBW) infants and is frequently associated with abnormalities in blood pressure, cerebral blood flow (CBF) or autoregulation.[1,2] Gestational age is the primary antenatal risk factor for adverse neurodevelopmental outcome[3] involving a number of contributing factors including intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL) which have both been long associated with alterations in cerebral blood flow.[4,5] The $PaCO_2$ level in the first 3 days of life has been implicated in the etiology of IVH[6-8] and PVL[9] and hence represents a significant risk factor. IVH is frequently observed in the premature infant brain and can lead to cerebral palsy, language delay and severe neurocognitive and motor function deficits in surviving infants.[10]

End tidal CO_2 ($etCO_2$) monitoring in infants can be an accurate reflection of $PaCO_2$ but is only available in ventilated patients. Further, it is subject to a number of issues that can affect the accuracy of the reading including the type of ventilation and position of the sampling tube. Due to these factors frequent blood gas analysis is required to insure reliability.[11-13] Transcutaneous CO_2 ($TC\text{-}CO_2$) monitoring provides a means of continuous tracking of CO_2 but while accurate, has to be moved from site to site every 4 hrs requiring recalibration. The system heats the skin to 43° C which has been associated with burns or skin irritation and the use of vasoactive drugs runs the risk of causing vasoconstriction in the skin, potentially compromising accuracy of the reading.[14]

Advances in managing pulmonary immaturity in the preterm infant with surfactants and ventilation assistance have dramatically improved survival of low birth weight infants. These interventions, however, present other challenges for tracking the blood gas response, requiring frequent blood draws for analysis which contributes to neonatal anemia and provides a relatively late indicator of $PaCO_2$. The impact of CO_2 levels on cerebral perfusion and the association with IVH strongly support close monitoring of CO_2, especially following changes in ventilatory settings.

We report here the results of experiments in normal, term piglets examining the response of common carotid flow and cerebral O_2 delivery to changes in $etCO_2$ caused by ventilatory rate changes to induce hypercapnia and hypocapnia at normal and reduced body temperatures.

The authors are with Somanetics Corporation, Troy, MI. This article was provided by Somanetics.

Materials and Methods

The procedures used in this study were reviewed and approved by the Providence Hospital Institutional Animal Care and Use Committee (IACUC) and conform to the standards described in the National Institutes of Health Guide of the Care and Use of Laboratory Animals [DHHS Publication No. (HIH) 86-23].

Surgical Preparation: Neonatal Yorkshire Duroc piglets of 10±1 days (range=6-14 days) of age weighing 2.5±0.1 kg (range=1.9-2.9 kg) were mechanically ventilated (Draeger Medical Apollo Anesthesia Machine; Draeger, Germany) and anesthesia maintained with 1.5-3.0% isofluorane following sedation with an intramuscular injection of ketamine (33 mg/kg) and atropine (0.05 mg/kg). Arterial O_2 saturation (SpO_2) and partial pressure of carbon dioxide ($PaCO_2$) were maintained in the normal range. A warming mat and hot air fan were used to maintain core body temperature at 38±0.5°C. Animals received intravenous (IV) heparin (200 units/kg/hour), and an IV maintenance solution of physiologic saline (10 mL/kg/h) throughout the experiment.

Serum glucose, lactate, base excess and electrolyte levels were monitored closely (iSTAT, Abbott Point of Care Inc, Princeton, NJ) and maintained in the normal range using 10 g/dL of dextrose-water ($D_{10}W$), sodium bicarbonate, potassium chloride and lactated Ringer's solution as needed.

Arterial blood pressure, heart rate, SpO_2 and body temperature were continuously monitored by Datex-Ohmeda monitor (GE Healthcare, Milwaukee, WI). End-tidal CO_2 ($ETCO_2$), fraction of inspired oxygen (FiO_2) and pulmonary compliance were also continuously monitored (Draeger Medical Apollo Anesthesia Machine; Draeger, Germany). Regional tissue O_2 saturation of the brain ($CrSO_2$), was monitored continuously by INVOS regional tissue oxygenation monitor (INVOS 5100C, Somanetics, Troy, MI) throughout the experiments.

The common carotid artery (CCA) was isolated and instrumented for continuous blood flow measurements using a T400 series ultrasonic flow-meter (Transonic Systems Inc, Ithaca, NY).

All data from the Datex-Ohmeda monitor, Apollo Anesthesia Machine, INVOS 5100C and the T400 were collected real time and stored on a personal computer for offline analysis (The RugLoop Program, Dmed Temse, Belgium).

Experimental Protocols

Hypercapnia and Hypocapnia: The first series of 5 animals were allowed to stabilize and the body temperature maintained

at normothermia (39°C) with ventilation settings to produce an end tidal CO_2 ($etCO_2$) of 25-30 mmHg. The ventilation settings were varied sequentially to reduce or increase the $etCO_2$ and maintain pH, SpO_2 and PaO_2 within normal limits with initial settings as follows: Pinsp=20, Freq=30, Tinsp=0.4, PEEP=3. The settings were adjusted depending on the individual animal's response and once stable values were achieved, the frequency was decreased by increments of 10 with 15 minutes between each change. Following the period of hypercapnia, hypocapnia was induced by increasing the frequency of ventilation. The frequency was increased in increments of 10 to a maximum of 80 with 5 or 15 minute periods between each change. Throughout the experiment the SpO_2 and tidal volume were maintained by modifying the fiO_2 and ventilatory pressure respectively.

Hypercapnia and Hypocapnia During Hypothermia: In a second set of 5 piglets the body temperature was allowed to decrease passively from 39° C to 32-33° C (103° to 93° F) and allowed to stabilize with ventilation settings to produce an $etCO_2$ of 25-30 mmHg. Ventilation settings were then varied sequentially as described above for normothermic animals.

Results

The common carotid flow rate and cerebral rSO_2 track $etCO_2$ closely in the normothermic piglet when the $etCO_2$ is varied by changing the respiratory rate as can be seen in Figure 1. Periodic blood gas analysis confirmed the $etCO_2$ accuracy. The animal appeared to be autoregulating cerebral flow during hypercapnia but in the later stage of hypocapnia begins to become pressure passive, indicating the loss of autoregulation. All animals maintained a 100% SpO_2 throughout the experiment.

The results from the same experimental protocol run in animals with reduced body temperature shown in Figure 2 reflects the reduced metabolic rate and the resultant limited $etCO_2$ changes in response to the same ventilatory change. The $etCO_2$ and the cerebral regional oxygen saturation of hemoglobin ($CrSO_2$) no longer track the common carotid flow and there is no significant increase in blood pressure until late in the hypocapnic period.

The lack of change in common carotid flow during hypothermia is likely due to the decreasing flow into the external carotid caused by vasoconstriction from cooling of the skin and counteracted by increasing flow into the internal carotid during hypercapnia as reflected in the increasing $CrSO_2$. Decreasing $CrSO_2$ observed during the hypocapnic period is accompanied by a decrease in the carotid flow.

Discussion

There is clear awareness of the relationship of hypercapnia and hypocapnia to neurodevelopmental complications. Clinicians have to rely on pulse oximetry and infrequent blood gas analysis to monitor the impact of changes in ventilatory settings which provides limited information for directing ventilatory management. The use of high frequency ventilation and positive airway pressure to keep the lungs open and insure adequate arterial saturation in premature infants has improved the survival rate but can lead to rapid loss of CO_2 and hypocapnia[15] if not closely monitored.

Near infrared spectroscopy (NIRS) provides a means of monitoring O_2 delivery to the brain and periphery in infants. Recent reports have established baseline readings of rSO_2 for cerebral, perirenal and ventral abdominal sites in term and preterm neonates[16-19] and preliminary reports have demonstrated the use of NIRS to track changes in blood flow to the brain, kidney and gut in a piglet model.[20-22]

The accuracy of $CrSO_2$ in reflecting internal jugular vein saturation in infants has been established in human and animal studies[20,23] and the rapid and sensitive response of $CrSO_2$ to changes in cerebral blood flow was demonstrated in piglets.[20]

Significant changes in CO_2 levels, whether from metabolic or respiratory shifts can alter cerebral vascular resistance, resulting in changes in cerebral blood flow and O_2 delivery. The response observed in these animal studies clearly demonstrates the value of NIRS in monitoring the cerebral response to CO_2.

$CrSO_2$ gives a venous weighted hemoglobin saturation value that reflects O_2 delivery to the brain and cerebral blood flow. There are a number of factors that can influence venous hemoglobin saturation, however, ranging from changes in blood flow to shifts in the hemoglobin dissociation curve. The impact of temperature and the Bohr Effect (high CO_2 and low pH) as well as 2,3 DPG levels are well recognized and can shift the O_2 dissociation curve to the right, decreasing hemoglobin O_2 affinity and increasing O_2 unloading at the tissue[23] potentially causing a decrease in venous saturation.

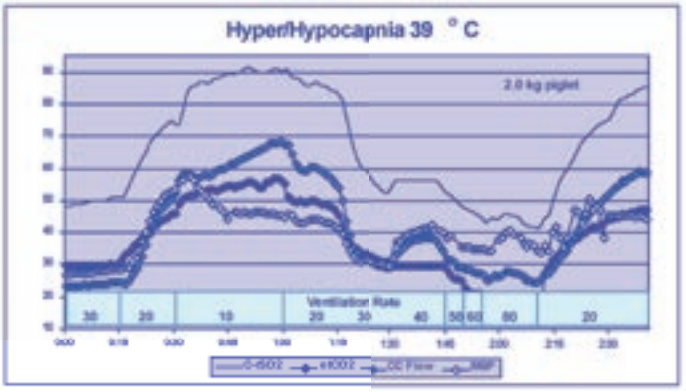


Figure 1. The cerebral perfusion response to hypercapnia followed by hypocapnia in a 2.0 kg, term, normothermic piglet demonstrating the ability of NIRS to track the cerebral blood flow response to changes in CO_2. CC Flow is common carotid flow, MBP mean blood pressure.

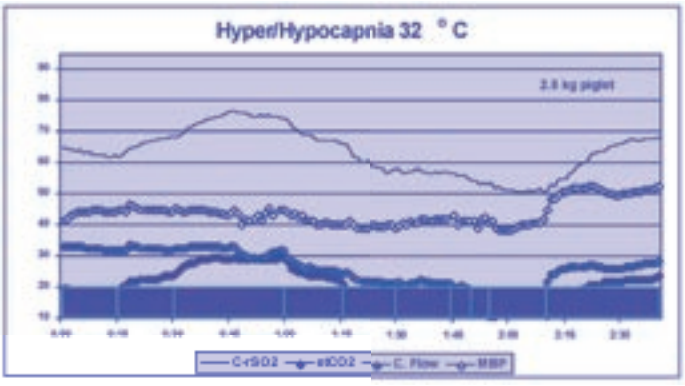


Figure 2. The $CrSO_2$ response to hypercapnia followed by hypocapnia in a 2.5 kg term, hypothermic piglet demonstrating a reduced $etCO_2$ response to ventilatory changes due to reduced metabolic rate. Common carotid flow decreased during hypocapnia but not hypercapnia and the $CrSO_2$ tracked $etCO_2$ changes as seen in the normothermic animals. CC Flow is common carotid flow, MBP mean blood pressure.

The use of hypothermia to prevent tissue and brain damage caused by hypoxia and tissue ischemia in neonates and adults has dramatically increased in the last decade and has improved survival and reduced morbidities. It became clear early on that the depth and duration of cooling as well as the rate of rewarming were critical components to successful improvement of outcome. These initial experiments in piglets have shown that hypothermia has the potential to alter the CO_2 response to ventilation changes as well as the vascular response to CO_2.

The rapid changes in $CrSO_2$ demonstrated that when CO_2 changes, rSO_2 will provide a rapid and accurate indication of the magnitude and extent of the change in blood flow. It needs to be kept in mind as mentioned above, however, when using NIRS to track changes in blood flow in response to CO_2 that venous hemoglobin saturation and hence $CrSO_2$ can also reflect changes in O_2 affinity when supply doesn't meet demand. Normally reduction in demand is slow and arterial saturation reflects O_2 supply changes.

NIRS can be a significant contribution to managing neonatal ventilation, aiding in recognizing dangerous alterations in CO_2 and helping to prevent neurocognitive complications of IVH and PVL. Combined with pulse oximetry rSO_2 can be used as a management tool to indicate when ventilation settings may be excessive and should be reviewed and blood gases ordered.

References

1 Perlman JM et al. 1985 Reduction in intraventricular hemorrhage by elimination of fluctuating cerebral blood flow velocity in preterm infants with respiratory distress syndrome. NEJM 312: 1353-1357.
2 Bada HS et al. 1990 Mean arterial pressure changes in premature infants and those at risk for intraventricular hemorrhage. J Pediatrics 117; 607-614.
3 Locatelli A et al. 2010 Antenatal variables associated with severe adverse neurodevelopmental outcome among neonates born at less than 32 weeks. Eur J Ob and Gyn Repro Biol epub.
4 Seri I 2004 Low SVC flow during the dirst postnatal day and neurodevelopment in preterm neonates. J Peds 145; 573-575. pdf.
5 Hunt RW et al. 2004 Low SVC flow and neurodevelopment at 3 years in very preterm infants. J Ped 145; 588-592.
6 Fabres J et al. 2007 Both extremes of arterial carbon dioxide pressure and the magnitude of fluctuations in arterial carbon dioxide pressure are associated with severe intraventricular hemorrhage in very low birth weight preterm infants. Pediatrics 119; 299-305.
7 Kaiser JR et al. 2006 Hypercapnia during the first 3 days of life is associated with severe intraventricular hemorrhage in very low birth weight infants. J Perinatol 26: 279-285.
8 McKee la et al. 2009 PaCO2 and neurodevelopment in ELBW infants. J Pediatrics 155; 217-221.
9 Wiswell TE et al. 1996 Effects of hypocarbia on the development of cystic periventricular leukomalacia in premature infants treated with HFJV. Pediatrics 98; 918-924.
10 Adams-Chapman I 2009 Insults to the developing brain and impact on neurodevelopmental outcome. J Communications Disorders 42; 256-262.
11 Choudry M et al. 2006 Arterial to end tidal CO_2 tension difference in children with congenital heart disease. J Cardiothor Vasc Anesth 20: 196-201.
12 Kugelman A et al. 2008 A novel method of distal end tidal CO_2 capnography in intubated infants; comparison with $PaCO_2$. Pediatrics 122: e1219-e1224.
13 Nishimura M et al. 1992 Capnometry during high frequency oscillatory ventilation. Chest 101: 1681-1683.
14 Tobias JD 2009 Transcutaneous CO_2 monitoring in infants and children. Ped Anesth 19: 434-444.
15 Laffey JG and Kavanagh BP 2002 Hypocapnia. NEJM 347; 43-53.
16 Bernal NP et al. 2010 Cerebral and somatic NIRS in normal newborns. J Pediatr Surg 45; 1306-1310.
17 McNeill S et al. 2010 Normal cerebral, renal and abdominal regional saturations using NIRS in preterm infants. J Perinat epub.
18 Tina LG et al. 2009 NIRS in healthy preterm and term newborns; correlation with GA and standard monitoring. Curr Neurovasc Res 6; 148-154.
19 Wider M and Booth E 2010 Cerebral and somatic regional oxygen saturation (rSO2) in neonates. J Perinat Neonat 23; 34-37.
20 Wider MD 2009 Hemodynamic management and regional hemoglobin oxygen saturation of the brain, kidney and gut. J Perinat Neonat 22; 57-60.
21 Hoffman G and Wider M 2008 Organ specificity of NIRS rSO2 measurement s during regional ischemia in piglets. Anesthesiology 109; A272.
22 Hoffman G and Wider M 2008 Changes in regional oxygenation by NIRS during global ischemia in piglets. Anesthesiology 109; A1512.
23 Abdul-Khaliq H et al. 2000 Comparison of regional transcranial oximetry with NIRS and jugular venous bulb oxygen saturation. Biomed Technik 45; 328-332.
24 Shappell SD et al. 1971 Adaptation to exercise; role of hemoglobin affinity for oxygen and 2,3 diphosphoglycerate. J Appl Physiol 30; 827-832.

Use of the Edi Catheter in Monitoring Post-Extubation Support in an Infant

This case study was provided by Tom Noblet, Manager of the Respiratory Therapy Department and its staff at St Vincent Women's Hospital in Indianapolis, IN. This case study previously appeared as a white paper from MAQUET Critical Care, Wayne, NJ, in 2009. It was later presented at the Open Forum, International Congress of Respiratory Care, AARC, in San Antonio, TX, in December 2009.[1]

Case

A 26-week-old preemie was intubated and received ventilatory support on the SERVO-i. The infant was on SIMV PC+PS. An Edi catheter was inserted to monitor and evaluate the diaphragm's electrical activity. [Edi is the diaphragm's electrical activity that occurs just prior to a contraction. The Edi is controlled by the brain's respiratory center, which sends a signal through the phrenic nerve to the diaphragm. The Edi catheter is similar to a nasal or oral tube, but contains an additional 10 sensors, located around the distal tip, that measure diaphragm electrical activity (Edi). This catheter can be used in conjunction with the SERVO-i ventilator. The ventilator can display the Edi waveform on its display screen and use the signal to control the ventilator when NAVA (neurally adjusted ventilatory assist) is selected as the mode.]

Following extubation, the preemie was placed on bubble CPAP of 5 cm H_2O, which was increased to 7 cm H_2O to improve oxygenation. The Edi catheter was kept in place to continue monitoring diaphragmatic electrical activity (Edi) with the bubble CPAP. Respiratory Therapist Joyce Henderson, RRT, NPS, commented, "The baby's work of breathing (WOB) appeared excessive during this time. There were sternal and intercostal retractions present and the infant was using accessory muscles to ventilate."

The medical team was considering re-intubation. However, because the catheter was still in place, the respiratory therapist was able to evaluate the Edi signal. The physical findings correlated with a peak Edi that ranged between 50 and 70 microvolts (from a few microvolts up to 10 microvolts is considered a normal range).[2] The high Edi level demonstrated the increased activity of the diaphragm during bubble CPAP.

Figure 1 shows the Edi waveform (bottom waveform) with the patient breathing on 7 cm H_2O of bubble CPAP. The range of the peak Edi value averaged 58 microvolts. (In Figure 1, the ventilator is on "standby" and not in use because the catheter was being used for monitoring only.)

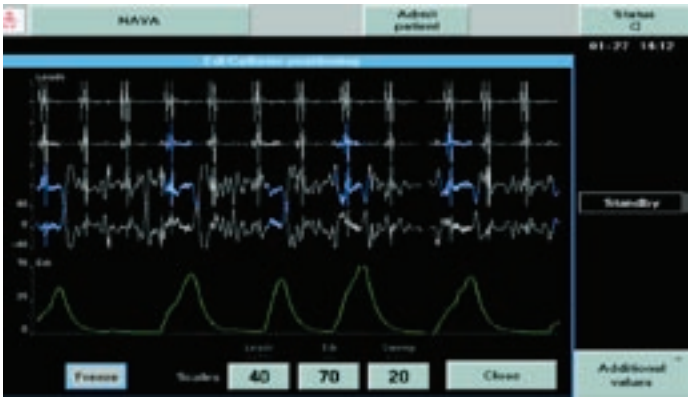


Figure 1: Infant on bubble CPAP of 7 cm H2O. The bottom waveform is the Edi signal.

Because of the high WOB evidenced on bubble CPAP, the infant was switched to a high-flow nasal cannula (HFNC) at 2 L/min. The amount of positive pressure generated with an HFNC is flow dependent, but it is not possible to measure the airway pressure with an HFNC device. The peak Edi was even higher on the 2 L/min HFNC than with the bubble CPAP. Thus, the drive to breath was not reduced at this flow setting (average 78 microvolts).

The HFNC was increased to 4 L/min and the peak Edi was seen to decrease to an average of 60 microvolts.

The HFNC was then increased to 6 L/min. The peak Edi continued to decrease, with only occasional breaths generating an Edi of more than 70 microvolts. These may have been "sigh" breaths. Most breaths were 35 microvolts or less (average 38 microvolts, excluding sigh) on 6 L/min.

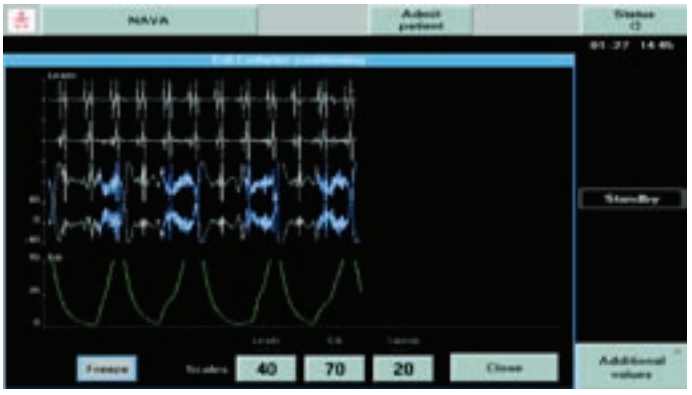


Figure 2: The infant is on an HFNC (Vapotherm) at 6 L/min (Lpm). Edi is the bottom waveform, with an average value of 38 microvolts.

Continued on page 56…

Why is the Cesarean Section Rate on the Rise in the USA?

Benamanahalli K. Rajegowda, MD; Muhammad Aslam, MD

The cesarean section (CS) rate in the United States is around 30%. In some regional hospitals the CS rate is even higher, reaching almost 50%. What has resulted in this rapid increase is debatable but several factors are worth considering, which include but are not limited to comfort for doctors or consumers, increase in high risk pregnancies due to the use of fertility drugs and in vitro fertilization, use of intrapartum electronic fetal monitoring (IEFM), fear of litigation, and finally, due to a repetition of the saying, "once a section, always a section."

Let me give you my (BK Rajegowda) experience as a neonatologist for over 40 years: In the 60s and 70s the CS rate was around 6-7%, when CS was mainly done for cephalopelvic disproportion, compound presentation, fetal bradycardia, and maternal hemorrhage. Subsequently—due to improvements in perinatal medicine, with advanced maternal-fetal well-being tests, use of technology in fetal assessment before and during labor, and trained sub-specialization in obstetrics, perinatology, along with improvement in neonatal care—CS has been liberalized and the rate has been going up slowly from the 70s onwards to the present level. There is evidence that fetomaternal risks which are identified during this advanced monitoring, with timely intervention, help to prevent fetal death, birth asphyxia, neonatal seizures, birth trauma, and of course neonatal death, along with improvement in neurodevelopment among survivors. It has been shown that IEFM has not decreased the incidence of stillbirth, cerebral palsy and perinatal mortality. On the other hand, CS does have a cost, as well as contributing to maternal and neonatal morbidity and mortality.

At present, IEFM is standard for every woman in labor who walks into the hospital. This has replaced the old standard of women who were ambulated until the full dilation of cervix and closely monitored for delivery by a midwife or an obstetrician. According to ACOG, the recent data shows approximately four million, or 85% of live births were assessed with IEFM, making it the most common obstetric procedure. However, IEFM during labor identified varied fetal risks and was the main contributing factor responsible for an increase in the CS rate. IEFM has advantages and disadvantages. If IEFM is used intrapartum along with clinical assessment at the bedside with fully trained staff instead of evaluating the fetal tracings from the office or the desk, this will have significant impact in lowering the CS rate. It has helped to deliver fetuses expeditiously when giving an alarming tracing, but due to normal course at delivery many infants could have been delivered vaginally without intervention. The fear of litigation and lawsuits are related mainly to IEFM tracings showing any form of variability that are used in courts. Because of this, the practitioner will not take any risk and go for delivery via CS even if the delivery can be accomplished without intervention. There are pitfalls of using IEFM tracings, and any such documented tracings are a root cause for attorneys to argue in favor of plaintiffs. This is the second most common risk factor for using CS.

Liability insurance has gone through the roof and many practitioners have given up their practice, resulting in a shortage of obstetricians in many parts of the country, with other obstetricians slowing down their obstetric practice of delivering babies. In addition, liability insurance has driven out midwives from their practices in delivering babies. A recent survey of professional liability of obstetricians revealed at least one professional liability claim against each surveyed obstetrician during his or her career. Forty-four percent had four or more claims. Many of these lawsuits have no merit but they do produce agony for practicing physicians. Of course no one disagrees that the patient who suffers deserves compensation if any malpractice has occurred. However, as long as the present healthcare system is without tort reform, the practitioner continues to practice defensive medicine, resulting in increased cost of care and a concomitant increase in the CS rate.

The third reason for increase in the CS rate is repeat c-section, although 80 to 85% of women will have successful vaginal deliveries after a cesarean section. However, the obstetricians will not take any risk delivering by VBAC after a previous c-section, given risk of complications and litigation. As such, there will be fewer and fewer vaginal deliveries. In our view, in the future, L&D will be labeled as an operating room procedure, since the CS rate will reach 50%.

The problem in the United States compares with other developed countries where the consumer wants everything done immediately. Physicians prefer CS even when it's not needed, do unnecessary tests, unnecessary consultations, write needless prescriptions and even prolong life without necessarily considering the need, the cost and the suffering. On the other hand patients want CS so they won't have to tolerate the pain of labor and its complications. This is a litigious society which assumes no personal responsibilities. Americans spent more than 15% of their budget on healthcare but they are far behind many countries on many healthcare issues. Money cannot buy everything and the citizens must take responsibility and apply the adage, "an ounce of prevention is worth a pound of cure." Women who want to get pregnant must plan their pregnancy,

Continued on page 56…

The authors are on the editorial advisory board of Neonatal Intensive Care.

Fetal Operation Followed by Cesarean Section May Have a Beneficial Effect Upon Neuromuscular Function in Spina Bifida Aperta

Renate Verbeek, Axel Heep, Natasha Maurits, Reinhold Cremer, Oebele Brouwer, Johannes van der Hoeven, Deborah Sival

Background

Spina bifida aperta (SBA) is associated with neurological dysfunction cranial and caudal to the meningomyelocele (MMC). Fetal surgery may ameliorate cranial abnormalities, but effects upon neuromuscular function caudal to the MMC are unclear. SBA myotomes cranial to the MMC are influenced by cerebral dysfunction, whereas myotomes caudal to the MMC are additionally influenced by the MMC. Increased muscle ultrasound density (MUD) reflects neuromuscular damage. By the intra-individual difference in MUD (dMUD=[MUDcaudal] - [MUDcranial]) the effect by the MMC upon neuromuscular integrity is derived. In the present study, we aimed to compare dMUD and neuromuscular function between fetally and postnatally-operated SBA patients.

Materials and Methods

We compared dMUD and neuromuscular function in 6 (age- and MMC-) matched pairs of fetally and postnatally operated SBA patients [age 0-3.5 years; lumbar (6) and lumbar-sacral (6) MMC]. In all patients, quadriceps muscle was innervated cranial- and calf muscle caudal- to the MMC. Fetally operated patients were delivered by cesarean section (CS) at Bonn; postnatally operated patients were delivered vaginally at Groningen.

Results

The dMUD was smaller in fetally than in postnatally-operated SBA patients [10 (-11 to 37) vs 28 (4 to 47), medians (ranges); $p<0.05$]. Comparing SBA patients, the results indicated more preserved neuromuscular function in fetally than postnatally operated patients [median difference: 1 and 1.5 myotome (ranges 1-3); motor and sensory function resp.; $p<0.05$)].

Conclusion

In SBA, dMUD provides a diagnostic tool to compare neuromuscular integrity between treatment groups. Present data suggest that fetal operation followed by CS has some beneficial effect upon neuromuscular outcome caudal to the MMC. Future assessment in SBA patients (treated by postnatal operation followed by CS) may allow further differentiation between the effect by operation and way of delivery upon neuromuscular outcome.

Verbeek, Maurits, Brouwer and Hoeven are with the Department of Neurology, University Medical Center Groningen, University of Groningen, the Netherlands; Heep is with the Department of Neonatology, University of Bonn; Cremer is with the Department of Pediatrics, Children's Hospital Cologne; Sival is with the Department of Paediatrics, University Medical Center Groningen.

for neonatal RDS

Infasurf®

(calfactant)
Intratracheal Suspension

Why we're little pharma.

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

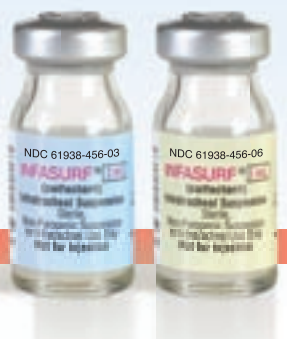
Sometimes, the smaller your organization, the more details matter. That's why ONY, Inc., our little company in Amherst, New York, produces only Infasurf ®(calfactant) – an area we pioneered over 20 years ago.

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

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

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

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



THE LITTLE THINGS MATTER MOST

Infasurf®

for neonatal RDS

(calfactant)

Intratracheal Suspension

Sterile Suspension for Intratracheal Use Only

Rx Only Rev. 06/09

DESCRIPTION

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

Infasurf is an off-white suspension of calfactant in 0.9% aqueous sodium chloride solution. It has a pH of 5.0 - 6.2 (target pH 5.5). Each milliliter of Infasurf contains 35 mg total phospholipids (including 26 mg phosphatidylcholine of which 16 mg is disaturated phosphatidylcholine) and 0.7 mg proteins including 0.26 mg of SP-B.

CLINICAL PHARMACOLOGY

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

Activity: Infasurf adsorbs rapidly to the surface of the air-liquid interface and modifies surface tension similarly to natural lung surfactant. A minimum surface tension of ≤5 mN/m is produced in vitro by Infasurf as measured on a pulsating bubble surfactometer. *In vivo*, Infasurf restores the pressure-volume mechanics and compliance of surfactant-deficient rat lungs. *In vivo*, Infasurf improves lung compliance, respiratory gas exchange, and survival in preterm lambs with profound surfactant deficiency.

Animal Metabolism: Infasurf is administered directly to the lung lumen surface, *in situ* of action. No human studies of absorption, biotransformation, or excretion of Infasurf have been performed. The administration of Infasurf with radiolabeled phospholipids into the lungs of adult rabbits results in the persistence of 50% of radioactivity in the lung alveolar lining and 25% of radioactivity in the lung tissue 24 hours later. Less than 5% of the radioactivity is found in other organs. In premature lambs with lethal surfactant deficiency, less than 30% of instilled Infasurf is present in the lung lining after 24 hours.

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

Infasurf versus Exosurf Neonatal®

Treatment Trial

A total of 1126 infants ≥72 hours of age with RDS who required endotracheal intubation and had an a/A PO_2 ≤ 0.22 were enrolled into a multiple-dose, randomized, double-blind treatment trial comparing Infasurf (3 mL/kg) and Exosurf Neonatal® (5 mL/kg). Patients were given an initial dose and one repeat dose 12 hours later if intubation was still required. The dose was instilled in two aliquots through a side port adapter into the proximal end of the endotracheal tube. Each aliquot was given in small bursts over 20-30 inspiratory cycles. After each aliquot was instilled, the infant was positioned with either the right or the left side dependent. Results for efficacy parameters evaluated at 28 days or to discharge for all treated patients from this treatment trial are shown in

Table 1: Infasurf vs Exosurf Neonatal® Treatment Trial

Efficacy Parameter	Infasurf (N=478) %	Exosurf Neonatal® (N=559) %	p-Value
Incidence of air leaks[1]	11	22	<0.001
Death due to RDS	4	8	0.05
Any death to 28 days	8	10	0.25
Any death before discharge	9	12	0.07
BPD[2]	5	6	0.41
Unsuspected other pathology[3]	4	6	1

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

Prophylaxis Trial

A total of 853 infants ≤29 weeks gestation were enrolled into a multiple-dose, randomized, double-blind prophylaxis trial comparing Infasurf (3 mL/kg) and Exosurf Neonatal® (5 mL/kg). The initial dose was administered within 30 minutes of birth. Repeat doses were administered at 12 and 24 hours if the patient remained intubated. Each dose was administered divided in 2 equal aliquots, and given through a side port adapter into the proximal end of the endotracheal tube. Each aliquot was given in small bursts over 20-30 inspiratory cycles. After each aliquot was instilled, the infant was positioned with either the right or the left side dependent. Results for efficacy parameters evaluated to day 28 or to discharge for all treated patients from this prophylaxis trial are shown in Table 2.

Table 2: Infasurf vs Exosurf Neonatal® Prophylaxis Trial

Efficacy Parameter	Infasurf (N=431) %	Exosurf Neonatal® (N=422) %	p-Value
Incidence of RDS	43	47	0.001
Incidence of air leaks[1]	10	15	0.01
Death due to RDS	2	5	0.01
Any death to 28 days	12	16	0.10
Any death before discharge	18	19	0.76
BPD[2]	16	17	0.60
Unsuspected other pathology[3]	0.2	1	0.004

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

Infasurf versus Survanta®

Treatment Trial

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

Prophylaxis Trial

A total of 417 infants ≤30 weeks gestation and ≤1251 grams birth weight were enrolled into a multiple-dose, randomized, double-blind trial comparing Infasurf (4 mL/kg of a formulation that contained 25 mg of phospholipids/mL rather than the 35 mg/mL in the marketed formulations) and Survanta® (4 mL/kg). The initial dose was administered within15 minutes of birth and repeat doses were allowed ≥6 hours following the previous treatment (for up to three doses before 96 hours of age) if the patient required ≥30% oxygen. The surfactant was given through a 5 French feeding catheter inserted into the endotracheal tube. The total dose was instilled in four equal aliquots with the catheter removed between each of the instillations and mechanical ventilation resumed for 0.5 to 2 minutes. Each of the aliquots was administered with the patient in one of four different positions (prone, supine, right, and left lateral). Results for efficacy endpoints evaluated at 28 days or to discharge for all treated patients from this prophylaxis trial showed an increase in mortality from any cause at 28 days (p=0.03) and in death due to respiratory causes (p=0.005) in Infasurf-treated infants. For evaluable patients (patients who met the protocol-defined entry criteria), mortality from any cause and mortality due to respiratory causes were also higher in the Infasurf group (p = 0.07 and 0.01, respectively). However, these observations have not been replicated in other adequate and well-controlled trials and their relevance to the intended population is unknown. All other efficacy outcomes (incidence of RDS, air leaks, BPD, and treatment failure) were not significantly different between Infasurf and Survanta® when analyzed for all treated patients and for evaluable patients.

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

INDICATIONS AND USAGE

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

Prophylaxis

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

Treatment

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

WARNINGS

Infasurf is intended for intratracheal use only.

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

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

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

PRECAUTIONS

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

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

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

ADVERSE REACTIONS

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

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

Complication	Infasurf (N=1001) %	Exosurf Neonatal® (N=978) %	Infasurf (N=431) %	Survanta® (N=662) %
Apnea	46	44	56	56
Patent ductus arteriosus	47	48	49	46
Intraventricular hemorrhage	29	31	36	36
Severe intraventricular hemorrhage[1] (VH and PVL)[2]	12	16	6	9
	7	7	5	5
Sepsis	20	22	28	27
Pulmonary air leaks	12	22	10	10
Pulmonary interstitial emphysema	9	17	10	10
Pulmonary hemorrhage	3	3	3	6
Necrotizing enterocolitis	9	9	17	10

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

Follow-up Evaluations

Two-year follow-up data of neurodevelopmental outcomes in 115 infants enrolled in 9 centers that participated in the Infasurf vs. Exosurf Neonatal® controlled trials demonstrated significant developmental delays in equal percentages of Infasurf and Exosurf Neonatal® patients.

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

FOR INTRATRACHEAL ADMINISTRATION ONLY

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

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

Dosage

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

Directions for Use

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

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

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

Dosing Procedures

General

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

Administration for Treatment of RDS

Initial Dose

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

Repeat Doses

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

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

Administration for Prophylaxis of RDS at Birth

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

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

Dosing Precautions

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

HOW SUPPLIED

Infasurf (calfactant) Intratracheal Suspension is supplied sterile in single-use, rubber-stoppered glass vials containing 3 mL (NDC 61958-450-02) and 6 mL (NDC 61958-450-06) off-white suspension.

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

Rx only

Manufactured by:
ONY, Inc.
Amherst, NY 14228

Rev. 06/09

Pulse Oximetry in the Newborn: Is the Left Hand Pre- or Post-ductal?

Christoph Ruegger, Hans Ulrich Bucher, Romaine Arlettaz Mieth

Abstract

Background: Over the past few years, great efforts have been made to screen duct-dependent congenital heart diseases in the newborn. Arterial pulse oximetry screening (foot and/or right hand) has been put forth as the most useful strategy to prevent circulatory collapse. The left hand, however, has always been ignored, as it was unclear if the ductus arteriosus influences left-hand arterial perfusion. The objective of our study was to evaluate the impact of the arterial duct on neonatal pulse oximetry saturation (POS) on the left hand.

Methods: In this observational study, arterial oxygen saturation on both hands and on one foot was measured within the first 4 hours of life.

Results: Two hundred fifty-one newborns were studied: 53% males and 47% were delivered by caesarean section. The median gestational age was 38 4/7 weeks (90% CI, 32 6/7-41 2/7 weeks), the median birth weight was 3140 g (90% CI, 1655-4110 g) and the median age at recording was 60 minutes (90% CI, 15-210 minutes). The mean POS for the overall study population was 95.7% (90% CI, 90-100%) on the right hand, 95.7% (90% CI, 90-100%) on the left hand, and 94.9% (90% CI, 86-100%) on the foot. Four subgroups (preterm infants, babies with respiratory disorders, neonates delivered by caesarean section, and newborns ≤15 minutes of age) were formed and analysed separately. None of the subgroups showed a statistically significant difference between the right and left hands. Additionally, multivariate logistic regression did not identify any associated factors influencing the POS on the left hand.

Conclusions: With the exception of some children with complex or duct dependent congenital heart defects and some children with persistent pulmonary hypertension, POS on both hands can be considered equally pre-ductal.

Background

Cardiovascular malformations are the commonest type of congenital malformation (6-8/1000) and responsible for more deaths in the first year of life than any other birth defects. A sixth of the affected children have a duct dependent circulation, with a persistent ductus arteriosus being necessary for survival.[1-3] Over the past few years, great efforts have been made to screen these duct-dependent congenital heart diseases (CHD) in the newborn. As ductal-dependent CHD may not be apparent at the time of early discharge examination,[4-5] post-ductal arterial pulse oximetry screening during the first 24 hours of life has been put forth as the most useful strategy to prevent circulatory collapse or death.[6-9] The ease of performing, minimal discomfort for the baby, low costs, and excellent detection rates of duct- dependent circulation are strong arguments to implement pulse oximetry as a basic routine in the nursery.[10,11]

In addition, pulse oximetry has been used for observing newborns with respiratory or cardiac disorders and has been found to be helpful in monitoring neonatal resuscitation. In this context, pre-ductal POS, the sensor applied to the right hand, must be used to monitor oxygen application. This is in contrast to the later measured post-ductal POS (foot) to rule out CHD as described above.

For both purposes, previous studies have focused on obtaining pulse oxygen saturation from one foot (post-ductal) and/or the right hand (pre-ductal). The left hand, however, has always been ignored, as it was unclear if the ductus arteriosus influences left-hand arterial perfusion. By means of pulse oximetry measurements, the purpose of the present study was to clarify if values of the left hand can be differentiated from the pre-ductal (right hand) and post-ductal (foot) values.

Methods

The study population of this observational study included infants born at the University Hospital of Zurich between 5 January and 26 April 2009. Newborn infants with pre- or post-natally diagnosed CHD were also measured, but not included in the overall analysis. The measurements were performed using a Nellcor-65 handheld pulse oximeter with a neonatal OxiMax adhesive sensor. An accuracy of ±2% for the measurement of functional oxygen saturation (SpO_2) was stated by the manufacturer. For each newborn, a neonatologist obtained the POS for both hands and one foot within the first 4 hours of life. The probe was secured to the wrist or palm and to the sole of the foot, following a random order. The same oximeter was used for all three sequential measurements. To avoid movement artifacts, the pulse was observed until a good waveform was obtained. It usually required 3-5 minutes for all 3 measurements to be performed.

As post-ductal (foot) pulse oximetry screening has become the standard of care at our institution, the two additional recordings (right and left hands) were considered a modification of the routine examination. In agreement with the Hospital Committee of Ethics, the parents were informed, but no written consent was obtained. On enrolment in the study, the following information of each infant was recorded: gestational age, gender, birth weight, mode of delivery, umbilical arterial pH, Apgar score at 5 minutes, and postnatal age.

Statistical analysis: A sample size was estimated based on the

The authors are with the Clinic for Neonatology, University Hospital Zurich, Switzerland.

Table 1: Baseline characteristics of the study population.

Characteristics:		Study group:
Female	No. (%)	117 (47)
Male	No. (%)	134 (53)
Gestational Age (week)	p0.5 (p0.05 - p0.95)	38 4/7 (32 6/7 - 41 2/7)
Fullterm	No. (%)	189 (75)
Preterm	No. (%)	62 (25)
Birth weight (g)	p0.5 (p0.05 - p0.95)	3140 (1655 - 4110)
Birth mode		
Spontaneous	No. (%)	98 (39)
Vacuum extraction	No. (%)	34 (14)
Caesarean section	No. (%)	119 (47)
Apgar score at 5 minutes	p0.5 (p0.05 - p0.95)	9 (7 - 9)
Umbilical artery pH	p0.5 (p0.05 - p0.95)	7.3 (7.1 - 7.4)
Age at commencement of recording (min)	p0.5 (p0.05 - p0.95)	60 (15 - 225)

p0.5 = 50th percentile = median, p0.05 = 5th percentile, p0.95 = 95th percentile

Table 2: Arterial oxygen saturation.

Subgroup	Performance	Right hand (%)	Left hand (%)	Foot (%)
All (N = 251)	Mean (90% CI) SD	95.7 (90 - 100) 3.7	95.7 (90 - 100) 4.0	94.9 (86 - 100) 4.6
Preterm (N = 62)	Mean (90% CI) SD	94.3 (90 - 100) 5.2	94 (87 - 100) 5.2	93.1 (85 - 100) 5.9
RDS (N = 57)	Mean (90% CI) SD	93.8 (89 - 99) 3.3	93.2 (88 - 98) 4.3	92.6 (85 - 100) 4.8
Caesarean section (N = 119)	Mean (90% CI) SD	95.2 (90 - 100) 4.6	94.9 (88 - 100) 4.8	94.1 (87 - 100) 5.2
Age at recording ≤15 min (N = 34)	Mean (90% CI) SD	95.3 (91 - 100) 3.0	95.1 (90 - 99) 3.2	92.9 (85 - 99) 4.3

Subgroup	Performance	Right hand - Left hand	Left hand - Foot	Right hand - Foot
All	p-value	0.41	<0.001	<0.001
Preterm		0.25	<0.001	<0.001
RDS		0.06	0.09	0.005
Caesarean section		0.12	0.01	<0.001
Age at recording ≤15 min		0.37	0.001	<0.001

Table 4: Effects of variables on the POS difference between the right hand and the foot.

Variable:	numDF	denDF	F-value	p-value
Age at recording	1	55	5.016	0.029
Birth weight	1	55	7.046	0.010
Mode of delivery (caesarean section)	2	55	0.734	0.484

numDF = degrees of freedom numerator, denDF = degrees of freedom denominator

number of independent variables included in our multivariate logistic regression. Starting from a minimum number of 10 observations needed for each parameter, a sample size of 110 infants was initially calculated. To be positive about the detection of even small effects, the sample size was doubled to 250. Further, a one-sided paired Student's t test was performed to determine differences between the three measurements, and finally multivariate logistic regression was conducted to identify associated factors. All statistical analyses were carried out with commercial software (Microsoft Excel 2008 for Mac and R, version 2.2.0.2 for Windows).

Results

During the study period, 739 babies were live born at our institution. Of these newborn infants, 254 (34%) were enrolled in the study. Recordings of the remaining newborns were not obtained for the following reasons: lack of staff, several simultaneous deliveries, and movement artifacts. In addition, three recordings were analyzed separately because of known or suspected CHD. The first newborn had trisomy 13 with an interrupted aortic arch; the arterial oxygen saturation showed values of 84%, 79% and 62% on the right hand, left hand, and foot. In a second newborn, echocardiography revealed a double outlet right ventricle with an oxygen saturation of 94%, 88% and 88%, respectively. A third newborn had a saturation of 89%, 86% and 85% on the right hand, left hand, and foot, respectively. A double inlet single ventricle was demonstrated on the echocardiogram. Consequently, data from 251 infants were recorded and analyzed. The median gestational age was 38 4/7 weeks (90% CI, 32 6/7-41 2/7 weeks) and the median birth weight was 3140 g (90% CI, 1655-4110 g). Further patient characteristics are given in Table 1. The median age at the beginning of recording was 60 minutes (90% CI, 15-225 minutes).

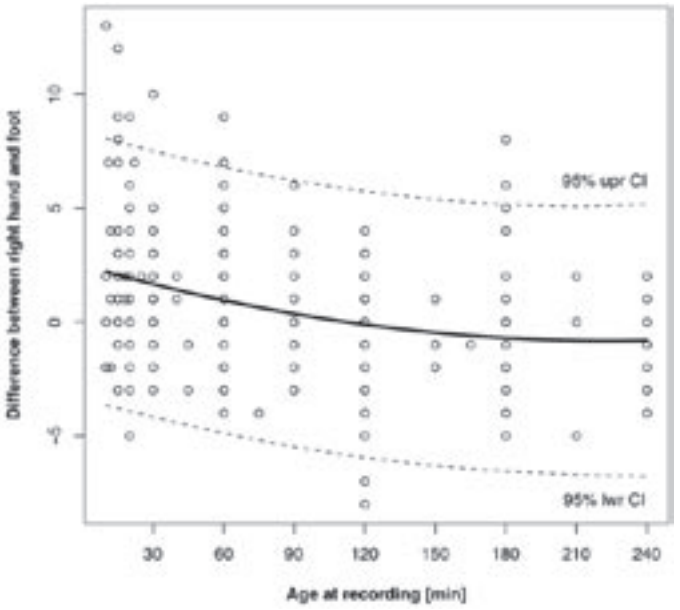


Figure 1. Difference between right hand and foot correlating with age at recording. Dotted lines = 5th/95th percentile, solid line = 50th percentile.

Recordings of the study population revealed identical mean oxygen saturations of 95.7% (90% CI, 90-100%) on the right and left hands (p-value=0.41). The post-ductal mean oxygen saturation was 94.9% (90% CI, 86-100%), which was 0.8% lower than both hands. In addition, the same analyses were carried out for different subgroups, such as preterm infants, babies with respiratory disorders, neonates delivered by cesarean section, and newborns measured within the first 15 minutes of life. All of the newborn subgroups were at higher risk for an elevated pulmonary artery pressure, and therefore most likely qualified to demonstrate an eventual effect on left-hand perfusion based on right-to-left shunting through the arterial duct. The results of oximetry measurements of the whole study population and the four subgroups are presented in Table 2.

As described under statistical analysis, the following associated variables for the differences between both hands were identified: Age at recording, respiratory disorder, and caesarean section. None of the variables had a significant impact on the difference between the right and left hand, as shown in Table 3 (p-values >0.05). For the differences between the right hand and the foot, birth weight and age at recording remained in the model [Table

4]. These differences were shown to decreases with postnatal age, as plotted in Figure 1. Again, the cesarean section was not suitable for further analysis.

Discussion

Right Hand-Left Hand: The present study demonstrates that arterial pulse oximetry measurements on the left hand do not significantly differ from the pre-ductal values on the right hand. Even with regard to the four subgroups, in which right-to-left shunting through fetal circulatory pathways resulting from persistent pulmonary hypertension can be assumed, no statistically significant difference was found. We conclude from our data that perfusion of the left hand is unaffected by the arterial duct and can be considered pre-ductal. In the subgroup consisting of babies with respiratory disorders, a trend, but no statistically significant difference between both hands was detected (p-value 0.06). This trend towards lower values on the left hand can physiologically be explained by a delayed decrease in pulmonary hypertension.

Right Hand-Foot: Other results fully correspond to those of previous studies. Our overall post-ductal POS levels were 0.8% lower compared to the pre-ductal POS levels.[12,13] In fact, the subgroup consisting of babies recorded within the first 15 minutes of life had post-ductal values that were 2.4% lower. An elevated pulmonary artery pressure during the first minutes of life is the main cause for this difference. Levesque et al[12] reported that postnatal age and the activity state, for example fussy and crying infants at the time of measurement were the most important factors affecting post-ductal POS. In the present study, multivariate logistic regression detected age at recording as one of two variables influencing the difference between pre- and post-ductal values. This is consistent with findings of other studies, in which POS has been shown to increase with time.[13-15] The second variable derived from multivariate logistic regression was birth weight, with a positive correlation to the difference between pre- and post-ductal values. This was unexpected and could neither be explained conclusively nor brought in line with the results of previous studies.

Other authors have focused on whether or not the mode of delivery could have an effect on saturation.[14-16] They all postulated lower post-ductal saturations due to greater retained fetal lung fluid after caesarean section. This is confirmed by our data which showed a significantly lower mean post-ductal saturation in infants delivered by caesarean section (94.1%) compared to infants delivered vaginally (96%, p-value=0.002). The difference between pre- and post-ductal values, however, was not significantly influenced by the mode of delivery.

Conclusions

Arterial pulse oximetry is a powerful tool to screen for life threatening CHD. Within the wide range of pre- and post-ductal oxygen saturation, the present study clearly demonstrates that even during the first hours of life, characterised by the process of adaptation, the right and left hand do not significantly differ. We therefore conclude that with the exception of some children with complex or duct dependent CHD and some children with persistent pulmonary hypertension, POS on both hands can be considered equally pre-ductal.

References

1 Abu-Harb M, Hey E, Wren C: Death in infancy from unrecognized congenital heart disease. Arch Dis Child 1994, 71:3-7.

2 Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, Ferguson TB, Ford E, Furie K, Gillespie C, Go A, Greenlund K, Haase N, Hailpern S, Ho PM, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott MM, Meigs J, Mozaffarian D, Mussolino M, Nichol G, Roger VL, Rosamond W, Sacco R, Sorlie P, Stafford R, Thom T, Wasserthiel- Smoller S, Wong ND, Wylie-Rosett J: Heart disease and stroke statistics—2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2009, 119(3):480-6.

3 Wren C, Reinhardt Z, Khawaja K: Twenty-year trends in diagnosis of lifethreatening neonatal cardiovascular malformations. Arch Dis Child Fetal Neonatal Ed 2008, 93(1):F33-5.

4 Wren C, Richmond S, Donaldson L: Presentation of congenital heart disease in infancy: implications for routine examination. Arch Dis Child Fetal Neonatal Ed 1999, 80(1):F49-53.

5 Mellander M, Sunnegardh J: Failure to diagnose critical heart malformations in newborns before discharge—an increasing problem? Acta Paediatr 2006, 95(4):407-13.

6 de-Wahl Granelli A, Wennergren M, Sandberg K, Mellander M, Bejlum C, Inganas L, Eriksson M, Segerdahl N, Agren A, Ekman-Joelsson BM, Sunnegardh J, Verdicchio M, Ostman-Smith I: Impact of pulse oximetry screening on the detection of duct dependent congenital heart disease: a Swedish prospective screening study in 39,821 newborns. BMJ 2009, 338:a3037.

7 Thangaratinam S, Daniels J, Ewer AK, Zamora J, Khan KS: Accuracy of pulse oximetry in screening for congenital heart disease in asymptomatic newborns: a systematic review. Arch Dis Child Fetal Neonatal Ed 2007, 92(3):F176-80.

8 Arlettaz R, Bauschatz AS, Monkhoff M, Essers B, Bauersfeld U: The contribution of pulse oximetry to the early detection of congenital heart disease in newborns. Eur J Pediatr 2006, 165(2):94-8.

9 Koppel RI, Druschel CM, Carter T, Goldberg BE, Mehta PN, Talwar R, Bierman FZ: Effectiveness of pulse oximetry screening for congenital heart disease in asymptomatic newborns. Pediatrics 2003, 111(3):451-5.

10 Meberg A, Brugmann-Pieper S, Due R Jr, Eskedal L, Fagerli I, Farstad T, Froisland DH, Sannes CH, Johansen OJ, Keljalic J, Markestad T, Nygaard EA, Rosvik A, Silberg IE: First day of life pulse oximetry screening to detect congenital heart defects. J Pediatr 2008, 152(6):761-5.

11 Arlettaz R, Bauersfeld U: Empfehlungen zum neonatalen Screening kongenitaler Herzfehler. Paediatrica 2005, 16(534-37 [http://www.neonet.ch/en/04_Recommendations/rec-ssn.php?navid=32].

12 Levesque BM, Pollack P, Griffin BE, Nielsen HC: Pulse oximetry: what's normal in the newborn nursery? Pediatr Pulmonol 2000, 30(5):406-12.

13 Kamlin CO, O'Donnell CP, Davis PG, Morley CJ: Oxygen saturation in healthy infants immediately after birth. J Pediatr 2006, 148(5):585-9.

14 Mariani G, Dik PB, Ezquer A, Aguirre A, Esteban ML, Perez C, Fernandez Jonusas S, Fustinana C: Pre-ductal and post-ductal O2 saturation in healthy term neonates after birth. J Pediatr 2007, 150(4):418-21.

15 Altuncu E, Ozek E, Bilgen H, Topuzoglu A, Kavuncuoglu S: Percentiles of oxygen saturations in healthy term newborns in the first minutes of life. Eur J Pediatr 2008, 167(6):687-8.

16 Rabi Y, Yee W, Chen SY, Singhal N: Oxygen saturation trends immediately after birth. J Pediatr 2006, 148(5):590-4.

Cost Comparison of Heel Stick Procedures and Transcutaneous Sample Methods for Bilirubin Evaluation

Jim McKenzie; Brian Palmer, BSEE, MBA

Abstract

Objective: There is concern about the cost of assessing each healthy term neonate for the risk of hyperbilirubinemia. It has been shown that universal screening does decrease the likelihood of severe hyperbilirubinemia through a blood draw or by using transcutaneous methods.[1] Our objective was to determine the cost differences associated with screening neonates prior to discharge per the American Academy of Pediatrics' guidelines.[2]

Methods: A multi-centered ethnographic cost-effectiveness analysis of bilirubin screening strategies was conducted at three birthing hospitals. An analytic decision model was used to determine the direct cost impact of transcutaneous bilirubin measurements using the BiliChek (Philips Children's Medical Ventures) noninvasive bilirubin device versus a total serum laboratory analysis. We analyzed the direct costs by analyzing purchasing records, current average sales prices from industry suppliers, and online hospital suppliers. Indirect costs were analyzed through a modified societal perspective of an online industry compensation analysis system. A depreciation analysis was not included because it would unnaturally bias lower cost equipment.

Results: Through an observational study and a staff interview process, a work flow pattern for transcutaneous and blood draw procedures was developed. The similarity of the studied facilities allowed for the development of a screening procedure chart (Chart 1). An analysis of procedure time and the use of products were categorized according to costs. The results indicate that the direct costs (procedure products) and indirect costs (cost of labor) of transcutaneous bilirubin measurements are lower than laboratory measurements.

Conclusion: The American Academy of Pediatrics supports screening for the risk of hyperbilirubinemia through laboratory or transcutaneous measurements.[2] The use of the BiliChek transcutaneous device is a lower cost screening solution for assessing the risk of hyperbilirubinemia in neonates than blood sampling methods.

Jim McKenzie is a Global Product Manager for Philips Children's Medical Ventures and manages the Jaundice Management product line. He is directly responsible for the development, marketing and revenue for the BiliChek noninvasive device. Brian Palmer is a Senior Field Marketing Manager for Philips Children's Medical Ventures and manages field marketing and the sales aspects of the Jaundice Management product line that includes the BiliChek noninvasive device. This article was provided by Philips Children's Medical Ventures.

Purpose

The purpose of this multi-centered ethnographic study was to observe and record the steps and time needed to conduct a heel stick bilirubin measurement and then determine the direct and indirect costs of performing blood sampling for serum bilirubin. This information would then be compared against the results of observing and recording a transcutaneous bilirubin test performed with the BiliChek noninvasive bilirubin assessment tool. This study compares the cost of performing a noninvasive bilirubin measurement with BiliChek to the cost of a bilirubin serum blood test.

Summary

The American Academy of Pediatrics recommends that all newborn infants be assessed for jaundice at 24 hours after birth and prior to discharge from the hospital.[2] Studies show that the visual assessment of jaundice or the estimation of bilirubin levels based on progressive changes in skin coloration to be inaccurate.[3] Both serum blood testing and transcutaneous measurements have been shown to be reliable methods for assessing and monitoring neonatal hyperbilirubinemia.[4] Customer opinion regarding the BiliChek's consumable calibration tip suggests that hospitals without a transcutaneous device are unwilling, or require the cost justification, to purchase the BiliChek transcutaneous device. This reluctance to purchase is due to the long-term operational use cost of the BiliChek which is related to the per-test cost of the devices' calibration and patient interface tip and not the purchase price of the device.[5] This study has determined that the true cost of a transcutaneous measurement with BiliChek's calibration tip and the labor cost involved to complete a transcutaneous measurement is lower in cost compared to the supplies and labor cost required for a heel stick.

Objectives

The objectives for this ethnographic bilirubin measurement study are described below.

1. A flow chart that documents the initiation, the steps of a transcutaneous test and a heel stick from lab draw through the logistical flow of the specimen to the electronic retrieval of the bilirubin test results
   a. Purpose

i. To gain a clear understanding of the serum blood test procedures and work flow (Chart 1)
ii. To record and understand the procedures involved in a serum-based bilirubin test measurement

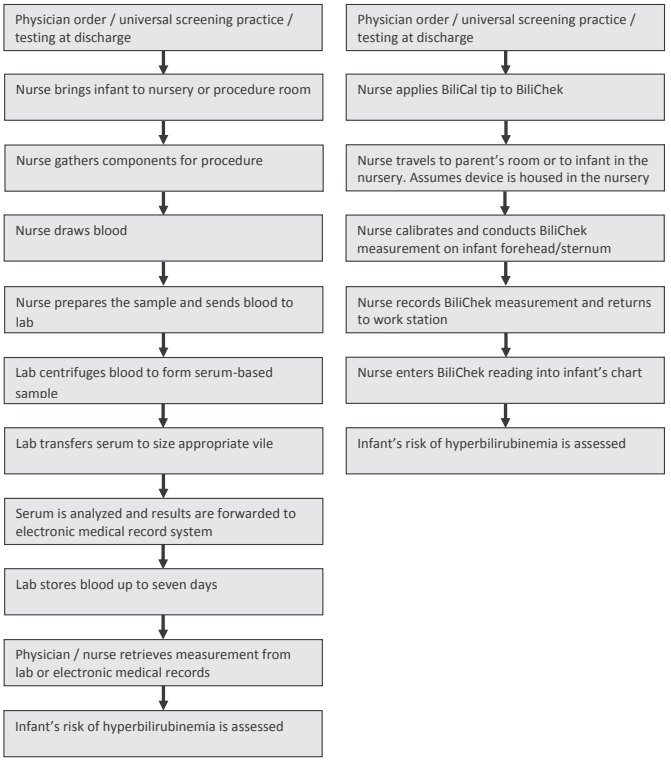
2. A spreadsheet with (a) the supplies required for a heel stick and BiliChek bilirubin measurement, (b) time required to perform a heel stick and BiliChek bilirubin measurement, and (c) cost comparison of the two methods
   a. Purpose
      i. To record the various items used in a heel stick lab draw for indirect and direct bilirubin to calculate cost
      ii. To assess the amount of labor time associated with each test method
3. A recommendation to the clinical leadership and administration teams to incorporate this information into their jaundice management program.

Conclusion/Recommendation

The cost of a heel stick performed in accordance with evidence-based best practices (which would include staff time to accomplish the procedure) can range from $13.42 to $21.65 compared to approximately $8.31 when employing a transcutaneous methodology for bilirubin measurement.

Chart 1: Comparative flow chart of heel stick blood draw activities for a nursing-based lab draw versus a BiliChek transcutaneous measurement

The following represents a general flow of activities observed at three different hospitals during the ethnographic study.



Time required for heel stick lab draws

The job title and activity information that follow were gathered during the time comparison study (Table 1 and Table 2). Hourly rate information was gathered by researching salaries on www.salary.com and using the 25 percent and 75 percent salaries as end points with Pittsburgh 15213 being the area used. The labor rate is an unburdened labor rate that does not include the cost of fringe benefits.

Identified heel stick blood draw supplies cost

The lancet manufacturer for a heel stick lab draw and part number information was gathered from hospitals and summarized in Table 3 according to low, medium and high. The costs also include the costs of warming the sample site with a heel warmer and administering a sucrose solution for pain management in the medium and higher levels of care. Information for pricing of these components was found through a national medical component distribution and through online medical suppliers. Refer to Appendix 1.

Cost comparison of two methods

The information presented below describes the mean total costs of a heel stick blood draw and a BiliChek transcutaneous procedure (Table 3). The heel stick procedure is divided into low, medium, and high costs to take into account different practices such as using heel warmers and pacifiers as well as the particular supplies used at each of the studied facilities (Appendix 2 for cost information). There is also a difference in labor costs to account for ranges in salary for a given area (Table 1).

Cost analysis

Table 3 describes the mean total costs of heel stick lab draw versus a BiliChek transcutaneous measurement procedure. The heel stick procedure is categorized into low, medium, and high cost to take into account different practices such as using heel warmers and pacifiers as well as the particular supplies used at each of the studied facilities. There is also a difference in labor costs related to low-high percentile ranges in salary for a given area.

Table 1

Bilirubin heel stick blood draw				
Job title / discipline	Activity	Unburdened hourly labor rate	Mean time required*	Total cost
Nurse	Infant lab blood draw procedure for bilirubin	$25.00-$35.00	15 minutes	$6.25-$8.75
Lab technician	Centrifuge blood, place in proper container, test sample	$18.00-$23.00	10 minutes	$3.00-$3.83
			Total	**$9.25-$12.58**

Table 2

Transcutaneous bilirubin measurement				
Job title / discipline	Activity	Unburdened hourly labor rate	Mean time required*	Total cost
Nurse	BiliChek transcutaneous measurement	$25.00-$35.00	2 minutes	$6.25-$8.75
			Total	**$0.83-$1.16**

*Note: Labor for a heel stick blood draw is based on an average of 15 minutes of time for a nurse to complete the procedure plus an average time of 10 minutes for medical laboratory technician to process the specimen. Labor for a BiliChek transcutaneous is based on an average of two minutes of a nurse's time. See Appendix 1 for heel stick procedure supplies and associated pricing information.

Table 3

Bilirubin heel stick vs. BiliChek transcutaneous						
	Heel Stick (low)	BiliChek (low)	Heel Stick (medium)	BiliChek (medium)	Heel Stick (high)	BiliChek (high)
Supplies	$4.17	$6.80	$7.04	$6.80	$9.07	$6.80
Nursing labor cost	$6.50	$0.83	$7.50	$1.00	$8.75	$1.17
Total supplies/nursing costs	**$10.67**	**$7.63**	**$14.54**	**$7.80**	**$17.82**	**$7.97**
Lab technician labor cost	$2.75	N/A	$3.41	N/A	$3.83	NA
Total supplies/labor costs	**$13.42**	**$7.63**	**$17.95**	**$7.80**	**$21.65**	**$7.97**

Analysis of the data concludes that the relative market price of supplies needed to conduct a BiliChek noninvasive assessment versus a heel stick blood draw is higher in the low range, $2.63, but lower in the medium and high ranges, $0.24 and $2.27, respectively (Table 3). When comparing the cost of nursing labor and supplies of a BiliChek noninvasive assessment versus

a blood draw, the study concludes that the low-range BiliChek assessment is 28% ($3.04) less expensive than the heel stick, and in the medium and high ranges, 46% ($6.74) and 45.2% ($9.85) less expensive, respectively (Table 3).

Appendix 1: General interview questions

The following questions/observations were used to discover and gather evidence to support the position and conclusion of this paper.

General interview questions

Questions	BiliChek	Heel stick blood draw
Do you have a protocol for jaundice assessment and management?		
Who makes the decision to obtain measurement?		
Who performs the measurement?		
When are bilirubin tests required?		
How often are bilirubin tests performed on each infant?		
How often is the product used on each infant?		
How long (in minutes) does it take to obtain the results?		

Observations

Questions	BiliChek	Heel stick blood draw
Where do you keep the equipment for bilirubin testing?		
Do you have to disturb the infant to perform the test? If yes, how long (in minutes) does it take to position the infant? How is infant positioned?		
Is the required equipment in close proximity to where the procedure takes place?		
How do you know you have a "good" reading?		
How many individuals are required to perform the test?		
Where do they put the device to get the baby ready for the test?		
Where is the bilirubin test performed?		
What is done with the device once the test is completed?		
What do you do with the results of the bilirubin test?		
Explain the process (the flow of activity) from the time the decision to obtain a bilirubin measurement is made to the time the results are interpreted.		
Where is the bilirubin test performed?		

Transcutaneous interview questions

Questions
How do you decide between transcutaneous and heel stick bilirubin measurements?
Who performs the test? (title and hourly rate)

Transcutaneous observations

Questions
How do you decide between transcutaneous and heel stick bilirubin measurements?
How do you know what buttons to press on the transcutaneous device?
How long does each test take to obtain a result?

Heel stick interview questions for nurses

Questions
When is a blood sample required for a bilirubin measurement?
Who handles the blood?
What are the chances for interchanging blood samples between patients?
Are the proper light-protected tubes being used?
Are there complications due to heel stick wounds? How often?

Heel stick blood draw observations

Questions
How are steps required for a blood sample determined?
How are laboratory activities for each blood sample determined?
How many people touch the blood?
Observe who obtains the blood and how it gets to the lab.
How long does it take to perform a heel stick procedure?
How long does it take to obtain the result?

Heel stick blood draw interview questions for biotech department

Questions
Who collects the tubes? How long does this take? (title and hourly rate)
Who performs the blood test? (title and hourly rate)
How long does this take? Does this test need to be observed or does it run on its own?
Is a separate container used to hold blood for this test?
Is blood ever lost transferring from test tube to holder?
How often is the equipment calibrated?
Are quality-control analyses performed? How often?
How are the results captured and sent to the physician? Who does this?
How long does this take?
How long does it take from the time the physician places the order to obtain the bilirubin level to the time results are returned?
Is all of the blood evaluated on one machine?
How are the data transmitted after the test?
How many people touch the blood?

Parts required for obtaining a bilirubin result

Indicate yes/no. If yes, indicate the number used.

Questions	BiliChek	Heel stick blood draw	Time needed to obtain equipment (minutes)	Cost
Discipline performing test				
Gloves				
Lancet				
Wipes (alcohol or saline)				
Bandages				
Pacifiers				
Sucrose				
Blood containers				
Bio-wipes				
Heel warmers				
Calibration solutions				
Blood additives / reagents				
Blood holders for machine				
BiliCal calibration tip				

Appendix 2: Supply costs for general heel stick blood draw procedure and Bilichek's calibration tips

Item	Manufacturer	Part number	Price per quantity	Price per piece	Source
Rubber gloves	Esteem	8812N	$23.95 Box of 100	$0.48 2 gloves	http://www.opticsplanet.net/cardinal-health-esteem-microtextured- stretchy-nitrile-examinationgloves-cardina-bbeaeb.html
			$23.95 Box of 100	$0.48 2 gloves	http://www.microscopes.com/ms-ch-lg-8812n.html
Lancets for heel stick	BD	368101	$138.50 Box of 50	$2.77	
	Gentle Heel	GHN (1.0mm depth X 2.5mm length)	$210 for 50	$4.20	
Blood containers for infants	Microtainer	365985	$164.77 50/sp, 4 sp/case $226.99	$0.82 $1.13	http://wilburnmedical.com/medical_supplies.php?iid=80239 http://www.opticsplanet.net/bd-list-5.html
Wipes (alcohol or saline)	Novaplus	V9100	$1.67 box of 200	$.008	http://app1.unmc.edu/busfin/gensupply/index.cfm?includethis=detail.cfm&ID=278
	Triad	10-3001	$52.41 box of 200 as part of case of 20 boxes (4000 pieces)	$0.02	http://www.overstock.com/Bulk-Medical-Supplies/Triad-200ct-Sterile-Med-Alcohol-Prep-Pads-Case-of-20/2498632/product.html http://www.healthproductsforyou.com/catalog/products/2580/Triad-Alcohol-Prep-Pads-And-Swabsticks/
Bandages	Kendall Curity	100165/ 963508	$7.77 box of 100	$0.07	http://www.amazon.com/dp/B002BTUWI8/ref=asc_df_B002BTUWI8877816?tag=the00420&creative=380333&creativeASIN=B002BTUWI8&li

					nkCode=asn
	Kendall Curity	100142/961347	$7.77 box of 100	$0.07	http://www.amazon.com/dp/B002BTUWI8/ref=asc_df_B002BTUWI8877816?tag=the00420&creative=380333&creativeASIN=B002BTUWI8&linkCode=asn
Gauze	Kendall Curity	2146 (2" x 2")	$4.35 box of 200	$.022	http://www.woundcareshop.com/curitygauzesponge-2x28plynonsterilepackageof200.aspx
	Kendall Curity	1806 (2" x 2")	Curity gauze 2" x 2", 8-ply, sponge sterile, 2 per pack, box of 50 packs	$.10	http://www.woundcareshop.com/sterilecuritygauzepads.aspx
Pacifier	Philips Children' Medical Ventures - Soothie	96003-N	$134.00/case of 100	$1.34	
Sucrose	Philips Children' Medical Ventures - SweetEase	99044	$34.50/box of 50	$0.69	
Heel Warmers	Cardinal Tiny Toes	11470-010T	$86.75/case of 100	$0.87	
	Philips Children' Medical Ventures - Heel Snuggler	99047	$25.99/case of 25	$1.04	
BiliCal	Philips Children' Medical Ventures - BiliCal tip	B800-50	$357.50/bag of 50	$7.15	
Bio-wipes	Unable to gather single accurate test data on this component				
Calibration solutions for blood analyzer	Unable to gather single accurate test data on this component				
Blood additives / reagents	Unable to gather accurate single test data on this component				
Blood holders for blood analyzer	Unable to gather accurate single test data on this component				

References

1 Reduction of severe hyperbilirubinemia after institution of predischarge bilirubin screening. Pediatrics, Vol. 125 No. 5, May 2010, pp. e1143-e1148.

2 Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics, Vol. 114 No. 1, July 2004, pp. 297-316.

3 Kramer L. Advancement of dermal icterus in the jaundiced newborn. A JDC.

4 Bental Y, Shiff Y, Dorsht N, Litig E, Tuval L, Mimouni F. Bhutani-based nomograms for the prediction of significant hyperbilirubinemia using transcutaneous measurements of bilirubin. Acta Paediatr., Jun 8 2009.

5 Children's Medical Ventures Bilirubin Measurement Survey, summary report, September 25, 2008.

Surveys of Mortality in UK Neonatal and Pediatric Intensive Care Trials, BRACELET Study

Claire Snowdon, Sheila E Harvey, Peter Brocklehurst, Robert C. Tasker, Martin P. Ward Platt, Elizabeth Allen, Diana Elbourne

Abstract

Background: The subject of death and bereavement in the context of randomized controlled trials in neonatal or pediatric intensive care is under-researched. The objectives of this phase of the Bereavement and RAndomised ControlLEd Trials (BRACELET) Study were to determine trial activity in UK neonatal and pediatric intensive care (2002-06); numbers of deaths before hospital discharge; and variation in mortality across intensive care units and trials and to determine whether bereavement support policies were available within trials. These are essential prerequisites to considering the implications of future policies and practice subsequent to bereavement following a child's enrollment in a trial.

Methods: The units survey involved neonatal units providing level 2 or 3 care, and pediatric units providing level II care or above; the trials survey involved trials where allocation was randomized and interventions were delivered to intensive care patients, or to parents but designed to affect patient outcomes.

Results: Information was available from 191/220 (87%) neonatal units (149 level 2 or 3 care); and 28/32 (88%) pediatric units. 90/177 (51%) eligible responding units participated in one or more trial (76 neonatal, 14 pediatric) and 54 neonatal units and 6 pediatric units witnessed at least one death. 50 trials were identified (36 neonatal, 14 pediatric). 3,137 babies were enrolled in neonatal trials, 210 children in pediatric trials. Deaths ranged 0-278 (median [IQR interquartile range] 2 [1, 14.5]) per neonatal trial, 0-4 (median [IQR] 1 [0, 2.5]) per pediatric trial. 534 (16%) participants died post-enrolment: 522 (17%) in neonatal trials, 12 (6%) in pediatric trials. Trial participants ranged 1-236 (median [IQR] 21.5 [8, 39.8]) per neonatal unit, 1-53 (median [IQR] 11.5 [2.3, 33.8]) per pediatric unit. Deaths ranged 0-37 (median [IQR] 3.5 [0.3, 8.8]) per neonatal unit, 0-7 (median [IQR] 0.5 [0, 1.8]) per pediatric unit. Three trials had a formal policy for responding to bereavement.

Conclusions: A substantial number of deaths after trial enrolment were identified, distributed over many trials and units. Few trial teams had responses to bereavement in place. Those with the largest numbers of deaths might be best placed to collaborate in developing and assessing responses to bereavement.

Background

The current emphasis on the need for good evidence to guide care,[1,2] and the establishment of the UK Medicines for Children Research Network (MCRN) to encourage and facilitate pediatric research, suggest that increasing numbers of children will be enrolled into randomised controlled trials. This includes extremely sick children in neonatal and pediatric intensive care units, of whom a proportion will die before discharge home. The subject of death and bereavement in the context of trials is, however, under-researched.

It is not known how many participants are enrolled in this setting, or how many survive or die. The parents of those who go on to die subsequent to trial enrolment may have a range of information and support needs and preferences but these have not yet been adequately described and explored. We do not know whether bereaved parents might wish to have further contact with a trial, and what services, if any, they might wish to access; we do not know what approaches clinicians and trial teams might feel able to offer.

An essential prerequisite to considering bereavement and trials is to ascertain the magnitude and distribution of post-trial mortality. This study therefore aimed to determine:

1. trial activity in UK neonatal and pediatric units;
2. the number and proportion of deaths among babies and children participating in trials in intensive care;
3. variation in mortality across units, and across trials;
4. whether any provision is made for bereavement within trials.

Authors Snowdon, Harvey, Allen and Elbourne are with the Medical Statistics Unit, London School of Hygiene and Tropical Medicine; Snowdon is also with the Centre for Family Research, University of Cambridge; Brocklehurst is with the National Perinatal Epidemiology Unit, University of Oxford; Tasker is with the University of Cambridge Clinical School, Department of Pediatrics; Ward Platt is with Newcastle Neonatal Service, Royal Victoria Infirmary, Newcastle upon Tyne. The authors are grateful to the trial teams, and unit staff who provided the data for this research. Sara Lewis and Maggie Redshaw at the National Perinatal Epidemiology Unit, and Roger Parslow at Pediatric Intensive Care Audit Network PICANET provided advice and helpful information. MCRN staff and MCRN Local Research Networks gave crucial assistance with data collection. The BRACELET Study Advisory Group (Ursula Bowler, Dr Gillian Colville, Professor Richard Cooke, Professor Bobbie Farsides, Merryl Harvey, Dr Andy Leslie, Fiona Lockett) commented on research methods throughout the research process.Reprinted from BioMed Central, Trials,

Table 1. NICU and PICU participation in RCTs (based on respondents to unit surveys).

No. RCTs	NICUs	PICUs
	Total, n=149 n (%)	n=28 n (%)
0	73 (49.0)	14 (50.0)
1	31 (20.8)	8 (28.6)
2	19 (12.8)	3 (10.7)
3	13 (8.7)	1 (3.6)
≥4	13 (8.7)*	2 (7.1)**
≥1 RCT	**76 (51.0)**	**14 (50.0)**

* 10x4, one each 5, 6, and 7
**One 4 and one 7

Table 2: Babies and children enrolled 2002-2006 by type of trial and by enrolling unit (neonatal or paediatric)

	No. enrolled from neonatal units	No. enrolled from paediatric units	Total no. enrolled
NEONATAL TRIALS			
No. of trials	29	2	29*
No. of units	36	2	38
No. of babies enrolled	3117	20	3137
No. of babies enrolled per recruiting unit; Median [IQR]	1-236 21.5 [8, 39.8]	4 and16**	1-236 20 [7.8, 39.3]
No. of babies enrolled per trial; Median [IQR]	1-1322 40 [13.5, 104]	4 and16**	5-1326 40 [14.5, 104]
PAEDIATRIC TRIALS			
No. of trials		9	9
No. of units		11	11
No. of children enrolled		210	210
No. of children enrolled per recruiting unit; Median [IQR]		1-53 11.5 [2.3, 33.8]	1-53 11.5 [2.3, 33.8]
No. of children enrolled per trial; Median [IQR]		2-53 10.5 [6, 39.3]	2-53 10.5 [6, 39.3]
ALL NEONATAL/PAEDIATRIC TRIALS			
No. of babies/children enrolled	**3117**	**230**	**3347**
No. of trials	29	11	38*

*includes two neonatal trials which recruited from both neonatal and paediatric units
** no median and IQR as only two trials

Methods

Although new trials are increasingly being registered, especially those involving new medical products, there is no single repository of trials through which all trials conducted in the UK over specified time periods and particular specialties can be identified. The BRACELET Study therefore required two linked surveys to achieve its objectives; the first survey involved neonatal and pediatric units to identify trials conducted in the UK in 2002-2006; the second survey involved trials to collate data on deaths across trials and across their collaborating neonatal and pediatric units (Figure 1).

Unit survey: The unit survey aimed to identify all trials open to recruitment in the UK from 1 January 2002 to 31 December 2006. Data were requested from all neonatal units providing care designated as Level 2 (high dependency and some short-term intensive care) or Level 3 (whole range of medical care but not necessarily specialist services such as surgery),[3] and all pediatric units with a pediatric intensivist in post which provide at least Level II intensive care (1:1 nurse:child ratio providing care for those requiring continuous nursing supervision, usually intubated and ventilated, or unstable non-intubated or recently extubated).[4]

Two hundred and twenty neonatal units and 32 pediatric units were identified through a process of cross-checking multiple sources.[3-9] Units were contacted by post but questionnaires were also made available on the BRACELET website bracelet-study.org.uk. One hundred and forty nine neonatal units reported their designated level of care as Level 2 or 3 and were eligible to participate in the study. Representatives at these 149 neonatal units, and at the 32 Level III pediatric units,[7-9] were asked to complete a questionnaire in April 2007. This asked respondents to list all trials open to recruitment in their unit in 2002-2006. The clinical lead for each unit was asked to permit the trial coordinating team for each trial to which they had recruited to release that unit's recruitment and mortality data to the BRACELET Study. Two reminders were sent via email or mail. Nurse Practitioners from MCRN made additional follow up contact where appropriate. Opportunistic and direct contact between study members and units also served as reminders. Data collection was concluded in May 2008.

Trials survey: The unit survey generated a list of trials which was supplemented by searches of specialized websites.[8-10] Many of the trials were also identified through other sources such as the UK Dept Health National Research Register, PubMed, PICS

Table 3: Hospital survivors and non-survivors overall by type of RCT – UK totals 2002-2006 (overall mortality data)

NEONATAL TRIALS (n=28)	
No. of babies enrolled	3088
No. of babies outcome unknown	2
No. of babies survived	2564
No. of babies died	**522**
Mortality rate % (based on known outcomes)	16.9
PAEDIATRIC TRIALS (n=9)	
No. of children enrolled	200
No. of children outcome unknown	0
No. of children survived	188
No. of children died	**12**
Mortality rate % (based on known outcomes)	6.0
NEONATAL and PAEDIATRIC TRIALS (n=37)	
No. of babies/children enrolled	3288
No. of babies/children outcome unknown	2
No. of babies/children survived	2752
No. of babies/children died	**534**
Mortality rate % (based on known outcomes)	16.2

Table 4: Numbers of deaths in NICUs and PICUs following enrolment into a trial 2002-2006 (unit-specific mortality data)

No. of deaths	NEONATAL INTENSIVE CARE UNITS	PAEDIATRIC INTENSIVE CARE UNITS
	No. (%) of Units (n=72)	No. of Units (n=12*)
None	18 (25)	6
1-4	24 (33)	5
5-9	13 (18)	1
10-14	8 (11)	0
15-19	4 (6)	0
≥20	5 (7)	0
Total no. of deaths in these units	434	14
No. (%) of units seeing at least one death	**54 (75)**	**6 (43)**

Table 5: Proportion of deaths in NICUs and PICUs following enrolment into a trial 2002-2006 (unit-specific mortality data)

Proportion of deaths	NEONATAL INTENSIVE CARE UNITS	PAEDIATRIC INTENSIVE CARE UNITS
	No. (%) of Units (n=72)	No. of Units (n=12*)
0	18 (25)	6
0-0.1	10 (14)	3
0.1-0.2	14 (19)	3
0.2-0.3	16 (22)	
0.3-0.4	7 (10)	
0.4-0.5	5 (7)	
≥0.5	2 (3)	

* No mortality information was available for two of the 14 Units

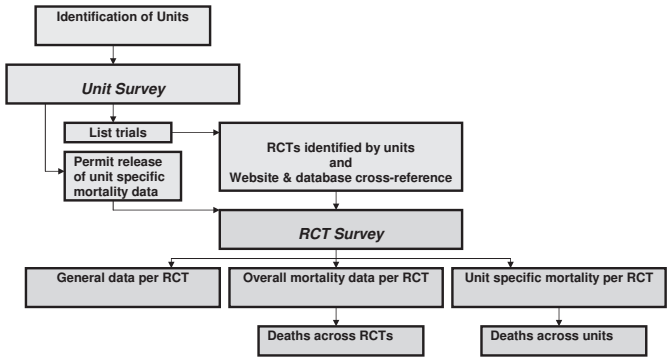


Figure 1. Structure of BRACELET Study Surveys.

website, and the European Society of Pediatric and Neonatal Intensive Care website.

Trials were eligible for the survey if: allocation was randomized; enrollment took place during the five year study period; parental informed consent was required; and the intervention was delivered to babies or children within ICUs or delivered by, or under the auspices of, a neonatologist or pediatric intensivist leading to ICU admission for ongoing care, or the intervention was delivered to parents but designed to affect outcomes for babies or children.

For each eligible trial, the chief investigator, trial manager or other appropriate contact was asked to complete an e-mailed questionnaire. Questionnaires were also made available on the BRACELET website and were followed up by telephone, direct contact and the assistance of MRCN, if necessary. The information received was supplemented by data from published papers, relevant websites and personal communication. Three types of data were generated, for the five year study period only: general data about trials (outcome measures, participating units, numbers enrolled); overall mortality data (UK mortality per trial before discharge from hospital) and unit-specific mortality data (deaths per unit per trial before discharge from hospital). Chief investigators, trial managers or other appropriate contacts were also asked to provide copies of the trial protocol and parent information leaflets for their trial.

Analysis: Descriptive data are presented as proportions and ranges, as appropriate. Analysis used the statistical package Stata 10 (StataCorp, College Station, TX, US). Variations in the denominators for some of the numbers reported in the results reflect different response rates for the unit survey and the trials survey, and incomplete release of mortality data by some units and some trials.

Response rates: Questionnaires were sent to 220 neonatal units; 191 (86.8%) responded, of which 149 were eligible units (82 providing Level 2 care and 67 Level 3). Questionnaires were also completed by 28 (87.5%) of the 32 Level II pediatric units surveyed.

Trials survey: The unit survey and associated searches identified 50 trials (36 neonatal and 14 pediatric trials). Some general data were obtained for 43 trials (32 neonatal, 11 pediatric). Overall UK mortality data were released for 37 trials (28 neonatal, 9 pediatric). Unit-specific mortality data were released for 33 trials (24 neonatal, 9 pediatric) for those ICUs which had permitted release of their data to the study in the unit survey.

Survey findings: The unit survey indicated that overall half of the ICUs enrolled one or more participants in one or more trials during the five year study period (76/149 neonatal units, 14/28 pediatric units) (Table 1).

A minority of the responding Level 2 neonatal units (N=27, 32.9%) and the majority of the responding Level 3 neonatal units contributed to a trial (N=49 (73.1%). Nine (13.4%) of the Level 3 neonatal units ran their own single centre trials but none of the Level 2 neonatal units did so. Five of the 14 responding pediatric units (17.9%) ran single center trials.

General data: Of the 76 neonatal units which enrolled to a trial, 72 provided details of the number of babies enrolled. A total of 3117 babies were enrolled by these neonatal units into the 29 neonatal trials for which some enrolment data for the five year study period were available. The number of babies enrolled per neonatal unit ranged 1-236 (median [IQR] 21.5 [8, 39.8]). An additional 20 babies were recruited into two multicenter neonatal trials by two pediatric units, bringing the total enrolled in neonatal trials to 3137 babies. Of these 480 (15.3%) were recruited into single centre trials and 2657 (84.7%) into multicenter trials (UK and international) (Table 2).

Of the 14 pediatric units that enrolled into a pediatric trial, 11

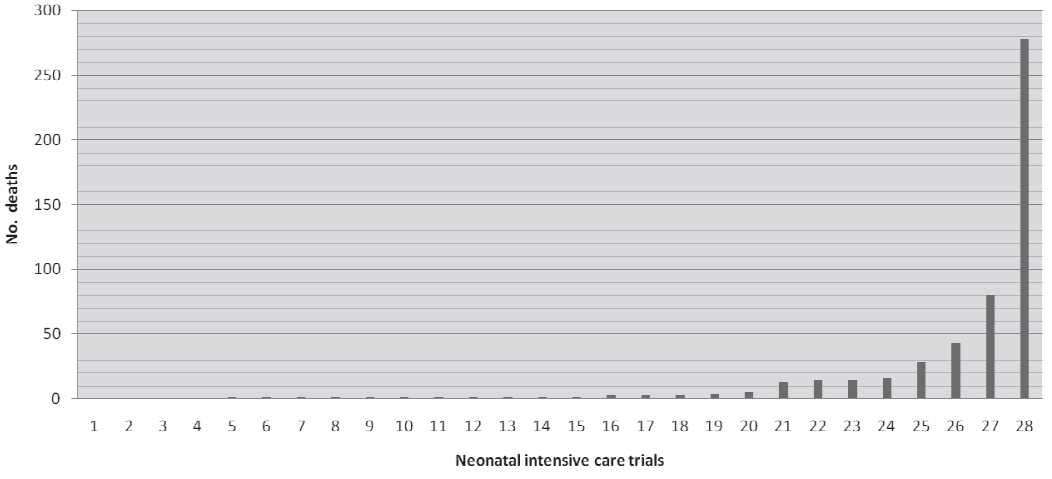


Figure 2. Variation in numbers of deaths across neonatal trials.

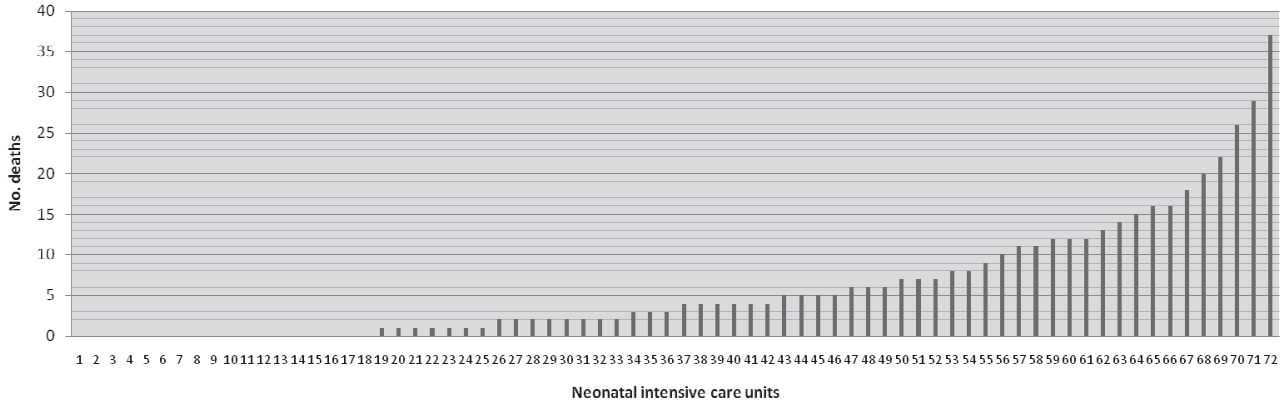


Figure 2. Variation in numbers of deaths across neonatal units.

provided details of the number enrolled. A total of 210 children were enrolled by these pediatric units into 9 pediatric trials for which some enrolment data for the five year study period were available. The number of children enrolled per pediatric unit into pediatric trials ranged 1-53 (median [IQR] 7,[2] 34). Of these 94 (44.8%) were enrolled into single center trials and 116 (55.2%) to multicentre trials (all of which were international) (Table 2).

Overall mortality data: Overall mortality data were available for 28 neonatal and 9 pediatric trials (Table 3). In total, 534/3288 (16.2%) children died following enrolment in these 37 trials. The 28 neonatal trials enrolled 3,088 babies, of whom 522 (16.9%) died. The number of deaths per neonatal trial ranged 0-278 (median [IQR] 2 [1, 14.5]) (Figure 2). Of the 28 neonatal trials, 24 had at least one death. The highest mortality rate amongst these trials was 29% (80 deaths). Most reported small numbers of deaths (only 8 trials reported >10). The majority of deaths, 429/522 (82.2%), occurred in four trials, three of which were multicenter (N=278 + 80 + 43 and one single center (N=28). Single center trials reported fewer deaths and a lower death rate (47/480 9.8%) than multicenter trials (475/2608 18.2%). In the nine pediatric trials for which mortality data were available, 12 (6.0%) out of 200 children died following enrolment into a trial. Six of the 9 trials had a least one death with the number of deaths ranging 0-4. Very few deaths occurred in single center pediatric trials (2/94 2.1%) compared to those in the neonatal single centertrials (47/480 9.8%) and the pediatric multicenter trials 10/106 (9.4%).

Unit-specific mortality data: Data on 434 deaths were released by 24 neonatal trials for 72 neonatal units with the permission of the neonatal units in question. The number of deaths per neonatal unit ranged 0-37 (median [IQR] 3.5 [0.3, 8.8]) (Figure 3). Whilst 54 neonatal units saw at least one death, more than half (42/72 58.3%) saw fewer than five deaths over this five year period (Table 4). Five Level 3 neonatal units had larger numbers (N=37, 29, 26, 22 and 20) and 30.9% of all deaths recorded by the units occurred in these five neonatal units. In around half of the units, the proportion of children who died following trial enrolment was 20% or more (Table 5). Nine pediatric trials released unit specific mortality data for 14 pediatric units. The number of deaths per pediatric unit ranged 0-7(median [IQR] 0.5 [0, 1.8]), with 6 pediatric units witnessing at least one death (Table 4). In all these units, the proportion of children who died following trial enrolment was under 20% (Table 5).

Trials survey—Practices in relation to bereavement care: Of the 50 RCTs, investigators for just over half (n=27) provided a copy of the full trial protocol. None of the protocols documented a policy relating to the care of parents bereaved following enrolment of their child into the RCT. Parent information leaflets were provided for 29 of the 50 trials. Two NIC trials (one multicenter and one UK-led international trial) provided a leaflet specifically for bereaved parents, expressing condolences, thanking them for their contribution and offering information about the trial. Details of support organizations were also given in the leaflets.

In one single-center NIC trial the investigator reported a different approach. Three deaths occurred following enrollment into this trial and the investigator sent a personalized letter to each set of parents to thank them for allowing their child to participate and to offer contact should they wish to discuss the trial or the continued use for their child's data in the trial.

Discussion

The BRACELET Study is the first to investigate randomized controlled trial activity in UK neonatal units and pediatric units, to report the numbers of babies and children enrolled into trials, and to determine the extent and distribution of mortality involved. An important strength of this study is the high response rates achieved. Several evidence-based strategies were used to maximise responses.[11] We are confident that all units were identified, and the comprehensive process of searching relevant research databases and websites as well as surveying these units is likely to have identified most of the trials recruiting in the UK. The establishment of mandatory trial registration will facilitate this process for future studies. There are, however, clear limitations to the study which relate to its narrow focus on mortality figures; in this regard the data raise rather than answer questions about bereavement in this context.

The study shows that in a five year period, over 3,000 babies and children were enrolled into pediatric and neonatal intensive care trials and 16% died, predominantly in the neonatal context. With over 500 deaths reported we suggest that a substantial number of bereaved parents, clinicians and trialists have encountered deaths among trial participants. We would also suggest that this is an underestimate as the BRACELET study focused only on deaths up to discharge from hospital; post-discharge deaths were not included. Other adverse outcomes for parents and families, such as disability and loss of quality of life in surviving babies are also important but were beyond the remit of the study.

As further trials are initiated and accrue more participants, the population of parents bereaved after agreeing to enroll their

child in a trial will accumulate; it is already sufficiently sizeable to warrant attention, but whether and how to respond to this population are complex questions. Provision for bereavement is often made within clinical centres but this body of parents, with potentially diverse experiences and needs, is largely scattered across a number of recruiting clinical centers; most deaths occurred as relatively isolated cases and the majority of centers witnessed small numbers of deaths per year. In the pediatric context where few deaths occurred, only one ICU reported more than one death. This is likely to make it difficult for many of the clinical centres to develop, assess and sustain specialized responses to post-trial bereavement themselves.

The patterns of mortality revealed by the BRACELET Study also suggest, however, that there were pockets of neonatal units and neonatal trials with substantial numbers of deaths. Five particularly research active Level 3 neonatal units saw 20 or more deaths each in the study period, and together they saw over a quarter of all reported deaths. In general, large ICUs draw upon well developed bereavement services,[12] and research-active centers such as these may be appropriate candidates to develop and assess dedicated trial-related bereavement practices.

The vast majority of deaths represented in the BRACELET Study, also occurred in only four trials. In trials where a substantial number of deaths is anticipated, it may be possible to develop and assess trial-related bereavement practices.

What form those practices might take is unclear. They may range from development of formal practices and supporting literature to a more simple policy of offering parents the opportunity to discuss a trial if they so wish.

Parents have not yet been asked about any support and information needs that they might have. Their preferences are likely to be varied and may include the wish for no further contact. It is however possible that some options that parents might appreciate, for instance access to specialized forms of support, may be beyond the capacity and expertise of current routine bereavement services, even in the larger centres, and may be difficult for trial teams to implement.

The BRACELET Study showed that three trials had already developed a response to bereavement such as preparing a bereavement leaflet for use in clinical centers or sending condolence letters directly to parents (for an example leaflet see http://www.npeu.ox.ac.uk/downloads/nest/NEST-Bereavement-Leaflet.pdf). Personal communications have revealed that some trials offer bereaved parents the option of receiving trial newsletters and results; some make a considered choice not to contact bereaved parents at all subsequent to a death.

To our knowledge, none of these policies have been subject to empirical evaluation, although descriptive accounts such as Strohm's report of a trial-related web-based message board for all parents of babies recruited to a trial, including those who are bereaved,[13] are helpful additions to the literature. Further reflection would be of value to future trials where deaths are likely.

The BRACELET Study has demonstrated that bereavement occurs in relation to trials of any size and type and with a range of clinical foci. The four trials which reported the majority of deaths in the five year period assessed very different interventions, from routine care practices to potentially life-saving technologies. They involved very different populations and were conducted in single centre, multicenter and international contexts. This suggests that bereavement in a trial context may be an issue of broad relevance in specialties such as intensive care, and that it could be particularly appropriate for large trials, or trials focusing on high risk situations, to plan for and assess their approach to bereavement with substantial research populations.

Trials are complex, highly collaborative endeavors between recruiting clinical centers and trial teams, groups which may feel a shared interest in and responsibility for parents bereaved in trials. Their collaboration might be exploited to good effect if experts within these fields take collective responsibility for the potential needs of the population identified here. If those trials and clinical centres with the greatest experience of post-trial bereavement develop effective approaches to care for and support bereaved parents, other smaller trials and centers may draw upon their recommendations and follow their lead. Even in the pediatric context where deaths occurred infrequently, individual trials may still involve severely compromised populations and so find that post-trial bereavement care is a salient issue.

It is, however, important that recommendations in this novel area should from an early stage be based on sound empirical evidence which draws upon views of all relevant parties with their potentially different perspectives and insights. Clinical teams often recruit to a number of trials concurrently and see bereaved parents in a variety of circumstances; they may be best placed to consider the broad range of bereavement-related issues that might occur in clinical contexts. Trial teams by comparison consider parents in the relatively more uniform circumstances set by the eligibility criteria for their particular trial; they may be best placed to consider bereavement practices which are tailored to fit the population and circumstances of a given trial. Research in this area is sensitive but it is essential that bereaved parents should also be consulted. Studies have demonstrated that bereavement-related research is feasible,[14-20] and suggest that bereaved parents might be willing and helpful participants on this challenging and sensitive subject.

The task ahead is for those with relevant insight and expertise, to collaborate to find a range of approaches which are sensitive to the variety of parents seen by clinicians and applicable and adaptable to the specific circumstances addressed in individual trials. As a first step in this process the BRACELET Study includes a second qualitative component which aims to explore death, dying and bereavement in the context of neonatal RCTs from the perspectives of trial team members, clinicians and bereaved parents.

References

1 McIntosh N, Bates P, Brykczynska G, Dunstan G, Goldman A, Harvey D, Larcher V, McCrae D, McKinnon A, Patton M, Saunders J, Shelley P. Guidelines for the ethical conduct of medical research involving children. Royal College of Pediatrics, Child Health: Ethics Advisory Committee. Arch Dis Child 2000;82(2):177-82.

2 Medical Research Council. Medical Research involving children. 2004. http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC002430- accessed 20 May 2010

3 British Association of Perinatal Medicine. Standards for hospitals providing neonatal intensive care. (Second edition). 2001.
4 Pediatric Intensive Care Society. Standards Document 2001. http://www.ukpics.org/documents/PICS%20Standards%20 2001.pdf -accessed 18 August 2008.
5 Redshaw M, Hamilton K. A survey of current neonatal unit organisation and policy. National Perinatal Epidemiology Unit 2005;http://www.npeu.ox.ac.uk/downloads/reports/bliss-final-report.pdf —accessed 18 August 2008.
6 Acolet D, Jelphs K, Davidson D, Peck E, Clemens F, Houston R, Weindling M, Lavis J, Elbourne D. The BLISS cluster randomised controlled trial of the effect of 'active dissemination of information' on standards of care for premature babies in England (BEADI) study protocol [ISRCTN89683698]. Implement Sci 2007;2:33.
7 Directory of Critical Care CMA Medical Data, 2006.
8 British Association of Perinatal Medicine. http://www.bapm.org/ —accessed 18 August 2008.
9 Pediatric Intensive Care Audit Network (PICANet). http://www.picanet.org.uk/ —accessed 18 August 2008.
10 National Perinatal Epidemiology Unit. http://www.npeu.ox.ac.uk/ —accessed 18 August 2008.
11 McColl E, Jacoby A, Thomas L, Soutter J, Bamford C, Steen N, Thomas R, Harvey E, Garratt A, Bond J. Design and use of questionnaires: a review of best practice applicable to surveys of health service staff and patients. Health Technol Assess 2001;5(31):1-256.
12 Harvey S, Snowdon C, Elbourne D. Effectiveness of bereavement interventions in neonatal intensive care: A review of the evidence. Semin Fetal Neonatal Med 2008;13(5):341-56.
13 Strohm B. 2007 The TOBY study parents online message board. Journal of Neonatal Nursing;13:107-112.
14 Brinchmann BS, Forde R, Nortvedt P. What matters to the parents? A qualitative study of parents' experiences with life-and-death decisions concerning their premature infants. Nurs Ethics 2002;9(4):388-404.
15 Brosig CL, Pierucci RL, Kupst MJ, Leuthner SR. Infant end-of-life care: the parents' perspective. J Perinatol 2007;27(8):510-6.
16 Kavanaugh K. Parents' experiences surrounding the death of a newborn whose birth is at the margin of viability. J Obstet Gynecol Neonatal Nurse 1997;26(1):43-51.
17 McHaffie HE, Lyon AJ, Hume R. Deciding on treatment limitation for neonates: the parents' perspective. Eur J Pediatr 2001;160(6):339-44.
18 Snowdon C, Elbourne DR, Garcia J. Perinatal pathology in the context of a clinical trial: attitudes of bereaved parents. Arch Dis Child Fetal Neonatal Ed 2004;89(3):F208-11.
19 Snowdon C, Elbourne DR, Garcia J. Perinatal pathology in the context of a clinical trial: attitudes of neonatologists and pathologists. Arch Dis Child Fetal Neonatal Ed 2004;89(3):F204-7.
20 Snowdon C, Elbourne D, Garcia J. Embedding a qualitative approach within a quantitative framework: an example in a sensitive setting. In: Lavender T, Edwards G, Alfirevic Z, editors. Demystifying Qualitative Research. London: Quay books, 2004.

Editorial…continued from page 4
lower; and the infant is described as uniformly enlivened and strengthened after the bath. The stomach, it is remarkable, has never once given way; and this must be solely attributed to the extreme care observed in regulating the proportions of nourishment, whether by the breast or by the spoon; and it has been remarked that the little creature seems uncommonly happy after her doses of wine and gruel. When lifted for necessary purposes, she does not fail to testify by her crying the sense she entertains of the annoyance.

Of the benefits to be derived, in such cases, from the judicious use of wine, there can be but little doubt; and, without wine, it seems almost certain the other nourishment would have been of little avail; and the same may be said of the proper regulation of the temperature—in this case hitherto exclusively artificial, except during the short periods when applied to the nurse's breast. At present all looks well, but the mother being dead, and the family arrangements requiring, at no distant period, the removal of the infant to the abode of the wetnurse, half a mile distant, the change is not to be viewed without suspicion as to its effects.

Determinants of Survival in Very Low Birth Weight Neonates in a Public Sector Hospital in Johannesburg

Daynia E. Ballot, Tobias F. Chirwa, Peter A. Cooper

Abstract

Background: Audit of disease and mortality patterns provides essential information for health budgeting and planning, as well as a benchmark for comparison. Neonatal mortality accounts for about 1/3 of deaths <5 years of age and very low birth weight (VLBW) mortality for approximately 1/3 of neonatal mortality. Intervention programs must be based on reliable statistics applicable to the local setting; First World data cannot be used in a Third World setting. Many neonatal units participate in the Vermont Oxford Network (VON); limited resources prevent a significant number of large neonatal units from developing countries taking part, hence data from such units is lacking. The purpose of this study was to provide reliable, recent statistics relevant to a developing African country, useful for guiding neonatal interventions in that setting.

Methods: This was a retrospective chart review of 474 VLBW infants admitted within 24 hours of birth, between 1 July 2006 and 30 June 2007, to the neonatal unit of Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) in Johannesburg, South Africa. Binary outcome logistic regression on individual variables and multiple logistic regression was done to identify those factors determining survival.

Results: Overall survival was 70.5%. Survival of infants below 1001 grams birth weight was 34.9% compared to 85.8% for those between 1001 and 1500 grams at birth. The main determinant of survival was birth weight with an adjusted survival odds ratio of 23.44 (95% CI: 11.22-49.00) for babies weighing between 1001 and 1500 grams compared to those weighing below 1001 grams. Other predictors of survival were gender (OR 3. 21; 95% CI 1.6-6.3), birth before arrival at the hospital (BBA) (OR 0.23; 95% CI: 0.08-0.69), necrotising enterocolitis (NEC) (OR 0.06; 95% CI: 0.02-0.20), hypotension (OR 0.05; 95% CI 0.01-0.21) and nasal continuous positive airways pressure (NCPAP) (OR 4.58; 95% CI 1.58-13.31).

Conclusions: Survival rates compare favorably with other developing countries, but can be improved; especially in infants <1001 grams birth weight. Resources need to be allocated to preventing the birth of VLBW babies outside hospital, early neonatal resuscitation, provision of NCPAP and prevention of NEC.

Authors Ballot and Cooper are with the Department of Paediatrics and Chirwa is with the Epidemiology and Biostatistics Division, School of Public Health, University of Witwatersrand Medical School, Johannesburg, South Africa. The authors wish to acknowledge and thank Dr Cheryl Mackay, for her review and comments on the manuscript and Prof Jacky Galpin for initial assistance with the statistical analysis. Reprinted from BioMed Central, BMC Pediatrics,

Background

The fourth Millennium Development Goal is to reduce the mortality of children under the age of 5 years by two thirds, before the year 2015. Neonatal mortality accounts for 37% of deaths below the age of 5 years and "improved neonatal and maternal care could save the lives of countless newborns."[1] In the Perinatal Problem Identification Program (PPIP) [ppip.co.za], a self reporting data base that covers about 40% of births in South Africa, the early neonatal mortality rate has been static over the past few years at about 9.5 per 1000 live births.[2] However, the majority of neonatal deaths remain unaudited and the national figure is thus probably higher. Very low birth weight (VLBW) infants represent a vulnerable group of newborns with a high mortality rate. There are many reports of factors affecting early survival of VLBW infants; these are summarized in Table 1.[3-22] The survival rate of VLBW infants worldwide ranges between 43% in developing countries such as Jamaica[21] to more than 90% in developed countries, such as the Netherlands,[7] with an average of about 73% (See Table 1). The mortality rate for VLBW infants in Soweto, Johannesburg, between 2000 and 2002 was reported at 71%,[22] which corresponds to developed countries in the mid 1980's (see Table 1).

There has been steady improvement in the overall early survival of VLBW infants over time (see Table 1) e.g. from 50% in 1977 to 81% in 1995 in Texas[3] and from 81% in 1986 to 90.3% in 1998 in New Zealand.[11] Malaysia, a developing country, showed a similar improvement from 62% in 1993 to 81.6% in 2003.[19] The degree of improvement, however, is less marked in more recent years—the NICHD showed almost no improvement in early VLBW survival between 1995/6 (84%) and 1997-2002 (85%).[14]

Audit of neonatal care by participating in a database such as the Vermont Oxford network (VON) assists quality control provides a benchmark for comparison and opportunities for research and collaboration with other neonatal units. In developing countries with busy, under-resourced neonatal units, participation in the VON is difficult as it requires appropriate information systems and additional dedicated staff members. There is therefore a lack of current, valid statistics from such units, even though large

Table 1: Survival of Very Low Birth Weight infants

Location	*Weight (Main inclusion criteria)*	*Time Period*	*Number of babies*	*Survival*	*Factors associated with survival of babies*	Reference
Texas	VLBW	1977 1995		50% 81%	Number of babies offered mechanical ventilation; Black females survival advantage	[3]
Israel	VLBW	1985-87	69	70%		[4]
Italy	VLBW ELBW	1987-1988	634	77% 44%	Lower Birth weight or gestational age, Gender, No antenatal steroids, 1 minute Apgar, No spontaneous respiration in delivery room, body temperature/pH on admission	[5]
Malaysia	VLBW	1989-1990	329	40%	Lower birth weight/gestational age	[6]
Netherlands	VLBW	1983 1995	1388 2006	75% 90%	Delivery in tertiary centre, prolonged artificial ventilation, Caesarean delivery	[7]
Taiwan	VLBW	1995-1998	162	78.4%		[8]
South America	VLBW	1997-1998	385 (11 neonatal units)	73% (49-89%)	Birth weight, gestational age, No antenatal steroids, air leaks	[9]
Sofia (Bulgaria)	VLBW ELBW	1998-1999	122 61	86% 54%	Birth weight, gestational age, low Apgar scores, Cord Ph < 7.1, Need for cardiac compressions/ adrenaline in delivery room	[10]
New Zealand	VLBW	1986 1998	413 1084	81% 90.3%	Delivery in tertiary centre, No antenatal steroids	[11]
Thailand	VLBW ELBW	1996	613	76% 49%	Gestational age, birth weight, delivery room resuscitation, Pneumothorax	[12]
East Anglia (England)	VLBW	1993-1997	1244	75-79%	Gestational age, Birth weight, No antenatal steroids	[13]
USA (NICHD)	VLBW	1995-1996 1997-2002		84% 85%		[14]
Turkey	VLBW	1997-2002	122	84%	Birth Weight	[15]
Spain	VLBW	2002 2005	8942	80.6% 84.8%	Outborn, birthweight	[16]
India	VLBW	3 years (not stated)	260	63%	Birth weight, gestational age, maternal bleed, 1 minute Apgar, apnoea, neonatal septicaemia, shock, hypothermia, no antenatal steroids	[17]
Brazil	VLBW	2004/5	579 (16 tertiary units)	84% (69-95%)	Gestational age, maternal hypertension, 5 minute Apgar, respiratory distress, place of birth	[18]
Malaysia	VLBW	1993 2003	69 60	62,3% 81,6%		[19]
Thailand	VLBW ELBW	2002/3	78	81% 52%	Birth weight, gestational age, congenital anomalies, No antenatal steroids, 5 minute Apgar, intubation in delivery room, respiratory distress syndrome	[20]
Jamaica	ELBW	2002/3	47	43%	Gestational age, birth weight, gender, No antenatal steroids, Caesarean delivery	[21]
South Africa	VLBW ELBW	2000-2002	2164	71% 32%	Birth weight, 1 & 5 minute Apgars, Caesarean delivery, antenatal care, gender	[22]

VLBW = Very low birth weight (< 1501 grams) ELBW = extremely low birth weight (< 1001 grams)

numbers of patients are treated annually. It is essential to have this information to guide forward planning for therapeutic interventions, budgeting and staffing, with the aim of improving outcome. Local data relevant to a developing country is essential to facilitate this planning; it is not possible to transpose data from one area to another.

The purpose of this study was to review the survival to hospital discharge and morbidity of VLBW infants at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), a busy neonatal unit in a developing country.

Methods

This was a retrospective record review of all neonates with a birth weight <1501 grams admitted to the neonatal unit of CMJAH within 24 hours of birth from 1 July 2006 to 31 June 2007. All inborn neonates were admitted directly to a labour ward nursery, so statistics included inborn babies who died shortly after birth. VLBW babies who were delivered at outlying primary level hospitals or clinics and those who were born before arrival in hospital (BBA) were also admitted to the neonatal unit. Data was entered from hospital records onto a Microsoft Access (2003) database. Maternal information obtained from the delivery records included age, parity, gravidity, antenatal care, administration of antenatal steroids, syphilis screening and treatment, human immunodeficiency virus (HIV) screening and prophylaxis, place of delivery, fetal presentation and mode of delivery. HIV screening followed a protocol of voluntary counseling and testing; mothers could refuse to be tested. Prophylaxis was only given to infants where mothers were proven to be HIV positive. Polymerase chain reaction (PCR) testing to confirm HIV infection in the neonate was only done from 6 weeks of chronological age. Neonatal intensive care unit (NICU) admission was not determined by HIV exposure.

The baby's weight, Apgar scores and details of delivery room resuscitation were also obtained from the delivery records. Gestational age was determined from a combination of maternal history (expected date of delivery, height of fundus, first trimester ultrasound) and the Ballard score, which was done by attending clinical staff. The birth weight was plotted on Fenton[23] growth charts to determine whether the baby was appropriate for gestational age

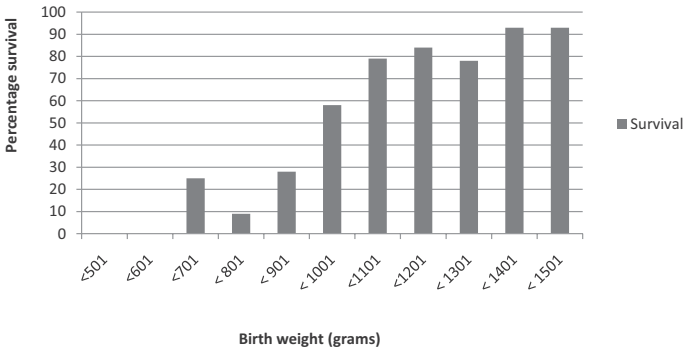


Figure 1. Survival by birthweight category.

(AGA), small for gestational age (SGA) or large for gestational age (LGA). Information was available on all patients until hospital discharge. Neonatal records were reviewed by the primary author (DEB) and the final diagnoses assigned by the attending clinical staff were confirmed using the available clinical information and results of investigations. The neonatal information included duration of hospital stay, respiratory diagnosis (including hyaline membrane disease (HMD)), duration of oxygen therapy, pneumothorax, neonatal jaundice (NNJ), phototherapy, exchange transfusion, patent ductus arteriousus (PDA) and treatment, necrotizing enterocolitis (NEC) and management, intraventricular hemorrhage (IVH) and grade, periventricular leukomalacia (PVL), hypotension, infection and causative organism blood results, retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD) (defined as oxygen requirement at 28 days of age), congenital anomalies, whether KMC was done and final outcome (discharge or death). IVH was graded according to Papile[24] the diagnosis of NEC was given if the baby had modified Bell's stage 2 or 3;[25] ROP was diagnosed by an ophthalmologist; PDA was confirmed on echocardiogram by a pediatric cardiologist.

The cause of death was reviewed by the primary author (DEB) and classified according to the PPIP classification. The PPIP was established in 1999 in South Africa as a national tool for perinatal death audit. In order to have manageable data, the single most likely cause of death is listed. Major categories include prematurity, asphyxia, infection and congenital anomaly. Each category is further subdivided into sub-categories; prematurity is subdivided into extreme immaturity, HMD, IVH, NEC and pulmonary hemorrhage. No postmortem examinations were done on the study patients. Details of ICU admissions include indication for ventilation, dates and type of ventilatory support, (IPPV or NCPAP) and surfactant therapy. Babies who received both NCPAP and IPPV were classified as needing ventilator assistance for the purposes of analysis.

Babies were managed according to the unit policies at the time. Ventilatory support was offered to babies above 900 grams birth weight, due to severely limited tertiary resources. Babies were not routinely intubated or given NCPAP in the delivery room; ventilatory support (including NCPAP) was commenced when the infant showed signs of respiratory failure. All babies, irrespective of birth weight, were provided with standard neonatal care (nursed in an incubator, given supplemental oxygen, intravenous fluids, antibiotic therapy, blood transfusion, phototherapy as needed and KMC). Surfactant therapy was only given as rescue therapy to babies on ventilatory support, usually to those patients who did not wean rapidly from supplementary oxygen. A second dose of surfactant could be given if the baby had responded to the initial dose and then deteriorated again. NCPAP was introduced to the neonatal unit March 2006. During the period of the study, there was no rooming in facility, so mothers could only do KMC intermittently during the day. KMC was introduced once a baby was in room air and tolerating full enteral feeds. Cranial ultrasound was done during the first week of life by a paediatric neurologist and, if indicated, repeated after 1 to 2 weeks and just prior to discharge. Babies who died within the first 72 hours may not have undergone a cranial ultrasound. Screening for retinopathy of prematurity was done by an ophthalmologist at 36 weeks post conceptional age. If babies were discharged prior to this age, an outpatient appointment was booked for the ophthalmology clinic. Babies were discharged home once they had established enteral feeds, were off supplemental oxygen, maintaining temperature and had achieved a weight of 1600 grams. Some babies were discharged to regional step down facilities for weight gain, close to the time of discharge home.

Statistical analysis: Statistical analysis was done on a personal computer using SPSS version 17 (SPSS Inc). Continuous variables were summarised using mean and 95% confidence intervals, while categorical variables were summarised as ratios and percentages. For the purposes of analysis, babies transferred out and those discharged home directly were combined as "survivors" and compared to those babies that died during their

Table 2: PPIP classification of mortality

Cause of death	*Cases*	*%*
Extreme mulitorgan immaturity	56	40
HMD	22	15.7
Asphyxia	17	12.1
NEC	14	10
Nosocomial sepsis	14	10
Septicaemia	3	2.1
Congenital infection	2	1.4
IVH	3	2.1
Congenital abnormality	4	2.8
Pulmonary Haemorrhage	2	1.4
Unspecified	3	2.1

Table 3: Obstetric related risk factors and prediction of mortality

Variable (Valid cases)		Category total	Survived (%)	Died (%)	P value	Odds ratio	95% CI of OR
SGA (461)	Yes	178	143 (80)	35 (20)	0.001	2.07	1.32 - 3.22
	No	283	188 (66)	95 (34)			
Gender (470)	Female	251	192 (76.5)	59 (23.5)	0.004	1.8	1.24 - 2.69
	Male	219	141 (64.4)	78 (35.6)			
Antenatal care (474)	Yes	256	197 (77)	59 (23)	0.001	1.97	1.32 - 2.95
	No	218	137 (63)	81 (37)			
Antenatal corticosteroids (474)	Given	173	131 (75.4)	42 (24.3)	0.057	1.51	0.99 - 2.30
	Not given	301	203 (67.4)	98 (32.6)			
HIV exposed (328)	Yes	120	84 (70)	36 (30)	0.057	0.61	0.36 - 1.02
	No	208	165 (80)	43 (21)			
Syphilis Exposed (474)	Yes	12	7 (58.4)	5 (42)	0.351	0.58	0.18 - 1.85
	No	462	327 (71)	135 (29)			
Place of birth (470)					< 0.001		
	Inborn	383	286 (74.7)	97 (25.3)		1	
	BBA	51	20 (39)	31 (61)		0.22	0.12 - 0.40
	Out born	36	24 (66)	12 (33)		0.68	0.33 - 1.41
Mode of delivery (464)					< 0.001		
	NVD	197	123 (62.4)	74 (37.6)		1	
	Vaginal Breech	25	13 (52)	12 (48)		0.65	0.28 - 1.50
	Elective CS	12	9 (75)	3 (25)		1.80	0.47 - 6.88
	Emergency CS	229	182 (79.5)	47 (20.5)		2.33	1.51 - 3.59
Presentation (448)	Vertex	401	290 (72.3)	111 (27.7)	0.541	0.82	0.43 - 1.57
	Breech	47	32 (68.11)	15 (31.9)			
Resuscitation at birth (474)	Yes	154	91 (59.1)	63 (40.9)	< 0.001	0.46	0.30 - 0.69
	No	320	243 (75.9)	77 (24.1)			
Hypothermia at birth (474)	Yes	13	5 (38.5)	8 (61.5)	0.01	0.25	0.08 - 0.78
	No	461	329 (71.4)	132 (28.6)			
5 minute APGAR Score (409)	Score >= 6	304	231 (76)	73 (24)	0.093	1.52	0.93 - 2.46
	Score < 6	105	71 (67.6)	34 (32.4)			

Note: Valid cases = those with no missing data, thus, a complete case analysis
Percentages are reported for rows

hospital admission. Cross-tabulations of categorical variables with survival were produced and statistical associations between these categorical variables and survival outcome were done using the Chi-Square test of association. Normally distributed continuous variables were compared using the unpaired t test and the Mann-Whitney U test was used to compare discrete variables and those continuous variables that were not normally distributed. Binary outcome logistic regression was done on individual variables to predict survival. Those variables which were significant at the univariate analysis were entered into a multiple logistic regression using the backward selection procedure. All the statistical tests were conducted at 5% significance level.

Results

Among the four hundred and eighty eight eligible VLBW babies who were admitted during the study period, 474 records (97.1%) of VLBW babies born to 448 mothers were retrieved and available for review. The overall survival was 334/474 (70.5%). The mean birth weight was 1133.5 grams (95% CI 1111.9-1155.0), mean gestational age was 29.9 weeks (95% CI 29.6-30.1) and mean duration of hospitalization was 25.8 days (95% CI 23.8-27.8). The mean age at time of death was 5.77 days (95% CI 3.66-7.88) and of discharge/transfer was 34.23 days (95% CI 32.13-36.32). The mean duration of supplemental oxygen was 8.2 days (95% CI 6.8-9.7) and mean duration of mechanical ventilation was 8.08 days (95% CI 6.15-10.01).

Table 4: Risk factors for mortality related to disease/treatment in the neonatal period

Risk factor (Valid cases)		Total	Survived (%)	Died (%)	P Value	Odds ratio	95% CI of Odds Ratio
HMD (437)	Yes	299	190 (63.5)	109 (36.5)	< 0.001	0.33	0.20 - 0.55
	No	138	116 (84.1)	22 (15.9)			
Mechanical ventilation (474)	Yes	99	71 (71.7)	28 (28.3)	0.76	1.08	0.66 - 1.76
	No	375	263 (70.1)	112 (29.9)			
Nasal CPAP (474)	Yes	96	80 (83.3)	16 (16.7)	0.002	2.44	1.37 - 4.35
	No	378	254 (67.2)	124 (32.8)			
Surfactant therapy (474)	Yes	90	73 (81)	17 (19)	0.014	2.02	1.15 - 3.58
	No	384	261 (68)	123 (32)			
Sepsis (445)	Yes	62	40 (64.5)	22 (35.5)	0.085	0.61	0.34 - 1.08
	No	383	287 (74.9)	96 (25.1)			
Gram Negative (474)	Yes	37	21 (56.8)	16 (43.2)	0.057	0.52	0.26 - 1.03
	No	437	313 (71.6)	124 (28.4)			
Gram Positive (474)	Yes	28	23 (82.1)	5 (17.9)	0.163	1.99	0.74 - 5.36
	No	446	311 (69.7)	135 (30.3)			
PDA (474)	Yes	26	18 (69)	8 (31)	0.887	0.94	0.4 - 2.21
	No	448	316 (71)	132 (29)			
Hypotension (474)	Yes	23	7 (30)	16 (70)	< 0.001	0.166	0.07 - 0.41
	No	451	327 (73)	124 (27)			
NEC grade 2/3 (474)	Yes	26	9 (35)	17 (65)	< 0.001	0.2	0.09 - 0.46
	No	448	325 (73)	123 (27)			
IVH (328)					0.004		
	No	253	209 (83)	44 (17)		1	
	Gr 1	11	8 (72.7)	3 (27.3)		0.56	0.14 - 2.20
	Gr 2	40	25 (62.5)	15 (37.5)		0.35	0.17 - 0.72
	Gr 3	16	12 (75)	4 (25)		0.63	0.19 - 2.05
	Gr 4	4	1 (25)	3 (75)		0.07	0.01 - 0.69
	PVL	4	2 (50)	2 (50)		0.21	0.03 - 1.53

Note: Valid cases = those with no missing data
Percentages are reported for rows

Birth weight and gestational age: The mean birth weight of survivors (1213 grams; 95% CI: 1192.5-1234.1) was significantly greater (p<0.001) than that for babies that died (942.5 grams; 95% CI: 904.5-980.5). The mean gestation period for survivors (30.7 weeks, 95% CI: 30.4-31.0) was significantly more advanced than that of those who died (27.6 weeks, 95% CI: 27.2-28.1). The median 5 minute Apgar score of those babies that survived, 8 (IQR: 1-9) was significantly higher than the non-survivors, 6 (IQR: 1-10) with p=0.005. Mortality by birth weight category is shown in figure 1. As survival seem to increase with birth weight, an association between a quadratic term was fitted which also showed significant association (p=0.010) with survival.

Survival was closely related to birth weight category, ranging from zero below 601 grams to 62% (32/52) from 901 to 1000 grams and 93% (67/72) from 1301 to 1500 grams. The survival of extremely low birth weight infants (<1001 grams) was 34.9% (50/143) compared to 85.8% (284/331) for babies with a birth weight from 1001 to 1500 grams. The adjusted survival odds ratio was 23.44 (95% CI: 11.22-49.00) for babies weighing from 1001 to 1500 grams compared to those weighing below 1001 grams.

The main cause of death according to the PIPP classification is shown in Table 2. The single most common cause of death was extreme multi-organ immaturity, in 40% of cases, followed by HMD in 15% of cases.

Maternal and delivery period: The mean maternal age was 26.5 years (95% CI: 25.8-27.1) and 37.3% (152/407) were primiparous. Risk factors for mortality related to antenatal care, labour and delivery are presented in Table 3. Emergency Caesarean section (CS) was done for fetal distress in 63/229 (27.5%) of cases. Where emergency CS was done for maternal indications, the most common reasons were pregnancy induced hypertension 45.6% (63/138) followed by antepartum hemorrhage in 13% (18/138). No CS was done for HIV infection alone.

Odds ratios with 95% confidence intervals are presented for each risk factor. Significant predictors of survival on univariate analysis were size for gestational age, gender, antenatal care, place of delivery, mode of delivery, the need for delivery room resuscitation and hypothermia at birth. Maternal HIV exposure, maternal infection with syphilis, the administration of antenatal

Table 5: Multivariate logistic regression analysis with adjusted estimates of Odds Ratio (95% CI).

Variable	Odds Ratio	95% Confidence Interval	P-Value
Birth Weight	1.008	1.006 - 1.01	< 0.001
Gender			
Male	1.00		
Female	3.21	1.6 - 6.31	0.001
Place of Birth			
Inborn	1.00		
BBA	0.23	0.08 - 0.69	0.008
Out born	0.35	0.10 - 1.20	0.096
Resuscitation			
No	1.00		
Yes	0.47	0.24 - 0.92	0.029
Nasal CPAP			
No	1.00		
Yes	4.58	1.58 - 13.31	0.005
Hypotension			
No	1.00		
Yes	0.05	0.01 - 0.21	< 0.001
NEC Grade 2/3			
No	1.00		
Yes	0.06	0.02 - 0.20	< 0.001

steroids and the presenting part at delivery did not predict survival. Only 69% of mothers had known HIV status and 36.5% of mothers had received antenatal steroids.

Neonatal period: Air leak was recorded in 3 patients (0.6%) and high frequency ventilation was used in 3 patients (0.6%). These variables were not included in the analysis due to small numbers. Bronchopulmonary dysplasia (BPD) (defined as oxygen requirement >28 days) was present in 42 (8.8%) of babies. Nevirapine prophylaxis was given to 97/120 (80.8%) of the HIV exposed infants; 25/354 (7%) of mothers offered HIV testing refused consent. 11/474 (2.3%) of the babies were put up for adoption. Only 87 (18.3%) of the babies were screened for ROP prior to discharge. Only two babies had ROP, both of which were stage 1. KMC was done by 211/474 (44.5%) of mothers.

Odds ratios and 95% confidence intervals for each risk factor related to the neonatal period (both disease and treatment) are shown in Table 4. HMD, NCPAP, surfactant therapy, hypotension, NEC and IVH were all predictive of survival. The need for mechanical ventilation, PDA and the presence of sepsis did not predict survival.

Multivariate analysis: Multivariate logistic regression is shown in Table 5 for complete cases, ie a complete case analysis with the entered variables defining a complete case. Variables entered into the model included birth weight, SGA, gender, antenatal care, place of birth, mode of delivery, NEC grade 2/3, hypotension, HMD, resuscitation at birth, hypothermia, surfactant therapy and NCPAP. Gestational age was not included in the model as it is highly correlated with birth weight (correlation coefficient 0.717 p<0.001) and birth weight is more accurate in our setting than estimation of gestational age. IVH was not included due to the large number of missing variables. The final model showed that birth weight, gender, resuscitation at birth, BBA, hypotension, definite NEC and provision of NCPAP were significant predictors of mortality in this population. The model predicted mortality correctly in 87% of cases. Birth weight was the single most important predictor of mortality, correctly predicting mortality in 82.9% of cases. The odds ratio for death for birth weight ≤1001 grams was 10.41 (95% CI 6.62 to 16.6) and for gestational age <28 weeks was 11.97 (95% CI 7.1-20.1).

Discussion

This retrospective review provides current survival rates and indicates where resources should be channeled in order to improve survival of VLBW infants in South Africa. The overall survival rate was 70.5% for VLBW infants at CMJAH 2006/2007. This is almost exactly the same as that reported from CH Baragwanath for 2000-2002 (71%),[22] which reflects the similarity in practice and disease profile between the two units, which form part of a single academic complex. This survival rate also compares favorably with the global average of 73% (see Table 1), but is substantially below that of developed countries.[7,10,11,13,14,16] The survival of ELBW infants in the present review of 35% was less than that in other developing countries, such as Jamaica[21] and Thailand[20] but once again very similar to that of CH Baragwanath (32%).[22] The most significant cause of death in this study was extremely low birth weight/extreme multi-organ immaturity. This is in close agreement with national data for South Africa from the same time period—46% of all neonatal deaths were immaturity related, of which 44.9% were due to extreme immaturity and 35.6% due to HMD.[26]

The main determinants of survival in the present study, birth weight, gender, being born before arrival in the hospital, resuscitation at birth, NEC, hypotension and NCPAP, are not surprising and very similar to other reports on VLBW outcome.[5-7,9-22] However, the study shows that, despite great improvements in neonatal care, the VLBW survival in South Africa is below that in other developing countries[8,9,12,15,18,20] and can improve

substantially. This can be achieved by simple interventions such as ensuring preterm infants are delivered in hospital, improved neonatal resuscitation and provision of NCPAP. A provincial neonatal resuscitation program has recently been introduced to improve the resuscitation skill of birth attendants. Patient education as to when to seek help during labor and improved emergency transport will be required to prevent preterm infant BBA. Although provision of antenatal steroids did not achieve statistical significance in this study, the number of women receiving antenatal steroids is unacceptably low (36%). This is a specific obstetric intervention that needs to be addressed and will improve neonatal outcome. Delivery by CS was advantageous, but may reflect those patients who have received antenatal care, including antenatal steroids and who delivered in hospital. It is not feasible to do elective CS on all preterm deliveries in our resource constrained setting.

South Africa is a developing country with limited health resources and high patient numbers; it is not possible to provide full tertiary support to every VLBW infant. For many years this problem has been addressed by limiting ventilatory support, including the administration of surfactant and NCPAP, to those neonates above a specified birth weight cutoff. Prior to the widespread use of NCPAP, this cutoff was 1000 grams. The ventilation cutoff was reduced to 900 grams just before the study period, with the introduction of NCPAP to the unit. The poor survival or our ELBW infants is undoubtedly influenced by this policy and NCPAP with surfactant should be provided to babies from 750 grams in order to bring our ELBW survival rate up to that in other developing countries.[12,20,21]

NEC and hypotension were the other significant predictors of mortality. The overall rate of NEC was 5.5%, which accounted for 10% of the deaths. Interestingly the rate of NEC was comparable to that in the VON in 2005, which represents well resourced settings. Prevention of NEC should also be a priority, including promotion of breastfeeding. Our rate of breastfeeding at the time of the study was extremely low, mainly due to the HIV epidemic. Only 69% of mothers were tested for HIV, but 36% were positive. The protocol during the study period was to formula feed HIV exposed babies. Of concern, is the high rate of untested mothers, the relatively high rate of refusal to be tested and failure to administer HIV prophylaxis in 16.4% of exposed mothers; this may reflect the mothers who were diagnosed after the early neonatal period. Ensuring that all mothers are counseled and tested for HIV is essential to prevent mother to child transmission and, in turn, facilitate the promotion of breastfeeding and reduction of NEC. Although 36% of screened mothers were HIV positive, HIV status did not predict neonatal outcome. This is in agreement with a study from Durban[27] which found that HIV exposed babies were not different from HIV unexposed neonates with regard to birth weight, gestational age, need for ICU admission, complications of ventilation, sepsis, IVH or death. Furthermore, most HIV exposed neonates are subsequently uninfected. HIV exposure is not a major determinant of neonatal survival and is not used as a criterion for ICU admission.

CMJAH represents a high risk obstetric population with many referrals for obstetric complications, the most frequent of which is pregnancy induced hypertension. Improved management of this obstetric complication may reduce the number of VLBW infants. There are also significant social problems with 2.6% of the babies delivered as a result of illegal termination of pregnancy and 2.3% being given up for adoption. The whole issue of preventing unwanted pregnancy is also pertinent in our population.

The low rate of in hospital screening for ROP is also an area of concern and needs to be improved. A significant number of babies are referred to the ophthalmologist at the time of their first follow up visit for ROP screening, but this may be too late in terms of adequate intervention.

Conclusion

Although the overall survival of VLBW infants in our unit compares with the global average (see Table 1), the survival of our ELBW infants can be significantly improved. NCPAP and surfactant should be provided to ELBW infants >750 grams birth weight. Prevention of VLBW deliveries outside the hospital, improved administration of antenatal steroids, universal screening for HIV, improved neonatal resuscitation and strategies to prevent NEC, will also improve the VLBW survival rate.

References

1 United Nations: Reduce Child Mortality. The Millennium Development Goals Report New York 2008:21-3.
2 Patrick ME: Neonatal deaths: Do they count? In Saving Children 2006: A survey of child healthcare in South Africa Edited by: Stephen CRPM. Pretoria: University of Pretoria, MRC, CDC; 2008:81-5.
3 Kaiser JR, Tilford JM, Simpson PM, Salhab WA, Rosenfeld CR: Hospital survival of very-low-birth-weight neonates from 1977 to 2000. J Perinatol 2004, 24:343-50.
4 Litt R, Seidman DS, Gross-Tsur V, Dollberg S, Gale R: A 2-year prospective study of very low birth weight infants. Isr J Med Sci 1992, 28:783-8.
5 de Vonderweid U, Carta A, Chiandotto V, Chiappe F, Chiappe S, Colarizi P, et al.: Italian Multicenter Study on Very Low Birth Weight Babies. Ann IST Super Sanita 1991, 27:633-50.
6 Boo NY: Outcome of very low birth weight neonates in a developing country: experience from a large Malaysian maternity hospital. Singapore Med J 1992, 33:33-7.
7 Anthony S, Ouden L, Brand R, Verloove-Vanhorick P, Gravenhorst JB: Changes in perinatal care and survival in very preterm and extremely preterm infants in The Netherlands between 1983 and 1995. Eur J Obstet Gynecol Reprod Biol 2004, 112:170-7.
8 Chang SC, Lin CH, Lin YJ, Yeh TF: Mortality, morbidity, length and cost of hospitalization in very-low-birth-weight infants in the era of National Health Insurance in Taiwan: a medical center's experience. Acta Paediatr Taiwan 2000, 41:308-12.
9 Grupo Colaborativo Neocosur: Very-low-birth-weight infant outcomes in 11 South American NICUs. J Perinatol 2002, 22:2-7.
10 Vakrilova L, Kalaidzhieva M, Sluncheva B, Popivanova A, Metodieva V, Garnizov T: [Resuscitation in very low birth weight and extremely low birth weight newborns in the delivery room]. Akush Ginekol (Sofiia) 2002, 41:18-23.
11 Darlow BA, Cust AE, Donoghue DA: Improved outcomes for very low birth weight infants: evidence from New Zealand national population based data. Arch Dis Child Fetal Neonatal Ed 2003, 88:F23-F28.
12 Tsou KI, Tsao PN: The morbidity and survival of very-low-birth-weight infants in Taiwan. Acta Paediatr Taiwan 2003, 44:349-55.
13 Dorling J, D'Amore A, Salt A, Seward A, Kaptoge S, Halliday S, et al.: Data collection from very low birth weight infants

in a geographical region: methods, costs, and trends in mortality, admission rates, and resource utilisation over a five-year period. Early Hum Dev 2006, 82:117-24.
14 Fanaroff AA, Stoll BJ, Wright LL, Carlo WA, Ehrenkranz RA, Stark AR, et al.: Trends in neonatal morbidity and mortality for very low birth weight infants. Am J Obstet Gynecol 2007, 196:147-8.
15 Atasay B, Gunlemez A, Unal S, Arsan S: Outcomes of very low birth weight infants in a newborn tertiary center in Turkey, 1997-2000. Tur J Pediatra 2003, 45:283-9.
16 Moro M, Figueras-Aloy J, Fernandez C, Domenech E, Jimenez R, Perez-Rodriguez J, et al.: Mortality for newborns of birth weight less than 1500 g in Spanish neonatal units (2002-2005). Am J Perinatol 2007, 24:593-601.
17 Basu S, Rathore P, Bhatia BD: Predictors of mortality in very low birth weight neonates in India. Singapore Med J 2008, 49:556-60.
18 de Almeida MF, Guinsburg R, Martinez FE, Procianoy RS, Leone CR, Marba ST, et al.: Perinatal factors associated with early deaths of preterm infants born in Brazilian Network on Neonatal Research centers. J Pediatr (Rio J) 2008, 84:300-7.
19 Ho JJ, Chang AS: Changes in the process of care and outcome over a 10-year period in a neonatal nursery in a developing country. J Trop Pediatr 2007, 53:232-7.
20 Sritipsukho S, Suarod T, Sritipsukho P: Survival and outcome of very low birth weight infants born in a university hospital with level II NICU. J Med Assoc Thai 2007, 90:1323-9.
21 Trotman H, Bell Y: Neonatal sepsis in very low birth weight infants at the University Hospital of the West Indies. West Indian Med J 2006, 55:165-9.
22 Velaphi SC, Mokhachane M, Mphahlele RM, Beckh-Arnold E, Kuwanda ML, Cooper PA: Survival of very-low-birth-weight infants according to birth weight and gestational age in a public hospital. S Afr Med J 2005, 95:504-9.
23 Fenton TR: A new growth chart for preterm babies: Babson and Benda's chart updated with recent data and a new format. BMC Pediatr 2003, 3:13.
24 Papile LA, Burstein J, Burstein R, Koffler H: Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr 1978, 92:529-534.
25 Bell MJ, Ternberg JL, Feigin RD, Keating JP, Marshall R, Barton L, et al.: Neonatal necrotizing enterocolitis: therapeutic decisions based upon clinical staging. Ann Surg 1978, 187:1-7.
26 Saving babies 2006-2007: Sixth perinatal care survey of South Africa. Edited by: Pattinson RC. Tshepesa Press, Pretoria; 2009.
27 Adhikhari M, Jeena P, Pillay T, Moodley A, Kiepiela P, Cassol S: The HIV-1 exposed neonate: Outcome of intensive care management in the first week of life. Indian Paediatrics 2005, 42:1215-1219.

Edi Catheter…continued from page 31
The HFNC was then increased to 8 L/min a few hours later. The peak Edi was below the 25 microvolt level (average 24 microvolts) at 8 L/min of HFNC. The patient physically appeared to exhibit less use of accessory muscles and had fewer intercostal and sternal retractions.

Monitoring the electrical activity of the diaphragm following mechanical ventilation and extubation helped avert re-intubation in this infant. He appeared to be resting comfortably on 8 L/min of HFNC and vital signs were stable.

The Edi catheter was valuable in monitoring the infant's drive to breath.

Tom Noblet commented, "Use of the Edi to evaluate post-extubation therapy helped determine optimum settings for this infant. This resulted in reduced work of breathing and helped avoid re-intubation and re-institution of ventilation of this infant, with their accompanying potential complications such as ventilator-associated pneumonia."

References

1 Noblet, T: Effect of Bubble CPAP and High Flow Nasal Cannula on the Electrical Activity of the Diaphragm in a Premature Infant. Respir Care 2009; 54:1537.
2 Beck J, Gottfried SB, Navalesi P, Skrobik Y, Comtois N, Rossini M, Sinderby C: Electrical activity of the diaphragm during pressure support ventilation in acute respiratory failure. Am J Resp Crit Care Med 2001; 164:419-424.2.

Cesarean Section Rate…continued from page 32
change their lifestyle, must receive a good prenatal care, which is available to all, must attend natural childbirth classes, and in this way they will have a very positive decision in delivering their babies vaginally. If they have doubts they should question their obstetrician, although they may not have time to get a second opinion, but they should demand natural childbirth as much as possible. Women are the ones who can make a major decision in bringing down the CS rate in this country by taking control of their fetal health by delivering in a family-centered child-birthing institution, and definitely not at home. CS for known maternal complications will still continue to be a life saving option for those where such risk factors are identified.

[Editorial comment by Les Plesko: While there's no question that cesareans are on the rise, I wonder, re the authors' comments, how much of the onus can really be placed on mothers, as per the concluding comments. Most moms get advice from their obstetricians, who often recommend CS, for whatever reason. The medico-legal complex has a vested interest in pushing c-sections. The edifice of healthcare provision has become daunting, increasingly complex, and confusing for many moms-to-be. While moms obviously want the best possible birth experience, they are of course reliant on their caregivers in such a coercive environment. Also, the claim that prenatal care is available to all is spurious. It is not. Finally, I would add that insurance companies play a major role in the increase in C-sections, with some providers denying vaginal birth coverage for moms who have had a previous CS.]

Analysis of Preterm Deliveries Below 35 Weeks' Gestation

Wei Yuan, Anne M. Duffner, Lina Chen, Linda P. Hunt, Susan M. Sellers, Andrés López Bernal

Background: Preterm birth remains a major public health problem and its incidence worldwide is increasing. Epidemiological risk factors have been investigated in the past, but there is a need for a better understanding of the causes of preterm birth in well defined obstetric populations in tertiary referral centres; it is important to repeat surveillance and identify possible changes in clinical and socioeconomic factors associated with preterm delivery. The aim of this study was to identify current risk factors associated with preterm delivery and highlight areas for further research.

Findings: We studied women with singleton deliveries at St Michael's Hospital, Bristol during 2002 and 2003. Two hundred seventy-four deliveries between 23-35 weeks' gestation (preterm group), were compared to 559 randomly selected control deliveries at term (37-42 weeks) using standard statistical procedures. Both groups were >80% Caucasian. Previous preterm deliveries, high maternal age (>39 years), socioeconomic problems, smoking during pregnancy, hypertension, psychiatric disorders and uterine abnormalities were significantly associated with preterm deliveries. Both lean and obese mothers were more common in the preterm group. Women with depression/ psychiatric disease were significantly more likely to have social problems, to have smoked during pregnancy and to have had previous preterm deliveries; when adjustments for these three factors were made the relationship between psychiatric disease and pregnancy outcome was no longer significant. 53% of preterm deliveries were spontaneous, and were strongly associated with episodes of threatened preterm labor. Medically indicated preterm deliveries were associated with hypertension and fetal growth restriction. Preterm premature rupture of the membranes, vaginal bleeding, anaemia and oligohydramnios were significantly increased in both spontaneous and indicated preterm deliveries compared to term controls.

Conclusions: More than 50% of preterm births are potentially preventable, but remain associated with risk factors such as increased uterine contractility, preterm premature rupture of the membranes and uterine bleeding whose aetiology is unknown. Despite remarkable advances in perinatal care, preterm birth continues to cause neonatal deaths and long-term morbidity. Significant breakthroughs in the management of preterm birth are likely to come from research into the mechanisms of human parturition and the pathophysiology of preterm labor using multidisciplinary clinical and laboratory approaches.

Authors Yuan, Duffner and Bernal are with the Department of Clinical Science at South Bristol, St Michael's Hospital; Chen is with the Department of Social Medicine, University of Bristol; Hunt is with the Department of Clinical Sciences at South Bristol, Institute of Child Life and Health; Sellers is with University Hospitals Bristol, Obstetrics and Gynaecology, St Michael's Hospital, Bristol, UK.

Background

Preterm birth remains a major cause of perinatal mortality and morbidity and efforts to predict and prevent its occurrence are difficult because of our lack of understanding of the biochemical mechanism of labor and the multiplicity of medical and socioeconomic factors associated with preterm delivery.[1] The incidence of preterm birth (deliveries before 37 weeks' gestation) ranges from 6-8% in Europe, Australia and Canada,[2,3] to 9-12% in Asia, Africa and the United States.[4,5] Preterm birth is recognized as a worldwide problem responsible for more than 80% of neonatal deaths and more than 50% of long term morbidity in the surviving infants.[6,7] The incidence of preterm birth has remained relatively constant over the past three decades and there are worrying trends that it is on the increase.[5,8] It is important to know whether risk factors have changed over the years and to look for new clinical and socioeconomic risks. This information is necessary to guide further research in this area. Epidemiological studies have identified a clear association between preterm birth and previous preterm delivery,[9] preterm premature rupture of the membranes[10] and maternal smoking during pregnancy.[11] However the association between preterm birth and other maternal and fetal complications of pregnancy is less consistent, due to social, ethnic and demographic differences among the populations studied.[7] In this study we have carried out a detailed comparison of preterm and term deliveries in a relatively homogeneous obstetric population attending a tertiary referral maternity hospital, to highlight areas where further research or intervention is needed in order to prevent preterm birth and improve perinatal outcome.

Methods

Study population: This survey was done at St Michael's Hospital, Bristol. This is a tertiary referral maternity center with approximately 5,500 deliveries a year; preterm deliveries (under 37 weeks' gestation) accounted for approximately 8% of all births during 2002 and 2003. In this survey we have focused on deliveries between 23-35 weeks' gestation (3% of all births) because these account for most of the perinatal mortality and

Table 1: General characteristics of the study groups.

	Control (≥ 37 weeks' gestation)	Preterm (<35 weeks' gestation)	P value
Number of deliveries	559	274	
Gestational age at delivery (completed weeks)	Median 40 (Range 37 - 42)	Median 33 (Range 23 - 34)	Not Applicable
Ethnicity			
Caucasian	464 (83.0%)	229 (83.6%)	0.46
Asian	45 (8.1%)	17 (6.2%)	
African	33 (5.9%)	22 (8.0%)	
Others	17 (3.0%)	6 (2.2%)	
Mean maternal age (years)	28.8 (SD 6.04) (Range 15-44)	29.7 (SD 6.46) (Range16-46)	0.045
Distribution of births			
Singletons	553 (98.9%)	228 (83.2%)	<0.001
Twins	6 (1.1%)	44 (16.1%)	
Triplets	0	2 (0.7%)	

morbidity and so improvements in management are likely to have a strong impact on neonatal outcome. We obtained lists of all deliveries below 35 weeks gestation from the hospital database for two complete years 2002 and 2003 (n=274). We used computer generated random numbers to draw separate samples from lists of all term babies delivered within each of the 2 years, using term: preterm ratios of 2:1 to increase power; 559 out of 8,204 term babies were included. Gestational age was based either on certain dates or a dating scan. Antenatal care was undertaken by an obstetrician or community midwife or a combination of the two professionals and followed standard UK practice.

This study was approved by the Central & South Bristol Research Ethics Committee.

Statistical analysis: Initial maternal and newborn information was taken from the hospital computer databases (STORK and Vermont Oxford Network). The hospital medical records of each delivery were retrieved and analysed in detail by a trained research midwife (AMD) using a structured proforma. Information recorded was anonymized by assigning a unique project number to each delivery. Data on maternal and fetal characteristics at birth were recorded, including maternal age and gestational age at delivery, ethnicity, gestational age at booking, complications of pregnancy and delivery, birth weight, Apgar score and baby gender. A wide range of potential risk factors—smoking and drinking status before and during pregnancy, history of drug use, socioeconomic status, past obstetric history (including previous history of termination, miscarriage and preterm birth) were recorded. Maternal body mass index (BMI) at booking was calculated using weight (kg)/ height (m)^2. The definition of lean was BMI <20 kg/m^2 and obese BMI ≥30 kg/m^2. Data was entered into a Microsoft excel 2003 database and imported into STATA version 10 for analysis.

Comparisons between cases and controls were made using standard statistical procedures. Continuous variables were summarized by mean (SD) except for gestational age, which was not normally distributed, where the median (range) was used instead. Means were compared using unpaired Student's t-tests. For categorical variables Chi-squared tests were used and two-tailed Fisher's Exact tests for 2 × 2 tables where expected frequencies were small. A 5% level of significance was used throughout. Multiple logistic regression was used to adjust for confounding factors and compute odd-ratios.

Results: The control and preterm groups had very similar ethnicity and maternal age but, as expected, multiple births were more common in the preterm group (Table 1). Eight of the multiple pregnancies were the result of assisted reproduction treatment (IVF). Since the obstetric management of multiple pregnancies differs from that of singleton pregnancies, we excluded all the multiple pregnancies from further analysis.

Maternal age and BMI: Previous reports have indicated that extremes of maternal age and low maternal weight predispose to preterm birth and we have confirmed that the incidence of preterm birth in women over 39 years of age remains significantly higher than in younger women (Table 2); however the proportion of teenage mothers in the two groups was similar. Both lean and obese mothers were more common in the preterm group (odds ratios 1.75 (95%CI 1.02 to 3.01) and 1.41 (95% 0.92-2.15) respectively; reference category was the normal BMI group), but the overall difference did not reach statistical significance (Table 2).

Table 2: Demographic and socioeconomic parameters in singleton pregnancies.

	Control (≥ 37 weeks' gestation)	Preterm (<35 weeks' gestation)	P value
Number of deliveries	553	228	
Median gestational age at delivery (completed weeks) and range	40 (Range 37-42)	33 (Range 23 - 34)	Not Applicable
Maternal age			
Mean maternal age at delivery (years)	28.8 (SD 6.04) (Range 15-44)	29.4 (SD 6.69) (Range16-46)	0.24
≤ 18 years	33 (6.0%)	13 (5.7%)	
19-39 years	509 (92.0%)	199 (87.3)	0.002
>39 years	11 (2.0%)	16 (7.0%)	(Comparison of proportions of mothers >39 years P < 0.001)
Body mass index			
Mean BMI at booking (kg/m^2)	25.03 (SD 5.29) (Range 16-49) (n = 531)	25.8 (SD 6.71) (Range 15-60) (n = 195)	0.10
Lean <20	42 (7.9%)	24 (12.3%)	0.054
Normal 20 - 29.9	402 (75.7%)	131 (67.2%)	
Obese ≥30	87 (16.4%)	40 (20.5%)	
Socioeconomic			
With social problems	60/548 (10.9%)	50/218 (22.9%)	<0.001
Smoking during pregnancy	114/553 (20.6%)	83/226 (36.7%)	<0.001
Drinking Alcohol during pregnancy	180/550 (32.7%)	75/228 (32.9%)	0.96
Using drugs during pregnancy	20/553 (3.6%)	12/226 (5.3%)	0.28

Socioeconomic factors: The proportion of women with at least one social problem (low income; poor housing; unsupported or single parent) was significantly higher in the preterm than in the control group (Table 2). Smoking before conception was not associated with preterm birth (data not shown); however the proportion of women who smoked during pregnancy was significantly higher in the preterm than in the control group. The proportion of smokers in women with and without social problems was 58.2% and 19.6%, respectively. The proportions of women who consumed alcohol or admitted using any recreational drugs (cannabis, amphetamines, barbiturate, crack, cocaine, heroin, methadone, ecstasy) during pregnancy were similar in the control and preterm groups.

History of previous pregnancies: About 70% of women in both groups had been pregnant previously and more than 56% had had previous deliveries (Table 3). The proportion of women with a previous preterm delivery (between 20 and 37 weeks' gestation) in the preterm group was significantly higher than in the control group. Analysis of previous pregnancies under 20 weeks' gestation revealed that terminations of pregnancy were significantly more common in the preterm group; however the proportion of spontaneous miscarriages in the two groups was similar.

Pre-existing medical conditions: The most common pre-existing medical conditions in the control and preterm deliveries are listed in Table 4. Hypertension (blood pressure >140/90 mmHg), psychiatric disorders and uterine abnormalities were significantly associated with preterm delivery. A history of cervical incompetence was found only in the preterm group. Multivariable analysis revealed that women with psychiatric disorders were significantly more likely to have social problems (P<0.001), to have smoked during pregnancy (P<0.001) and to have had previous preterm deliveries (P=0.007). When adjustments were made for the effect of these three factors the

Table 3: Previous pregnancies.

	Control (≥37 weeks' gestation)	Preterm (<35 weeks' gestation)	P value
Number of deliveries	553	228	
Gravida 0	176 (31.8%)	62 (27.2%)	0.20
Gravida >0	377 (68.2%)	166 (72.8%)	
Para 0	239 (43.2%)	100 (43.9%)	0.87
Para >0	314 (56.8%)	128 (56.1%)	
Number of women with previous preterm delivery (≥ 20 and <37 weeks' gestation).	30 (5.4%)	58 (25.4%)	<0.001
Termination of pregnancy (< 20 weeks' gestation)	88 (15.9%)	55 (24.1%)	0.007
Spontaneous miscarriage (< 20 weeks' gestation)	30 (5.4%)	9 (3.9%)	0.39

relationship between psychiatric disorders and preterm birth was no longer significant (odds-ratio [95%CI] reduced from 1.6 [1.1-2.4] to 1.2 [0.8-1.8]).

Complications of pregnancy: The incidence of maternal, fetal and other complications of pregnancy is shown in Table 5. Episodes of threatened preterm labor were the most common maternal complication in preterm deliveries, and occurred almost exclusively in the preterm group. Vaginal bleeding, anaemia (haemoglobin <10.5 g/dl) and proteinuria (1+ or more on dipstick, excluding urinary tract infection) occurred in both control and preterm pregnancies, but were significantly increased in the latter. Hypertension with proteinuria (pre-eclampsia) was significantly increased in the preterm group. Hypertension without proteinuria (pregnancy induced hypertension) was low in both groups. Raised alpha feto protein (AFP) levels were more common in preterm pregnancies, but the incidence was low. Other common complications such as urinary tract infection (UTI), the presence of pathogens in high vaginal swabs (HVS) and the observation of reduced fetal movements were similar in both groups (Table 5).

Fetal complications were more frequent in the preterm group, especially oligohydramnios, followed by fetal growth restriction and fetal abnormalities (including both structural and chromosomal abnormalities) (Table 5). Preterm premature rupture of the membranes (PPROM) and prolonged rupture (>48 hours) of the membranes were significantly more common in the preterm group.

Multivariable analysis indicated that women with pre-eclampsia were more likely to have fetal growth restriction; moreover each of the two factors was an effect modifier for the other (supported by significant interaction in logistic regression P=0.026). For example, the association of fetal growth restriction with preterm birth was much greater in the presence of pre-eclampsia than in its absence (OR 45.4 [95% CI 5.8-354.6] versus 3.71 [1.65-8.33], respectively). Women with both premature and prolonged rupture of the membranes were the most likely to have oligohydramnios (P<0.001). Finally, women with vaginal bleeding were more likely to have PPROM or episodes of threatened preterm labor (P<0.001 for both).

Labor and delivery: 65% of women in the control group went into spontaneous labor and 35% had an elective delivery (cesarean section or induction of labor) indicated for medical or obstetric reasons. In the preterm group 53% of women had spontaneous labor and 47% were delivered electively (P=0.002). When the incidence of complications of pregnancy is presented separately in spontaneous and elective deliveries (Figure 1) very different patterns can be observed. Spontaneous preterm deliveries were clearly associated with threatened preterm labor, PPROM and vaginal bleeding. The occurrence of one or more episodes of vaginal bleeding at any stage of pregnancy was relatively common in both term and preterm spontaneous deliveries, but the incidence was significantly higher in the preterm group. By contrast, elective preterm deliveries were strongly associated with anaemia, hypertension and fetal growth restriction (Figure 1). Interestingly, vaginal bleeding, oligohydramnios, PPROM and, to a lesser extent, threatened preterm labor were significantly increased in both spontaneous and elective preterm deliveries.

Neonatal outcome: Metabolic complications including jaundice, hypoglycemia and hypothermia were relatively common in both control and preterm groups, although the incidence was significantly higher in the latter (data not shown). Severe complications of prematurity such as respiratory distress (56%), patent ductus arteriosus (11%), intracerebral damage (9%) and necrotising enterocolitis (4.5%) were diagnosed almost exclusively in the preterm group. There were 15 stillbirths, 21 neonatal deaths (deaths within 28 days of birth) and 6 postneonatal deaths (after 28 days) in the preterm group compared to only 2 stillbirths, 2 neonatal deaths and 1 postneonatal death in the control group. The main causes of death in the preterm group were severe prematurity, infection and congenital abnormalities; in the control group deaths were associated with congenital abnormalities.

Discussion

This manuscript provides information on clinical factors

Table 4: Pre-existing medical conditions.

	Control (≥37 weeks' gestation)	Preterm (<35 weeks' gestation)	P value
Number of deliveries	553	228	
Anaemia	103 (18.6%)	45 (19.7%)	0.72
Respiratory problems	89 (16.1%)	39 (17.1%)	0.73
Depression/ Psychiatric Disease	83 (15.0%)	50 (21.9%)	0.019
Hypertension	51 (9.2%)	34 (14.9%)	0.020
Renal Disease	34 (6.1%)	18 (7.9%)	0.37
Sexually transmitted diseases	33 (6.0%)	16 (7.0%)	0.58
Cardiac disease	24 (4.3%)	9 (3.9%)	0.80
Thyroid Disease	14 (2.5%)	3 (1.3%)	0.29
IVF	12 (2.2%)	6 (2.6%)	0.70
Diabetes	11 (2.0%)	3 (1.3%)	0.52
Hepatitis B	10 (1.8%)	5 (2.2%)	0.72
Bleeding disorders	8 (1.4%)	3 (1.3%)	>0.99*
Uterine abnormalities	10 (1.8%)	14 (6.1%)	0.001
Cervical incompetence/ cervical suture	0	5 (2.2%)	0.002*

*Two-tailed Fisher's Exact test

associated with preterm delivery in a tertiary referral hospital in the UK. The study benefits from its relatively homogeneous ethnic population and its setting in a maternity hospital with unified management guidelines in the central delivery suite. Moreover, it highlights the main risk factors that remain associated with preterm birth, and emphasizes the need to promote research into the basic mechanisms of parturition as the best way to develop effective management for spontaneous preterm labor.

In our predominantly Caucasian population, teenage pregnancies were not significantly associated with preterm birth; however, our data confirm that older mothers have an increased risk of preterm delivery.[12,13] A low BMI is associated with increased risk of spontaneous preterm birth[14] and this was reflected in our population. Previous preterm delivery is a strong risk factor for subsequent preterm birth, with a five fold higher rate of previous preterm delivery in the preterm compared to the control group; this indicates that maternal factors are important, however the mechanism remains unclear. A history of preterm delivery has long been recognised as a strong risk factor for subsequent preterm birth[9] and is the basis for most risk scoring systems.[15] Moreover, our data confirm that hypertension and fetal growth restriction are major predisposing factors for elective preterm delivery.[7,16]

Episodes of threatened preterm labor were strongly associated with spontaneous preterm deliveries. Thus, spontaneous preterm labor is characterized by remarkable uterine hyperactivity. The mechanism requires further investigation but it probably results from increased sensitivity of the uterus to stimulatory agonists such as oxytocin, prostaglandins or other endogenous mediators,[1] as well as a premature loss of inhibitory pathways involving myometrial ion channels.[17] We have recently shown that spontaneous preterm labor is associated with increased GTP bound RHO proteins in myometrial tissue, a pathway for enhanced uterine contractility through calcium sensitization.[18] Uterine contractions are the most common presenting sign of preterm labor but in a high percentage of women the contractions stop without the need for tocolytic treatment.

Table 5: Complications of pregnancy.

	Control (≥37 weeks' gestation)	Preterm (<35 weeks' gestation)	P value
Number of deliveries	553	228	
Maternal complications			
Threatened preterm labour	17/553 (3.1%)	126/228 (55.3%)	<0.001
Vaginal bleeding	130/553 (23.5%)	117/228 (51.3%)	<0.001
Anaemia	53/513 (10.3%)	76/224 (33.9%)	<0.001
Hypertension with proteinuria	43/514 (8.4%)	52/224 (23.2%)	<0.001
Hypertension without proteinuria	13/514 (2.5%)	4/224 (1.8%)	0.54
Urinary tract infection	56/514 (10.9%)	35/224 (15.6%)	0.072
HVS B Strep.	26/514 (5.1%)	12/224 (5.4%)	0.87
HVS Other organisms	70/514 (13.6%)	35/224 (15.6%)	0.47
Hyperemesis	16/514 (3.1%)	3/224 (1.3%)	0.16
Gestational Diabetes	14/514 (2.7%)	4/224 (1.8%)	0.45
Late booker	16/513 (3.1%)	8/223 (3.6%)	0.74
High Down's Risk	16/513 (3.1%)	7/224 (3.1%)	>0.99
Raised AFP	4/513 (0.8%)	6/224 (2.7%)	0.075*
Fetal complications			
Reduced fetal movements	140/514 (27.2%)	76/224 (33. 9%)	0.066
Oligohydramnios	49/514 (9.5%)	65/224 (29.0%)	<0.001
Fetal growth restriction	12/514 (2.3%)	41/224 (18.3%)	<0.001
Large for dates	27/514 (5.3%)	8/224 (3.6%)	0.32
Fetal abnormalities	14/553 (2.5%)	15/228 (6.6%)	0.007
Other complications			
Preterm premature rupture of membranes	5/553 (0.9%)	100/228 (43.9%)	<0.001
Prolonged rupture of membranes	49/553 (8.9%)	49/228 (21.5%)	<0.001

*Two-tailed Fisher's Exact test

Separating imminent spontaneous preterm labor from recurrent but transient episodes of uterine contractions remains a major clinical challenge.

Bleeding in pregnancy was strongly associated with both spontaneous and elective preterm deliveries. Women with vaginal bleeding have an increased risk of induction of labor and cesarean section and the condition is associated with other pregnancy complications such as PPROM, oligohydramnios and fetal growth restriction.[19] The mechanism by which intrauterine bleeding may lead to spontaneous preterm labor is not known, but it has been proposed that thrombin activation in the decidua leads to uterine contractions.[20,21] Moreover thrombin increases matrix metalloproteinase activity in the fetal membranes providing a link between intrauterine bleeding and rupture of the membranes.[21,22]

Anemia is one of the most common nutritional problems in pregnant women throughout the world and, after smoking, is the most important preventable risk factor for preterm birth. Our data show that even moderate anemia (<10.5 g/dl) in pregnancy is associated with preterm birth and this agrees with observations in other tertiary referral hospitals.[23] Ascending intrauterine infection is often quoted as a pathogenic mechanism for preterm labor,[7] however in our survey the proportion of women with bacterial pathogens in high vaginal swabs was similar in the control and preterm groups.

Preterm babies continue to die in the perinatal period or have severe neonatal complications which predispose to a high incidence of neurodevelopmental impairments and sensory deficits. The early administration of glucocorticoids to the mother and impressive advances in neonatal care have steadily

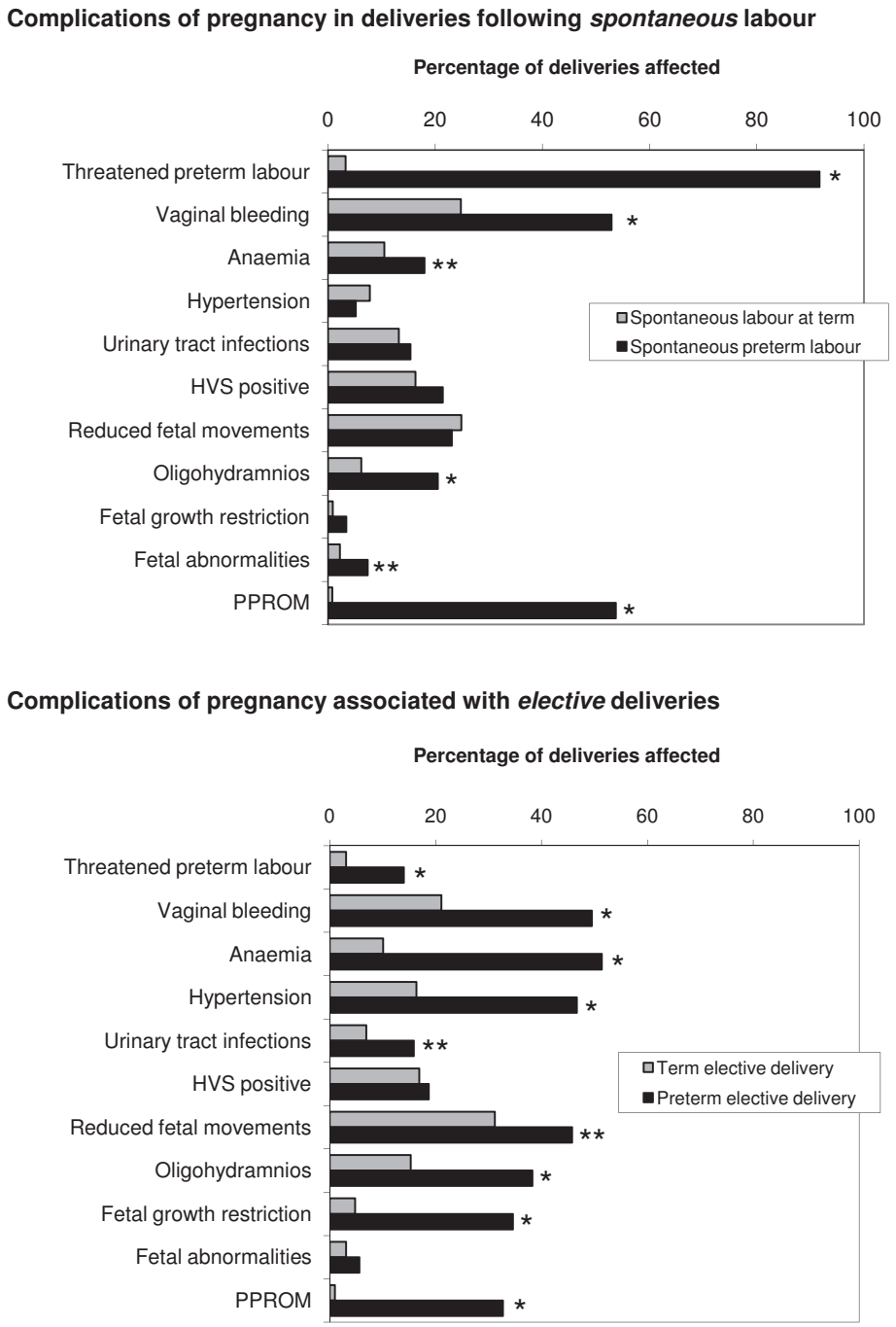


Figure 1. Complications of pregnancy in spontaneous and medically indicated elective preterm deliveries (23-35 weeks' gestation) compared with spontaneous and elective term controls (≥37 weeks' gestation). HVS: high vaginal swab. PPROM: preterm premature rupture of the membranes. Significant differences: * $p < 0.001$; ** $p < 0.05$

improved neonatal survival rates over the past three decades; however it is unrealistic to expect that improvements in neonatal intensive care will decrease neonatal mortality and the sequelae of prematurity much further.[24] The onus is now on understanding the causes and mechanisms of parturition, so that spontaneous preterm labor can be prevented and preterm birth is only allowed to happen electively for the benefit of the mother and her baby.[25] The proportion of elective preterm deliveries in our survey is considerably higher than in similar UK and European hospital populations in the 1970s and 1980s.[6,26] This reflects a growing confidence among young obstetricians that justified intervention in preterm pregnancies results in good obstetric and neonatal outcome, but significant morbidity should not be forgotten.

This study has limitations because it has surveyed a population of several hundred women in a single tertiary hospital. The factors associated with preterm birth would be better addressed through prospective study of a very large geographical cohort. Furthermore, we believe that over the next decade epidemiological data will be supplemented by advances in uterine physiology and materno-fetal endocrinology which will improve our understanding of human parturition and help devise successful strategies to prevent preterm labor.

Conclusions

The data from this study show that more than 50% of preterm births follow spontaneous preterm labor and further research to clarify the mechanism by which risk factors such as increased uterine contractility, premature rupture of the membranes and uterine bleeding result in preterm labor will be clearly beneficial. Moreover, it is important to address the major causes of elective preterm delivery, namely hypertensive disorders and intrauterine growth restriction. This may be achieved through the discovery of the etiology of pre-eclampsia and a better understanding of the control of fetal growth and placental function. The reduction of spontaneous preterm labor is a realistic aim; however our lack of knowledge of the process of labor is a major handicap in devising effective strategies. It is essential to promote research into the physiological and physiopathological pathways that increase uterine activity during pregnancy. The combination of laboratory and clinical research will provide the necessary breakthroughs to improve the prevention of preterm birth.

References

1 López Bernal A: Mechanisms of labor—biochemical aspects. Bjog 2003, 110(Suppl 20):39-45.
2 Tucker J, McGuire W: Epidemiology of preterm birth. Bmj 2004, 329:675-678.
3 Wen SW, Smith G, Yang Q, Walker M: Epidemiology of preterm birth and neonatal outcome. Semin Fetal Neonatal Med 2004, 9:429-435.
4 Martin JA, Kung HC, Mathews TJ, Hoyert DL, Strobino DM, Guyer B, Sutton SR: Annual summary of vital statistics: 2006. Pediatrics 2008, 121:788-801.
5 Beck S, Wojdyla D, Say L, Betran AP, Merialdi M, Requejo JH, Rubens C, Menon R, Van Look PF: The worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity. Bull World Health Organ 2010, 88:31-38.
6 Rush RW, Keirse MJ, Howat P, Baum JD, Anderson AB, Turnbull AC: Contribution of preterm delivery to perinatal mortality. British medical journal 1976, 2:965-968.
7 Goldenberg RL, Culhane JF, Iams JD, Romero R: Epidemiology and causes of preterm birth. Lancet 2008, 371:75-84.
8 Langhoff-Roos J, Kesmodel U, Jacobsson B, Rasmussen S, Vogel I: Spontaneous preterm delivery in primiparous women at low risk in Denmark: population based study. Bmj 2006, 332:937-939.
9 Bakketeig LS, Hoffman HJ, Harley EE: The tendency to repeat gestational age and birth weight in successive births. Am J Obstet Gynecol 1979, 135:1086-1103.
10 Iams JD, Stilson R, Johnson FF, Williams RA, Rice R: Symptoms that precede preterm labor and preterm premature rupture of the membranes. Am J Obstet Gynecol 1990, 162:486-490.
11 Burguet A, Kaminski M, Abraham-Lerat L, Schaal JP, Cambonie G, Fresson J, Grandjean H, Truffert P, Marpeau L, Voyer M, et al.: The complex relationship between smoking in pregnancy and very preterm delivery. Results of the Epipage study. Bjog 2004, 111:258-265.
12 Schempf AH, Branum AM, Lukacs SL, Schoendorf KC: Maternal age and parity-associated risks of preterm birth: differences by race/ethnicity. Paediatric and perinatal epidemiology 2007, 21:34-43.
13 Hall MH, Danielian P, Lamont RL: The importance of preterm birth. In Preterm labor Edited by: Elder MG, Romero R, Lamont RL. New York: Churchill Livingstone; 1997:1-28.
14 Hendler I, Goldenberg RL, Mercer BM, Iams JD, Meis PJ, Moawad AH, MacPherson CA, Caritis SN, Miodovnik M, Menard KM, et al.: The Preterm Prediction Study: association between maternal body mass index and spontaneous and indicated preterm birth. Am J Obstet Gynecol 2005, 192:882-886.
15 Creasy RK: Preventing preterm birth. N Engl J Med 1991, 325:727-729.
16 Steer P: The epidemiology of preterm labor. Bjog 2005, 112(Suppl 1):1-3.
17 Sanborn BM: Relationship of ion channel activity to control of myometrial calcium. J Soc Gynecol Investig 2000, 7:4-11.
18 Lartey J, Smith M, Pawade J, Strachan B, Mellor H, Lopez Bernal A: Up-Regulation of Myometrial RHO Effector Proteins (PKN1 and DIAPH1) and CPI-17 (PPP1R14A) Phosphorylation in Human Pregnancy Is Associated with Increased GTP-RHOA in Spontaneous Preterm Labor. Biol Reprod 2007, 76:971-982.
19 Chan CC, To WW: Antepartum hemorrhage of unknown origin—what is its clinical significance? Acta Obstet Gynecol Scand 1999, 78:186-190.
20 Elovitz MA, Baron J, Phillippe M: The role of thrombin in preterm parturition. Am J Obstet Gynecol 2001, 185:1059-1063.
21 Erez O, Espinoza J, Chaiworapongsa T, Gotsch F, Kusanovic JP, Than NG, Mazaki-Tovi S, Vaisbuch E, Papp Z, Yoon BH, et al.: A link between a hemostatic disorder and preterm PROM: a role for tissue factor and tissue factor pathway inhibitor. J Matern Fetal Neonatal Med 2008, 21:732-744.
22 Stephenson CD, Lockwood CJ, Ma Y, Guller S: Thrombin-dependent regulation of matrix metalloproteinase (MMP)-9 levels in human fetal membranes. J Matern Fetal Neonatal Med 2005, 18:17-22.
23 Lone FW, Qureshi RN, Emanuel F: Maternal anaemia and its impact on perinatal outcome. Trop Med Int Health 2004, 9:486-490.
24 Saigal S, Doyle LW: An overview of mortality and sequelae of preterm birth from infancy to adulthood. Lancet 2008, 371:261-269.
25 Iams JD, Romero R, Culhane JF, Goldenberg RL: Primary, secondary, and tertiary interventions to reduce the morbidity and mortality of preterm birth. Lancet 2008, 371:164-175.
26 Di Renzo GC, Roura LC: Guidelines for the management of spontaneous preterm labor. J Perinat Med 2006, 34:359-366.

Anesthesia for Cesarean Section in the Presence of Multivalvular Heart Disease and Severe Pulmonary Hypertension

Demet Coskun, Ahmet Mahli, Sibel Korkmaz, Figen S. Demir, Gozde Karaca Inan, Dilek Erer, M. Emin Ozdogan

Abstract

Introduction: Pulmonary hypertension is a rare condition and in combination with pregnancy, it can result in high maternal mortality. Mitral stenosis is one of the complicated cardiac diseases that may occur during pregnancy. In this report, we describe our management of such a case, which was even more difficult in combination with pulmonary hypertension, mitral stenosis, and aortic and tricuspid valve insufficiency requiring emergency cesarean section under general anesthesia.

Case presentation: A 29-year-old primipara was presented to the anaesthetic department for an urgent cesarean section with a diagnosis of severe pulmonary hypertension in combination with mitral stenosis. The patient was hospitalized prepartum and received oxygen therapy and anticoagulation with heparin. The patient was monitored during labor and delivery with oximetry and arterial and central venous pressure line. Pulmonary arterial lines were not used due to an increased risk and questionable usefulness. Echocardiography revealed a systolic pulmonary arterial pressure of 75 mmHg, and mitral stenosis, aortic and tricuspid valve insufficiency.

We decided to proceed under general anesthesia. Anesthesia was induced with etomidate, and succinylcholine. Dopamine and nitroglycerin infusion was preoperatively started and infusion was also preoperatively continued. Hemodynamic parameters were stable during delivery. Neonatal weight and apgar score were satisfactory. After the delivery of a healthy baby, oxytocin was administered. Surgery was completed uneventfully. During the postoperative period, the patient received furosemide and morphine. As the arterial blood gas analyses were stable and the chest-ray was normal, the patient was extubated postoperatively in the second hour in ICU.

Conclusion: Patients with significant multivalvular heart disease require careful preoperative, multidisciplinary assessment and anesthetic planning before delivery in order to optimize cardiac function during the peripartum period and make informed decisions regarding the mode of delivery and anaesthetic technique.

Authors Coskun, Mahli, Korkmaz, Demir and Inan are with the Department of Anesthesiology; Erer and Ozdogan are with the Department of Cardiovascular Surgery, Gazi University Faculty of Medicine, Bsevler, Ankara, Turkey.

Introduction

Pulmonary hypertension is a rare condition and in combination with pregnancy, it can result in high maternal mortality. Mitral stenosis is one of the complicated cardiac diseases that may occur during pregnancy. Furthermore, despite the improvements in medical, obstetric, anaesthetic, and intensive care, mortality rates still remain disappointingly high.

In this report, we describe our management of such a case, which was even more difficult in combination with pulmonary hypertension, mitral stenosis, and aortic and tricuspid valve insufficiency requiring urgent Cesarean section under general anesthesia.

Case Report

A 29-year-old Turkish primigravid parturient with a height of 160 cm and a weight of 80 kg was presented to the anesthetic department for an urgent cesarean section with a diagnosis of severe pulmonary hypertension and associated multivalvular disease. At 35 weeks' gestation, she experienced palpitations, shortness of breath, dizziness, and dyspnea so she was referred for cardiology consultation. During examination, a systolic murmur (grade 2/6) was present in all auscultation areas. There was some evidence of pulmonary edema in the chest X-ray; although she did not have hepatomegaly, there was 1+/1+ peripheral edema. The electrocardiogram showed a sinus rhythm of 95 beats.min^{-1} with a normal axis, borderline right ventricular hypertrophy and an arterial blood pressure of 118/62 mmHg. She underwent echocardiography that revealed severe pulmonary hypertension with a systolic pulmonary artery pressure of 75 mmHg and an associated mitral stenosis with a mitral valve area of 1.3 cm^2. The right ventricle was dilated; the echocardiography demonstrated a mild mitral regurgitation, moderate-severe aortic regurgitation and moderate tricuspid regurgitation. Hematological and biochemical investigations were within normal limits except an Hb value of 9,42 gr.L^{-1}. She was hospitalized in coronary intensive care unit and treated with diuretics. At home, she was anticoagulated with low molecular heparin (Clexane), whereas cardiologists started heparin infusion at a rate of 1000 U.hr^{1} when she was hospitalized. Serial ultrasound and cardiotocography tracings confirmed that fetal growth was normal. At 36 weeks' gestation when active labour began, it was decided that she should undergo cesarean section because induction of labor was considered inappropriate.

In the operating room, non-invasive arterial pressure monitoring, 6-lead ECG with ST-segment analysis, and pulse oximetry were applied. She was tachycardic and tachypneic. Preoperative and

perioperative hemodynamic and respiratory parameters were recorded. Preoxygenation and cricoid pressure were applied; general anesthesia was induced with etomidate 0.3 $mg.kg^{-1}$, succinylcholine 1 $mg.kg^{-1}$, and lidocaine 1 $mg.kg^{-1}$. The patient was intubated and ventilated with 100% oxygen until delivery. Arterial and central venous catheterization was attempted, and then invasive arterial pressure and central venous pressure were monitored and arterial blood gas analyses were obtained every two minutes perioperatively. Infusions of glyceryl trinitrate and dopamine were started preoperatively and continued perioperatively. Central venous pressure was maintained at 5-10 mmHg throughout the operation. After a healthy 2,450 g baby was delivered with an Apgar score of 9 at the 1st and 5th minutes and an infusion of oxytocin (20 U for more than 2 hours) was started. Anesthesia was maintained with isoflurane, and 50% nitrous oxide in oxygen and 0,05 $mg.kg^{-1}$ vecuronium, and 100 µg IV fentanyl were administered. During delivery, the patient's pulmonary edema increased, and a decrease in oxygen saturation was observed. Pulmonary edema during delivery was rapidly resolved after diuretic administration. Surgery was completed uneventfully. After the operation, the patient was admitted to the intensive care unit where artificial ventilation and continuous monitorization were continued. During the postoperative period, the patient was sedated using an infusion of propofol and received morphine, furosemide, and glyceryl trinitrate at adequate doses. When the arterial blood gas analyses and the chest-X-ray were normal, the patient was extubated postoperatively in the second hour in the intensive care unit. She was discharged home in good condition after one week following the operation and was advised to undergo cardiac surgery.

Discussion

Cardiovascular stress owing to pregnancy, labor, delivery, and the postdelivery period induce different degrees of cardiac failure in every cardiac patient, and concomitant cardiac medication and therapeutic anticoagulation interfere with the anesthetic management. Adequate cardiovascular invasive monitoring is essential and should be administered and maintained in the postpartum period with the same criteria that reduce morbidity and mortality in cardiac patients undergoing general surgery.

In our case, standard vascular access included a radial artery catheter, an internal jugular central venous line, and a large venous catheter for rapid fluid infusion. We preferred not to attempt to insert central venous and arterial catheters until the patient was intubated as we considered that this procedure would be too stressful for this anxious patient and was likely to result in a further increase in heart rate.

This patient received her diagnosis late in pregnancy, beyond the time at which a therapeutic termination could have been performed. She was managed with a multidisciplinary approach, and her care included cardiologists and obstetricians but she was not consulted to anesthesiologists until delivery. But still, general anesthesia and cesarean section were successfully performed. She received aggressive anticoagulation as deep venous thrombosis and pulmonary embolism are important causes of postpartum mortality in patients with pulmonary arterial hypertension. Cesarean delivery was planned at 36 weeks' gestation to maximize fetal lung maturation and to avoid deterioration in maternal cardiac status.

There are no controlled studies examining the best type of anesthetic technique in these patients, and guidelines and standards are lacking. Although no curative agent has been identified, the practitioners' knowledge of the existing treatment options, pathophysiology, and the implications of various anaesthetic agents and techniques is required to ensure the highest level of patient safety and care. Experts recommend individualizing the anaesthetic management according to the parturient's cardiovascular status and general pathophysiological concepts. Some authors have described the use of general anesthesia with good maternal outcome. However, others have reported increased pulmonary arterial pressure during laryngoscopy and tracheal intubation; moreover, adverse effects of positive-pressure ventilation on venous return may ultimately lead to cardiac failure.

As this patient was anticoagulated aggressively, general anesthesia was preferred. Opioid-based techniques are recommended for anesthesia in patients with valvular disease as they have a minimally depressive action on the cardiovascular system and provide excellent analgesia. But we were concerned that use of opioids in induction could result in respiratory depression of neonate, so fentanyl was not administered until delivery. However, to avoid an increase in systemic and pulmonary pressures resulting from laryngoscopy and tracheal intubation, lidocaine was administered and glyceryl trinitrate infusion was started preoperatively and continued postoperatively. Also, depths of analgesia and anesthesia levels were maintained adequately throughout the surgery in order to avoid tachycardia and hypertension. We tried to provide lower peak inspiratory pressures to avoid these adverse effects of artificial ventilation.

A systolic pulmonary artery pressure of above 50 mmHg is associated with cardiac complications during pregnancy as functional status worsens more rapidly in pregnant than in non-pregnant patients with mitral valve stenosis. Cardiac decompensation and pulmonary edema may occur in pregnant women with overt or silent mitral valve stenosis during the second or third trimester. Fluid restriction, diuretics, and control of atrial fibrillation are basic measures that can prevent pulmonary congestion.

The postpartum period is the most critical period for acute pulmonary hypertension decompensations. Symptomatic therapy during the postpartum period may include inhaled nitric oxide and epoprostenol infusion or inhaled iloprost. For women with unexpected primary pulmonary hypertension who need emergency cesarean section, inhaled nitric oxide is used. In this case, pulmonary edema that occurred after delivery was resolved with diuretics with no need of using inhaled nitric oxide or other pulmonary vasodilators.

Conclusion

Patients with significant multivalvular heart disease require careful preoperative, multidisciplinary assessment and anaesthetic planning before delivery in order to optimize cardiac function during the peripartum period and make informed decisions regarding the mode of delivery and anesthetic technique. Particularly the period after delivery carries a high risk of maternal death. Therefore, prolonged intensive care for both pre and postpartum periods is essential.

GE Healthcare

The Giraffe Family

The best of all worlds

Exceptional healing environments for high-acuity newborns

Designed to address the changing demands of the NICU patients, you can count on Giraffe to provide:

- Comfortable, consistently controlled thermal environments
- Developmentally-supportive, family-centered care solutions
- Improved patient access and visibility
- User-friendly, high tech features and functionality
- Reliable clinical performance
- Reduced stress for the patient, the caregiver and the family

Giraffe OmniBed
There's just no other bed like this.

Giraffe Warmer
Reshaping neonatal care

Giraffe Incubator
Promoting healthy growth