NEONATOLOGY TODAY

News and Information for BC/BE Neonatologists and Perinatologists

Volume 7 / Issue 10
October 2012

IN THIS ISSUE

Upcoming Medical Meetings
(See website for additional meetings)

Contemporary Management of Neonatal Pulmonary Disorders Conference
Nov. 1-2, 2012; Tempe, AZ USA
www.nalweb.com/cmnpdconference

3rd International Congress of UENPS Congress
Nov. 14-17, 2012; Porto, Portugal
www.uenps2012.org/uenps

Hot Topics in Neonatology Conference
Dec. 3-4, 2012; Washington, DC USA
www.hottopics.org

NEO: The Conference for Neonatology
Feb. 21-24, 2013; Orlando, FL USA
www.neoconference.com

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Neonatology Today (NT) is a monthly newsletter for Neonatologists and Perinatologists that provides timely news and information regarding the care of newborns and the diagnosis and treatment of premature and/or sick infants.

Wolff-Parkinson-White (WPW) Syndrome Causing Cardiogenic Shock and Multi-Organ Failure in Greenlandic Newborn

By Karen Bjorn-Mortensen, MD; Inga Hjuler, MD; Nikolaj Ihlemann, MD

Key words: arrhythmia, tachycardia, heart failure, multiorgan system failure, acute metabolic derangement

Abbreviations: None

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A 5-week old infant, born 4 weeks before term and previously healthy, was admitted to Dronning Ingrid's Hospital with respiratory distress, supraventricular tachyarrhythmia, severe metabolic acidosis, intestinal bleeding and abnormal kidney and liver function.

The boy was reported as a previously healthy baby boy until two days prior to hospitalization. The parents contacted the local nursing station in an isolated village outside one of Greenland's northernmost cities due to, what the parents described as sudden coldness of the infant's extremities and cheeks. The baby had been crying during the night for 2 days, but had been well during the day. Feces had turned green, but otherwise, the boy had showed normal responses in respect to eating, drinking and urine output.

At the local nursing station, the boy was diagnosed as having pneumonia due to laxity, cyanosis and tachypnea. An oral antibiotic was started, since nobody present was qualified to gain intravenous access.

Before arriving in Nuuk, the capital of Greenland, another 24 hours was spent at a local hospital in Northern Greenland where doctors made the diagnose of pneumonia and continued antibiotic treatment with intramuscular injection of ampicillin. The reports were of a critically-ill infant, who needed to be evacuated as soon as possible. Due to the local weather conditions, the boy and his mother did not reach Nuuk until 4 days after onset of symptoms.

At the time of admittance to Dronning Ingrid's Hospital, the boy had tachypnoea of 100 breaths per minute and tachycardia with a heart rate of 280, but peripheral saturation and capillary responses were normal. Venous gases showed a metabolic acidosis with respiratory compensation, with Base excess -14 mmol/l, pH 7.34, pCO_2 29 kPa and pO_2 69. No significant leucocytosis and only a small rise in C-reactive protein were present. Blood sugar was very low 0.6 mmol/L.

An ECG showed a regular tachyarrhythmia with narrow complexes (see Figure 1); chest

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*A post hoc analysis excluding Retinopathy of Prematurity (ROP); photoreceptor sensitivity assessed by full-field electroretinogram.

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Abbott
A Promise for Life

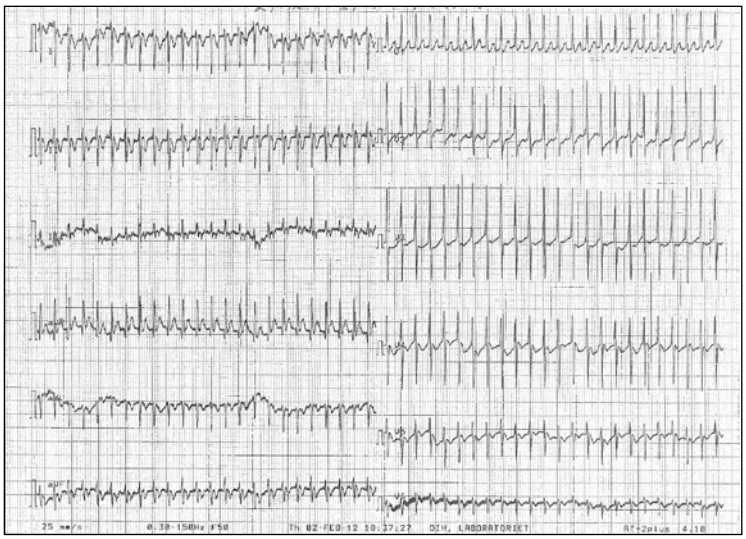

Figure 1: Initial ECG, showing a fast regular tachyarrhythmia with narrow complexes.

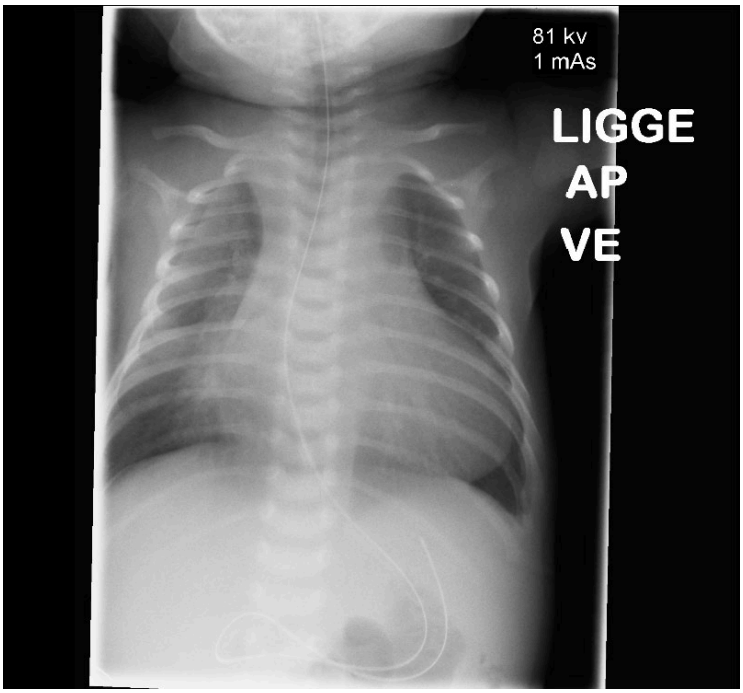

Figure 2: Initial chest x-ray. The heart shadow shows a dilated heart.

x-ray and echocardiography (see Figure 2) showed a massively dilated heart with decreased contractility, but no structural abnormalities.

On the suspicion of a septic state with cardiogenic impact, intravenous ceftriaxon and fluids were started immediately after arrival. To ease the infant's breathing he was treated with C-PAP and the hypoglycemia with 10% glucose.

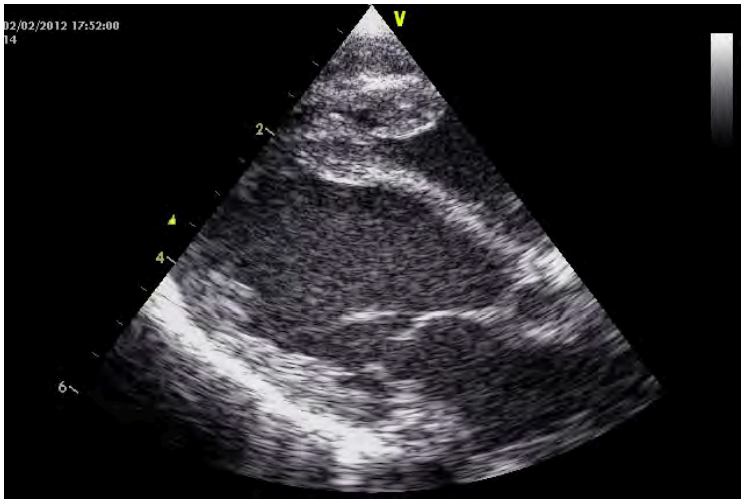

Figure 3: Echocardiography on the morning after conversion to sinus rhythm. Parasternal view showing a dilated left ventricle, left ventricle internal diameter of 24 mm.

In an attempt to convert the supraventricular tachycardia, intravenous adenosine was given in a dose of first 150 µg/kg; then a dose of 300 µg/kg repeated two times was administered with no effect. Hereafter, a loading dose of digoxin was supplied with no immediate effect, and two more doses were planned. After a while the heart rhythm briefly changed to ventricular tachycardia, and then finally changed to sinus rhythm, with a heart rate of 185. A new echocardiography showed some improvement in the contractility, but the heart was still dilated.

Despite conversion to sinus tachycardia the infant's condition worsened during the next hour. Black, sweetly smelling feces were noted, the bowels turned silent, the stomach bloated and blood appeared in the nasogastric probe. Intravenous pantoprazole was given and blood transfusions prepared. Suddenly the boy turned grey, had apnea and desaturations, and was quickly intubated. New gases showed severe acidosis with pH 7,00, Base excess -21.[4,9] Blood samples showed a high creatinine and carbamide, and since the boy had not been urinating since a catheter was placed in the bladder at arrival, acute kidney failure was suspected. Altogether the boy was diagnosed with a probable intraabdominal disaster causing severe septicemia resulting in multi-organ failure. Due to the severe lacidosis, kidney failure, liver failure, decreased contractility of the heart and apnea, treatment seemed difficult and hopes of the boy surviving were small.

Despite all odds the boy did not die. A couple of hours later he had turned pink, muscle tone, reflexes, respiration and pulse had normalized and the boy seemed hungry. Repeated venous gases, creatinine, carbamide and liver values gradually normalized. Diapers were repeatedly wet, and feces turned to a normal color again. His stomach was soft and bowel sounds normal.

A new echocardiogram showed an almost normally contracting heart and an almost normal heart size (see Figure 3), with a further reduction in heart size on the second day after conversion (see Figure 4). Heart rate was normal.

Due to exhaustion he still needed C-PAP, but during the next 12 hours his condition continued to improve until his heart rate suddenly switched to a supraventricular tachyarrhythmia again. A higher dose of Adenosine was given which instantly converted his heart rate back to normal. ECG recorded, showed a characteristic delta wave (see Figure 5), and the diagnosis of Wolff-Parkinson-White Syndrome was made. Treatment with beta blocker was initiated to prevent further tachyarrhythmia.

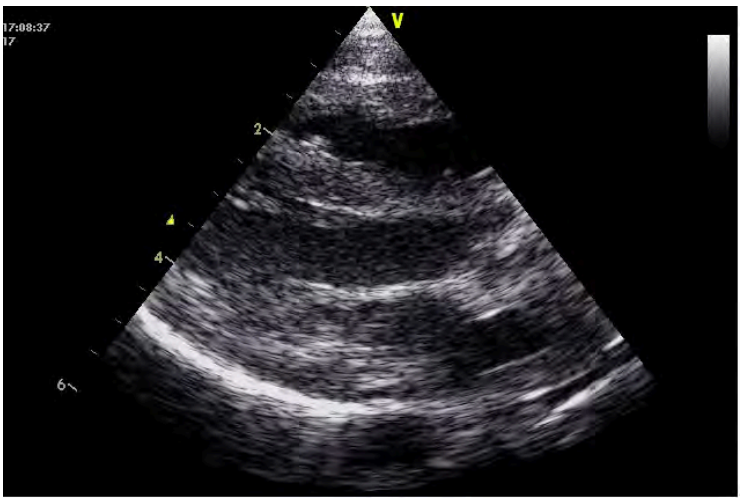

Figure 4: Echocardiography two days after conversion to sinus rhythm. Parasternal view showing a normal ventricle, left ventricle internal diameter of 19 mm.

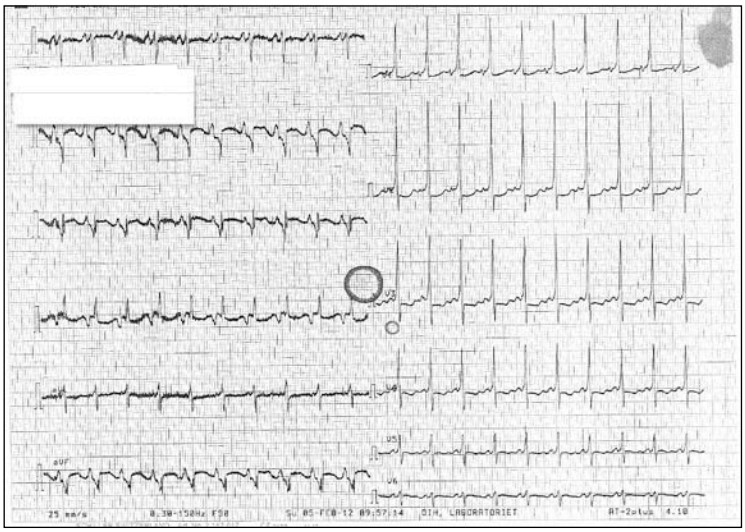

Figure 5. ECG after conversion with adenosine. Regular sinus rhythm with characteristic delta waves most prominent in V1-V3.

Discussion

Fetal and neonatal cardiac arrhythmias are not common, but well-known; the same is true for infants as well. We report this case not only because of the finding of Wolff-Parkinson-White Syndrome, but also because of the unusual presentation of the infant's condition. Due to local and geographical conditions the boy had been ill for four days before reaching our department. Most likely he survived four days with a WPW tachyarrhythmia without treatment. The incessant tachyarrhythmia caused a cardiogenic shock and multi-organ failure making it difficult to determine whether the case was a primary arrhythmia or arrhythmia due to septicemia. Rarely do doctors get to follow the symptoms and complications caused by an untreated cardiac arrhythmia in infants. Reduced left ventricular function,[1] palpitations, syncope, chest pain, heart failure and cardiogenic shock have all been reported and associated with WPW,[2] but the presentation with cardiogenic shock and multi-organ failure is not common. Heart failure due to WPW is more often seen in infants at an older age[3] and only after prolonged period of untreated supraventricular tachycardia.[4]

The prognosis of WPW presenting before 1 year of age is usually good, with the disappearance of the syndrome in more than 80% of cases;[5] preventive treatment with beta blockers is possible without long-term side effects. Treatment with radio frequency catheter ablation is possible,[6] but should be postponed until the child weights approximately 15 kg, and is at least age 12 months, especially as a high percentage of very young children show spontaneous resolution.

In this case long-term prognosis had been irrelevant, if the attempt to convert his supraventricular tachycardia had been unsuccessful. Even though we suspected a late state of septicemia, the infant was still treated with adenosine and digoxin, possibly leading to a change in heart rhythm. The importance of differential diagnosis in pediatric patients with severe metabolic acidosis and multi-organ failure is clear.

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Biographical Sketch of Corresponding Author

Graduated from the University of Copenhagen, Denmark, in January 2010. Since then she has been working as a physician at Queen Ingrids Hospital in Nuuk, Greenland, her main focus being internal medicine, infectious diseases and pediatrics. Currently she is working with primary care and doing research on HIV and tuberculosis in Greenland.

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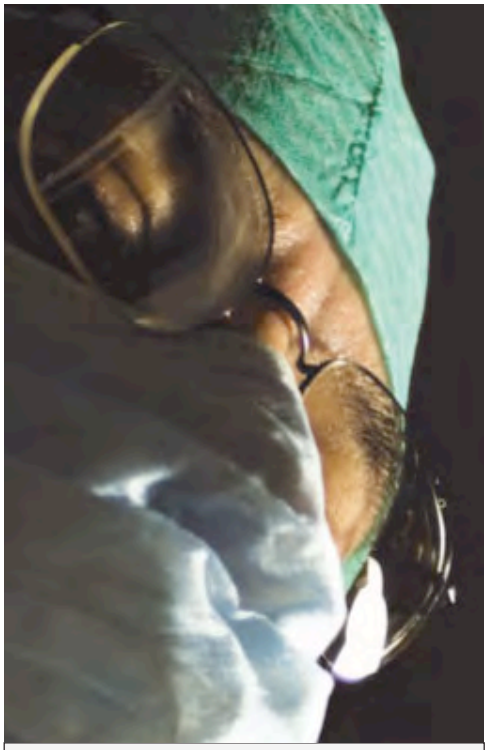

NEONATOLOGY TODAY

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- Optionally, a picture of the author(s) may be submitted.
- No abstract should be submitted.
- The main text of the article should be written in informal style using correct English. The final manuscript may be between 400-4,000 words, and contain pictures, graphs, charts and tables. Accepted manuscripts will be published within 1-3 months of receipt. Abbreviations which are commonplace in pediatric cardiology or in the lay literature may be used.
- Comprehensive references are not required. We recommend that you provide only the most important and relevant references using the standard format.
- Figures should be submitted separately as individual separate electronic files. Numbered figure captions should be included in the main Word file after the references. Captions should be brief.
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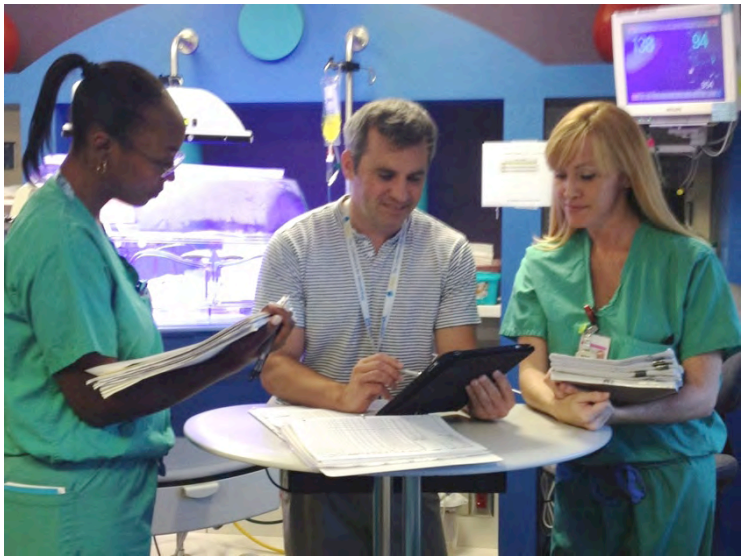
Using an iPad in the NICU

By Benton E. Cofer, MD

I acquired my first iPad approximately two years ago. I use it extensively both personally and professionally. In my personal opinion, the only limit to its use is the user. For me, it is an eReader, consultant, reference library, networker, note pad, and personal assistant. I have found a handful of apps and techniques that make my iPad a wonderful resource in the NICU and I will share these.

The first and most obvious categorical use involves direct patient care employments. The iPad's portability makes it an easy staple for patient rounds. With a secure hospital Wi-Fi connection, I pull up patient labs at the bedside right at the point of care. I do this daily when making rounds and it is a tremendous tool for streamlining patient care. I can also pull up patient x-rays for viewing at the bedside, another huge step in quality and efficiency of care. The patient care team in our facility uses a handwritten flow sheet to collect daily patient data for rounding and formulating a plan. I have an app called *Notetaker HD* which allows me to annotate PDF files. I use *Notetaker HD* to fill out a scanned copy of the flow sheet and then print it. Essentially, I never have to find a blank flow sheet and am always prepared to gather the data that I need in the proper format. This can be done with virtually any form that is filled out with any frequency. In theory, as the electronic medical record evolves, one will be able to do all documentation quickly and efficiently at the bedside on the iPad.



I use my iPad extensively for administrative tasks. Obviously, having portable email is the cornerstone of these uses. I also use an app called *Dropbox* for a number of operations. I currently serve as the secretary for my practice's weekly business meeting. I use *Notetaker HD* to complete the minutes and then email them to a Google Group for the practice so that all members receive the minutes very promptly. Any document that I have in electronic format can be shared by way of our Google Group or by providing a link in *Dropbox*. Once again, any electronic document that I receive by email can be opened in *Notetaker HD*, signed and returned by email. Many times, if I have a paper copy of a document that I wish to share with the rest of my practice, I photograph it with my iPhone and then send the photo to our Google Group. Lastly, I use the iPad's *Reminders* app to organize my to-do list and stay on track.

My iPad is a tremendous portable resource for obtaining desired information. I have a number of textbooks stored in the eReader app, Kindle for iPad. This places an entire library at my fingertips while attending in the NICU. There are also a large number of online resources for physicians and many of these can be easily accessed using an iPad. This can be done quickly at the bedside and I take advantage of these resources often. With *Keynote* for iPad, I can also very quickly and efficiently put together a short slideshow presentation for residents and staff which can be done before, after, or during rounds.

My Top Five iPad Apps for the NICU

Alpha Calc:
Alpha Calc is a universal calculator app for iPhone and iPad. It has a great user interface with buttons that are large and easy to press. The best part is that it allows the user to add customizable buttons for frequently used numbers. This works great in the NICU where all fluid calculations are done in mL/kg/day. I have my keypad set up with buttons for every 10 mL increase starting with 80 and going to 160. I also have a button for 24 as most calculations are done for 24 hrs/day. This allows for easy hourly rate calculations. As such, I can perform fluid calculations very quickly and easily. There are also plans in the works to release an upgrade with specific NICU functions and buttons.

NICU Tools:
NICU Tools is not available in the app store, but is a free mobile web app. It can be added to one's home screen by visiting : http://mobile.nicutools.org on the iPad or iPhone. The user can then add the page to their home screen for easy access. NICU Tools provides a quick plug in for calculating Glucose Delivery, Preterm Outcomes, and more.

Kindle for iPad:
Kindle for iPad is my go to ebook reading app. A number of text books are available for download from the Amazon Kindle store. These textbooks can then be accessed with the app on iPad or iPhone.

Note Taker HD:
Note Taker HD is a great app for taking notes on the iPad. I have a stylus that I use to write simple notes in the app. You can also import PDF files and use them as a background to write directly on.

3D Brain:
This is a really great app whether you are in the medical field or not. It has beautiful graphics and smooth manipulation of the structures. Everything is well labeled, and there are multiple views of different brain structures. I actually use this app to explain common brain pathology to the parents of my patients. It's free to download from the app store.

All the apps mentioned above except NICU Tools can be found at the Apple Store

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Medical News, Products & Information

Newly-Published Study Compares SURFAXIN® with Animal-Derived Surfactants in Well-Established Model of RDS

Discovery Laboratories, Inc. a specialty biotechnology company dedicated to advancing a new standard in respiratory critical care, announced the publication of SURFAXIN® (lucinactant) preclinical data in Pediatric Research. Using a well-established preterm lamb model of Respiratory Distress Syndrome (RDS), study investigators concluded that early intervention with SURFAXIN may mitigate progression of pulmonary pathophysiological consequences of RDS when compared with the animal-derived surfactants Curosurf® and Survanta®. The newly-published data can be found in the September 2012 issue of *Pediatric Research*, a peer-reviewed medical journal widely read by academic neonatologists and other neonatal health care professionals.

According to study findings, subjects receiving surfactant replacement therapy (SRT) using SURFAXIN® had improved sustained oxygenation and lower ventilatory pressure requirements ($p < 0.05$) compared with no SRT or SRT using Curosurf or Survanta. In addition, SURFAXIN® treatment resulted in an attenuated lung and systemic inflammatory response as well as a more uniform and robust preservation of lung structural integrity.

“Findings such as these improve our understanding of the role of SURFAXIN® in modulating lung inflammation and preserving lung structure, and suggest that SURFAXIN® may provide protection to the lung on both a mechanical and cellular level for potentially improved clinical outcomes,” said Dr. Marla R. Wolfson, lead investigator and Professor of Physiology, Pediatrics, and Medicine at the Temple University School of Medicine. “The use of this RDS model allows us to further our understanding of potential mechanistic differences between surfactants in a way that may explain observations from clinical trials.”

Investigators found that the lungs of preterm lambs that were treated with SURFAXIN® were more homogenously expanded both within and between lung regions, a finding that is suggestive of more uniform distribution of surfactant throughout the lung. Investigators also found that the lungs of SURFAXIN-treated lambs had less cellular debris and fewer inflammatory cells when compared with the lungs of non-treated lambs and the lambs treated with Curosurf and Survanta. The investigators also noted lower levels of inflammatory mediators following treatment with SURFAXIN compared with negative controls as well as both animal-derived surfactants.

RDS is a condition in which premature infants are born with an insufficient amount of pulmonary surfactant, a substance produced naturally in the lungs and essential for breathing. Today, infants with RDS often require surfactant replacement therapy along with mechanical ventilation to survive. Approximately 90,000 premature infants in the United States are treated annually with currently available animal-derived surfactants made from cow or pig lung extract.

This is the first publication of these data, which have been presented previously in part at medical conferences. The study was funded in part by a grant from Discovery Laboratories, Inc. Dr. Marla Wolfson does not have a financial interest in Discovery Laboratories, Inc.

SURFAXIN (lucinactant intratracheal suspension) is the first surfactant approved by the United States Food and Drug Administration in the 21st century and the only approved synthetic, peptide-containing surfactant. SURFAXIN® is indicated for the prevention of Respiratory Distress Syndrome (RDS) in premature infants at high risk for RDS. The safety and efficacy of SURFAXIN for the prevention of RDS in premature infants was demonstrated in a large, multinational phase 3 clinical program that included 1294 patients. Discovery Labs anticipates that SURFAXIN will be commercially available in late 2012.

SURFAXIN® (lucinactant intratracheal suspension) is intended for intratracheal use only. The administration of exogenous surfactants, including SURFAXIN®, can rapidly affect oxygenation and lung compliance. SURFAXIN® should be administered only by clinicians trained and experienced with intubation, ventilator management, and general care of premature infants in a highly supervised clinical setting. Infants receiving SURFAXIN should receive frequent clinical assessments so that oxygen and ventilatory support can be modified to respond to changes in respiratory status.

Most common adverse reactions associated with the use of SURFAXIN® are endotracheal tube reflux, pallor, endotracheal tube obstruction, and need for dose interruption. During SURFAXIN® administration, if bradycardia, oxygen desaturation, endotracheal tube reflux, or airway obstruction occurs, administration should be interrupted and the infant’s clinical condition assessed and stabilized. SURFAXIN is not indicated for use in acute respiratory distress syndrome (ARDS).

For more information about SURFAXIN, please visit www.surfaxin.com.

Gene 'Switch' May Explain DiGeorge Syndrome Severity

The discovery of a 'switch' that modifies a gene known to be essential for normal heart development could explain variations in the severity of birth defects in children with DiGeorge Syndrome.

Researchers from the Walter and Eliza Hall Institute made the discovery while investigating fetal development in an animal model of DiGeorge Syndrome. DiGeorge Syndrome affects approximately one in 4,000 babies.

Drs. Anne Voss and Tim Thomas led the study, with colleagues from the institute's Development and Cancer division, published today in the journal *Developmental Cell.*

Dr. Voss said babies with DiGeorge Syndrome have a characteristic DNA mutation on chromosome 22 (22q11 – chromosome 22, long arm, band 11), but exhibit a range of mild to severe birth defects, including heart and aorta defects. "The variation in symptoms is so prominent that even identical twins, with the exact same DNA sequence, can have remarkably different conditions," she said. "We hypothesised that environmental factors were probably responsible for the variation, via changes to the way in which genetic material is packaged in the chromatin," Dr Voss said.

Chromatin is the genetic material that comprises DNA and associated proteins packaged together in the cell nucleus. Chemical marks that sit on the chromatin modify it to instruct when and where to switch genes on or off, making a profound difference to normal development and cellular processes.

The research team found a protein called MOZ, the 'switch' which is involved in chromatin modification, was a key to explaining the range of defects seen in an animal model of DiGeorge Syndrome. "MOZ is what we call a chromatin modifier, which means it is responsible for making marks on the chromatin that tell genes to switch on or off," Dr. Voss said.

"In this study, we showed that MOZ regulates the major gene, called Tbx1, in the 22q11 deletion. Tbx1 is responsible for heart and aortic arch development. In mouse models that have no Moz gene, Tbx1 does not work properly, and the embryos have similar heart and aorta defects to those seen in children with DiGeorge Syndrome. We showed that MOZ is crucial for normal activity of Tbx1, and the level of MOZ activity may contribute to determining how severe the defects are in children with DiGeorge Syndrome," Dr Voss said.

Dr. Voss said the study also showed that the severity of birth defects in DiGeorge Syndrome could be compounded by the mother's diet, particularly if the MOZ switch is not working properly. The research team showed that reduced MOZ activity could conspire with excess retinoic acid (a type of vitamin A) to markedly increase the frequency and severity of DiGeorge Syndrome.

"In our mouse model, we saw that retinoic acid exacerbated the defects seen in mice with mutations in the Moz gene. In fact, in mice that had one normal copy of MOZ and one mutated copy, the offspring look completely normal, but if the mother's diet was high in vitamin A, the offspring developed a DiGeorge-like Syndrome. This suggests that MOZ, when coupled with a diet high in vitamin A (retinoic acid), may play a role in the development of DiGeorge Syndrome in some cases.

"This interaction between the chromatin modifier MOZ, the Tbx1 gene, and retinoic acid in the diet gives a rare insight into how the environment and genetic mutations can interact at the chromatin level to cause birth defects."

The work is supported by the National Health and Medical Research Council of Australia, British Heart Foundation, Australian Stem Cell Centre and the Victorian Government.

BabyFirst's Hot Topic Panel Webinar Series

Neonatal webinars are supported by Drager Medical Systems and NICU University[sm]. Sit down with their Key Opinion Leaders as they discuss the hot topics in neonatology. You will also be able to ask questions directly to the Key Opinion Leaders through an online forum.

The topic on Webinar 1 is "NICUization of Labor & Deliver" and begins on October 18th and will be available for 3 weeks.

The topic on Webinar 2 is "Non-Invasive" in Neonatal Care: Is Less More?" and begins on November 15th and will be available for 3 weeks.

To watch these webinars, or to learn more information go to: www.babyfirst.com. You may also follow them on Twitter - @BabyFirstNews1

Ochsner Medical Center Installs a Free Webcam Service in the NICU

PRNewswire -- In May, Ochsner Medical Center installed a free webcam service in the Neonatal Intensive Care Unit (NICU), thanks to a generous donation from the Brees Dream Foundation, founded by Drew and Brittany Brees. These cameras became especially important during Hurricane Isaac, when many parents had to evacuate without their babies or were unable to visit the hospital.

The NICVIEW cameras allow a view into Ochsner's 42 NICU beds so parents can be with their babies virtually when they cannot be there physically. The NICVIEW web service allows those with a hospital-issued username and password to watch a secure, continuous video stream of their new bundle of joy.

After Hurricane Isaac subsided on Thursday, August 30th, Paige and Paul Prechter were finally able to visit their five and a half week old twin daughters, Juliana and Savana. They had been watching them via the NICVIEW cameras during the storm.

"They were safer here at Ochsner than at home because of power [issues]," Paige said. "It was very comforting to know that we were able to see them. Being able to see that they were okay made you feel great inside." She added, "We got a bit spoiled by the NICVIEW cameras. It's the next best thing you can get to seeing them in person."

"Parents need a sense of security, especially on a night like tonight," said Harley Ginsberg, MD, Section Head, Neonatology, Ochsner Medical Center, late on the evening of August 28th. "Even though they had to relocate, they know their child is safe and sound here at Ochsner."

DECEMBER MEDICAL MEETING FOCUS

Hot Topics in Neonatology (Dec. 3-4)
and
Neonatal Quality at Hot Topics (Dec. 2)
Washington, DC USA
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Hot Topics Agenda Include:
- In Utero Therapies
- Probiotics and NEC
- Cooling and ECMO
- Delivery Room Management of Babies
- High Flow Nasal Cannula and CPAP
- Breaking News

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- *Jay Greenspan, MD, MBA*; Robert L. Brent Professor and Chairman; Department of Pediatrics; Nemours / Alfred I. duPont Hospital for Children / Thomas Jefferson University

Keynote Speaker: Thomas H. Hansen, MD

Hot Topics Faculty Includes: *Beau Batton, MD; Robert L. Brent, MD, PsD, Dsc; Lugi Cattarossi, MD; David A Clark, MD; Roberto Copettu, MD; Jennifer F. Culhane PhD, MPH; Peter Davis, MD, MBBS; David Dysart, MD; David Field, DM; Alan W. Flake, MD, Holly L Hendrick, MD; Jerold F. Lucey, MD, FAAP; Helmut D. Hummler, MD, MBA; Bo Jacobson, MD, PhD; Anup Katheria, MD; Haresh Kirpalani, MD; Matthew M Laughon, MD, MPH; Brett James Manley, MBBS, FRACP; Richard Poulin, MD; Thomas Shaffer, MSE, PhD; John W. Sleasman, MD; Alan R. Spitzer, MD; David Stevenson, MD; Karl G. Sylvester, MD; Andrew R. Wilkinson, MD, ChB, FRCP, FRCPCH; Bradley A. Yoder, MD*

Hot Topics Moderators: *David Edwards, MBBS, DSc, FMed Sci; Avroy A. Farnoff, MD; Eric Gibson, MD; Jay S. Greenspan, MD, MBA*

Neonatal Quality at Hot Topics Agenda Include:
- Quality Initiatives
- Reducing Infant Mortality

Neonatal Quality at Hot Topics Program Director:
- *Ursula Nawab, MD*; Assistant Professor of Pediatrics; Thomas Jefferson University; Clinical Director of Intensive Care Nursery; Thomas Jefferson University Hospital

Neonatal Quality Faculty Includes: *Allen Fischer, MD; Brian Glybb, BS, RRT; Uma Kotagal, MBBD, MSc; Stephen T. Lawless, MD, MBA; Raymond Malloy, RRT, MHA; Stephen A. Pearlman, MD, MSHQS; James Pelegano, MD, MS; Kenneth I. Shine, MD; Alan R. Spitzer, MD; Eric J. Thomas, MD, MPH; Lloyd N. Werk, MD, MPH; David Wirtschatter, MM, MSc*

See website for additional details

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Documenting Women's Experiences with Chromosome Abnormalities Found in New Prenatal Test

We often hear that "knowledge is power." But, that isn't always the case, especially when the knowledge pertains to the health of an unborn child, with murky implications, at best. A new study, led by researchers from the Perelman School of Medicine at the University of Pennsylvania, begins to document this exception to the general rule.

Barbara Bernhardt, MS, CGC, a genetic counselor at the Hospital of the University of Pennsylvania, and colleagues contacted a small group of women who are participating in a larger Columbia University study investigating the use of a genetic test called a DNA microarray to identify the possibility of prenatal chromosomal abnormalities. Bernhardt is also Co-Director of the Penn Center for the Integration of Genetic Healthcare Technologies.

The study's goal: To document a woman's experience upon learning that her child's genetic material contained chromosomal abnormalities. The women's responses to this type of news were mostly negative, ranging from saying they "needed support" after getting the results to describing the results as "toxic knowledge," that they wish they hadn't received.

DNA microarrays represent a relatively new approach to genetic testing. Classically, chromosomal abnormalities are detected with karyotyping, which uses DNA staining and microscopy to identify such large-scale abnormalities as trisomy 21, associated with Down's Syndrome. Yet the technique lacks the resolution to detect smaller – yet still significant -- chromosomal changes.

That's where DNA microarrays come in. Microarrays use an array of DNA "probes" to search for matching bits of DNA from across the genome. In theory, if a piece of DNA is missing or duplicated, that change can be detected on a microarray, even if it is too small to be detected by karyotyping.

DNA microarrays are often used by physicians following birth to identify chromosomal abnormalities in children with unexplained developmental delays or congenital defects. However, the technique is also being applied prenatally. The problem, though, unlike some genetic changes that definitely lead to disease, is that the significance of the changes DNA microarrays identify (called copy-number variants) isn't always clear. Nor is it necessarily obvious what actions parents, doctors, and genetic counselors should take in light of the findings.

Bernhardt set out to document the experiences of women receiving such information. Of the 4,450 women enrolled in the Columbia University trial, Bernhardt and her team selected 54 who had received chromosome microarray results that showed abnormalities in the previous six months. Of those, they interviewed 23 regarding the subjects' recollections of their informed-consent discussions, genetic counseling, test results, and follow-up.

The team identified five "key elements" that describe the women's experiences:

- "An offer too good to pass up." Many of the women accepted the offer for testing because it was offered at no cost and posed no additional risk to them or their unborn child. Yet they did so without necessarily considering the potential significance and ambiguity of the information they could receive.
- "Blindsided by the results." Women reported being caught off-guard by the microarray data, which generally arrived one to two weeks after preliminary (and seemingly normal) karyotype information.
- "Uncertainty and unquantifiable risks." Women had difficulty making sense of the test results, as copy-number variants are often of either uncertain clinical significance, or produce a wide array of possible developmental outcomes. As a result, the women's time-critical and emotionally charged decisions about whether to terminate a pregnancy, for instance, were complicated.
- "Need for support." The women reported needing support from counselors, spouses or partners to digest and consider the information they had received and to make critical decisions regarding their pregnancies.
- "Toxic knowledge." The women noted that in many cases the array results constituted "toxic knowledge" that they, in retrospect, wish they hadn't learned, because it negatively impacted their pregnancy, birth, and postnatal experiences. As Bernhardt describes it, "They watch their babies like hawks, … always waiting for the other shoe to drop."

According to Bernhardt, chromosomal microarrays pose the same ambiguities after birth as prenatally. The difference is that postnatal testing is done because the child already exhibits an unexplained abnormality, and physicians hope the test can pinpoint its cause. "But when you find [an abnormality] in a fetus it puts the woman and couple into a tailspin because they have no clue what to expect," she says. "And the couple is immediately faced with whether or not to terminate the pregnancy."

The take-home message, Bernhardt says, is that genetic counselors must be prepared to spend more time with parents to help them explore their reasons for wanting microarray testing. Counselors also need to emphasize to parents the potentially ambiguous nature of the microarray results, how to consider potential responses, and how to make the best decisions they can based on both available scientific data and the clients' beliefs.

The study, "Women's experiences receiving abnormal prenatal chromosomal microarray testing results," was published online September 6 in the *Journal Genetics in Medicine*. Additional authors include Penn researcher Danielle Soucier; as well as Karen Hanson, Melissa Savage, and Ronald Wapner from Columbia University College of Physicians and Surgeons; and Laird Jackson, Drexel University College of Medicine.

This work was supported by funding from the National Human Genome Research Institute, National (P50HG004487) and from the National Institute of Child Health and Development (R01HD055651-01 and R01HD055651-03S1).

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Coping Skills, Marital Satisfaction Help Pregnant Moms Manage Stress When Fetus Has Heart Defect

Newswise — Expectant mothers who learn from prenatal diagnosis that they are carrying a fetus with a congenital heart defect (CHD) commonly suffer post-traumatic stress, depression and anxiety. However, a healthy relationship with one's partner and positive coping mechanisms can reduce this intense stress, according to new research from the Cardiac Center of The Children's Hospital of Philadelphia.

The study was published in the September 2012 issue of *The Journal of Pediatrics.*

"Receiving the news of carrying a fetus with a CHD is a stressful event which can potentially influence a mother's anxiety level," said study leader Jack Rychik, MD, Medical Director of the Fetal Heart Program in the Cardiac Center

at The Children's Hospital of Philadelphia. "Prenatal diagnosis is helpful in that it gives parents time to learn about the defect, review treatment options, plan for necessary interventions and consider their options. While this is intrinsically a stressful time for parents, there has previously been little research on the details of this stress and ways to buffer it."

The researchers surveyed 59 pregnant mothers, ranging in gestational age from 17 to 31.5 weeks, who were recruited by nurse coordinators at either the initial visit to the Fetal Heart Program or a follow-up visit, then followed throughout the rest of their gestation. Participants intended to continue the pregnancy, and to plan for follow-up with the Fetal Heart Program. All were carrying fetuses with serious CHD requiring neonatal evaluation and postnatal surgical or catheter-based intervention within the first six months of life.

Using psychological evaluation tools and self-report instruments, the study team measured traumatic stress, depression and anxiety among the mothers. The researchers also measured partner satisfaction and collected demographic data.

More than 39% of the women experienced clinically important traumatic stress, 22% experienced depression, and 31% experienced state anxiety. Lower partner satisfaction and lower income were both associated with higher levels of depression, anxiety and traumatic stress. When the researchers controlled for partner satisfaction and income, they found denial to be most important factor contributing to depression.

"Prenatal diagnosis of CHD is a traumatic event for many pregnant women. In our study we found that a substantial proportion of mothers exhibited evidence for traumatic stress, with nearly 40% exceeding clinical cut-off points for post-traumatic stress disorder," said Guy S. Diamond, PhD, a psychologist at The Children's Hospital of Philadelphia who participated in this study.

"While individual coping skills are important, partner satisfaction may better predict a more resilient response to the stress of prenatal CHD," Diamond added. We have identified 'denial' as an important contributor to depression and that on-going counseling sessions should focus on this risk factor."

"This study is the beginning, and more research needs to be done to ensure we are giving mothers the very best multidisciplinary care. In one way, the families are fortunate to know in advance that their baby has a CHD and in another way given more stress with that knowledge. In the future, optimal management strategies to improve outcomes for both mom and fetus will include stress reduction techniques, which should accompany the diagnosis of CHD prior to birth," added Rychik.

Dr. Rychik's co-authors are Denise D. Donaghue, RN, MSN; Suzanne Levy, PhD; Clara Fajardo, MS; Jill Combs, RN, MSN; Xuemei Zhang, MS; Anita Szwast, MD, and Guy S. Diamond, PhD, all from The Children's Hospital of Philadelphia.

Dr. Rychik is supported in part by the Robert and Dolores Harrington Endowed Chair in Pediatric Cardiology.

For more information, visit www.chop.edu.

Dangerous Experiment in Fetal Engineering

A new paper just published in the *Journal of Bioethical Inquiry* uses extensive Freedom of Information Act findings to detail an extremely troubling off-label medical intervention employed in the US on pregnant women to intentionally engineer the development of their fetuses for sex normalization purposes.

The paper is authored by Alice Dreger, Professor of Clinical Medical Humanities & Bioethics at Northwestern University Feinberg School of Medicine and is co-authored by Ellen Feder, Associate Professor of Philosophy & Religion at American University, and Anne Tamar-Mattis, Executive Director of Advocates for Informed Choice.

The pregnant women targeted are at risk for having a child born with the condition congenital adrenal hyperplasia (CAH), an endocrinological condition that can result in female fetuses being born with intersex or more male-typical genitals and brains. Women genetically identified as being at risk are given dexamethasone, a synthetic steroid, off-label starting as early as week five of the first trimester to try to "normalize" the development of those fetuses, which are female and CAH-affected. Because the drug must be administered before doctors can know if the fetus is female or CAH-affected, only one in eight of those exposed are the target type of fetus.

The off-label intervention does not prevent CAH; it aims only at sex normalization. Like Diethylstilbestrol (DES) -- which is now known to have caused major fertility problems and fatal cancers among those exposed in utero -- dexamethasone is a synthetic steroid. Dexamethasone is known -- and in this case intended -- to cross the placental barrier and change fetal development. Experts estimate the glucocorticoid dose reaching the fetus is 60 to 100 times what the body would normally experience.

The new report provides clear evidence that:

- For more than 10 years, medical societies repeatedly but ultimately impotently expressed high alarm at use of this off-label intervention outside prospective clinical trials, because it is so high risk and because nearly 90% of those exposed cannot benefit.
- Mothers offered the intervention have been told it "has been found safe for mother and child," but in fact, there has never been any such scientific evidence.
- The US Food and Drug Administration has indicated it cannot stop advertising of this off-label use as "safe for mother and child" because the advertising is done by a clinician not affiliated with the drug maker.
- A just-out report from Sweden in the *Journal of Clinical Endocrinology and Metabolism* documents a nearly 20% "serious adverse event" rate among the children exposed in utero.
- Clinician proponents of the intervention have been interested in whether the intervention can reduce rates of tomboyism, lesbianism and bisexuality, characteristics they have termed "behavioral masculinization."
- The National Institutes of Health has funded research to see if these attempts to prevent "behavioral masculinization" with prenatal dexamethasone are "successful."

The United States' systems designed to prevent another tragedy like DES and thalidomide -- involving de facto experimentation on pregnant women and their fetuses -- appear to be broken and ineffectual.

The paper is available for free download at: http://www.springerlink.com/content/m1523l7615744552/?MUD=MP

Global Neonatology Today Monthly Column - How to Get the Global NMR and IMR Data

By Dharmapuri Vidyasagar, MD, FAAP, FCCM

The Millennium Development Goals (MDG) #4 and 5 call for reduction in Maternal Mortality Ratio (MMR), Neonatal Mortality Rate (NMR), Infant Mortality Rate (IMR) and children <5 years old mortality rates by 2015. As we are fast approaching the target dates of 2015, we continue to evaluate the progress being made. One of the major question most of us fail to recognize is how do we get accurate NMR/IMR data? As simple as it may sound, it depends on the availability of information of each birth and death in each country; it is not a simple task. Developed countries in North America and European have maintained accurate birth and death certificates for a long time, which enable us to derive accurate NMR/IMR data from these countries. However, developing countries do not have well-established recording of births and neonatal deaths.

Only 60 counties of 193 countries in the world have fully functioning sources of mortality data, the rest of the countries, according to UNICEF (United Nations Children's Fund), rely on surveys.

The epidemiologists and health policy makers have great difficulties in calculating the IMR and child mortality rates of developing countries. It is in these countries where we need to understand the causes of death, and thus implement interventional policies and strategies.

According to a recent paper, by Trevor Stokes entitled, "Plunge in Child Mortality Leaves UN Unsatisfied," different countries have different approaches to collecting birth and death data. The most common data source globally for child and neonatal mortality is retrospective household surveys, which rely on birth histories and do not report neonatal outcomes. The neonatal period has historically received little attention in data collection and analyses.

Most data of IMR is based on sampling method. UNICEF's Multiple Indicator Cluster Surveys (MICS) are an increasing source of national estimates for under-age-five mortality.

"Only 60 counties of 193 countries in the world have fully functioning sources of mortality data, the rest of the countries, according to UNICEF (United Nations Children's Fund), rely on surveys."

These surveys are also affected by many extraneous factors. It is found that mortality data collection is even more difficult in countries with ongoing or recent civil unrest or disaster - most often due to breakdown of collection systems or because data collection risks compromising the security of participants. In our study, the 17 countries that had no relevant, recent data of any kind include countries that have experienced recent civil unrest.

In summary, we must all try to get the best data possible to know where we were, and where we are going; however, it will not be an easy task.

The Clock is Ticking !!!

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References: 1. Steele C, et al. Microbiology and Infection Control. In: Robbins ST, et al eds. *Infant Feedings: Guidelines for Preparation of Human Milk and Formula in Health Care Facilities*. 2011;108-121. **2.** Baker RD. *Pediatrics*. 2002;110:833-835.

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