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neonatal INTENSIVE CARE

The Journal of Perinatology-Neonatology

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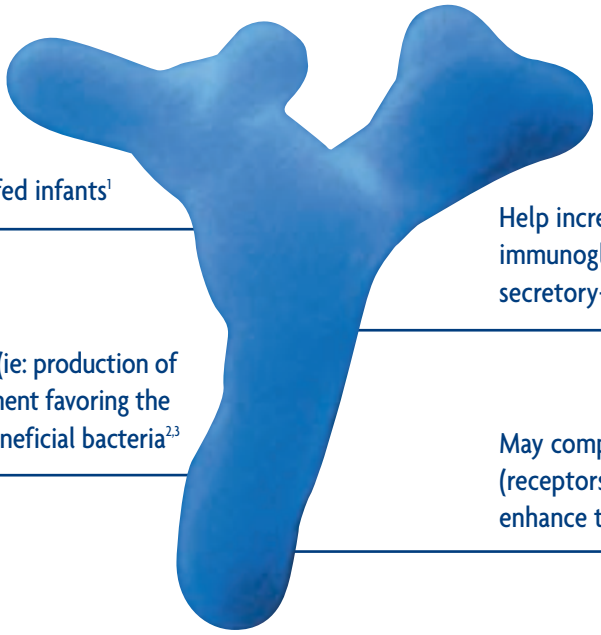

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20.9

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Editorial

Prevention of Perinatal AIDS

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Over 25 years ago a mysterious puzzling disease was identified among the gay community in San Francisco. This disease was later described as Acquired Immune Deficiency Syndrome (AIDS) caused by Human Immune Deficiency virus (HIV). First thought of as a disease of gay men, it was later identified in injection drug users, multiple sex partners with unprotected sex and prostitutes. The disease was also found to spread through infected blood transfusions and from infected mothers to their children. The first pediatric case of AIDS was described in 1982 and it puzzled the physicians, regarding the mode of its spread to children. Much attention was not given to childhood AIDS until the late 1980s, when it was evident that the infection in a child occurs mainly through mother-to-child transmission. The infection can be transmitted during pregnancy, during labor and delivery and after birth. In a small number of cases, a child can acquire the infection through breastfeeding from an infected mother, sexual abuse by an infected individual and transfusion of infected blood or blood products. The infection does not transmit by casual person to person contact; however, one should avoid blood contamination.

Since the 1980s and 1990s, HIV-AIDS has become one of the most serious health problems in the world, including the USA. Forty million people worldwide are living with AIDS. In the USA one million people are infected with HIV and one quarter of them are not aware of their illness. This latter group will not only develop a full-blown disease but will also spread infection to others. The women of child bearing age in this group contribute towards mother-to-child transmission, and this continues to occur despite public health initiatives including public education, offering confidential HIV testing, and treatment of those found to be infected, along with preventive sexual behavior practices.

The landmark 1994 Pediatric AIDS Clinical Trial Group (PACTG - 076) study concluded that the treatment of infected pregnant mothers prenatally with Zidovudine (AZT), beginning in second trimester of pregnancy, during labor and delivery, and treatment of the infant after birth, along with avoiding breast feeding, could reduce the transmission rate of HIV infection from 25% to 8%. Highly active anti-retroviral therapy (HAART) along with elective Cesarean delivery in cases of high maternal viral load and decreased CD4 count would even cut down the transmission rate to 1-2%. Despite all public health initiatives, six to seven thousand HIV positive women give birth each year in USA, with approximately 300 infants infected each year. More than 40% of infected infants are born to mothers who are not identified prenatally, as many of them do not seek early prenatal care or refuse testing, which is voluntary at present. The best possible mode of prevention is to bring these people to prenatal care for counseling and testing, since the treatment and prevention is available and effective.

In New York State, HIV testing began in 1995 and 1997 with "step-up" informed consent. When this program began, the statewide mother-to-child transmission rate was 10.9% with 97 infected infants. The infection rate was brought down to 2.8%, with only 16 infected infants reported in 2004. This was the result of effective screening prenatally and in the intrapartum period, with expedited HIV testing (SUDS method in 1999 and Ora-Quick in 2004) and treatment of HIV-positive mothers and infants with intrapartum AZT. New York State has launched a new initiative to further reduce or eliminate mother-to-child HIV transmission with four

Continued on page 13…

neonatal INTENSIVE CARE

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Table of Contents

neonatal INTENSIVE CARE

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News

☐ July-August 2007

FESS UP

Voluntary reporting of mistakes made while caring for very sick newborns is more effective than compulsory reporting, says research published in the Fetal & Neonatal Edition of the Archives of Disease in Childhood, but it's unclear what impact error reports have on improving safety. The findings are based on an extensive trawl of research databases, showing published studies of incident reporting in neonatal intensive care. When all the information was analyzed in detail from 10 relevant studies, it showed that errors in prescribing or administering drugs were the most common type of reported mistake. Failure to follow procedures, insufficient attention paid to the task, poor record keeping and/or communication were all to blame. Most of the studies indicated that voluntary reporting boosted the number of incidents filed compared with compulsory, punitive systems. The rate of medication error reports was around 13 times higher in voluntary systems. Potentially harmful incidents featured in almost every study. Changes were made to processes following the reports, but the guaranteed anonymity of voluntary systems prevented further detailed analysis of the causes of the mistakes. Complex errors, such as failure to prioritize clinical tasks appropriately or carry out assessments, which could equally affect the outcome of care, are often not reported, because they are difficult to measure, say the authors. The full article, reported by Medical News Today, is available from the British Medical Journal, bmj.com.

BACTERIUM DEATHS

Six premature babies died and 50 others were sickened recently by a bacterium in the neonatal ward of Sainte-Justine's Hospital a Montreal pediatric hospital over an 18-month period, according to a media report. The problem lingered and children's lives continued to be threatened throughout 2004 and 2005 because of chronic plumbing problems at the Sainte-Justine Hospital pediatric hospital, the Radio-Canada television program Zone Libre Enquêtes reported. The hospital's medical director confirmed there have been four deaths definitely linked to the bacterium, as well as two other suspected deaths. Dozens of children fell ill. But she said a series of measures have been implemented to prevent infections and a new neo-natal unit is being built at the hospital. Published reports said it appeared the babies were infected because of blocked water-drainage pipes, which backed up, leading to water and sinks that were contaminated. The hospital now washes babies only in sterile water and hospital staff on the ward must disinfect their hands in addition to washing them. The director of Quebec Public Health, said, initially, it was believed that the problem was with incubators used for the premature babies and they were all replaced. It was only later that the infections were traced to plumbing problems. Tracing the source of the problem was complicated, because the deaths and illnesses occurred sporadically and a number of the babies had serious underlying health problems. In its story, Zone Libre quoted a number of parents as saying they had not been told about the true cause of the death of their babies. The suggestion of a cover-up sparked angry political reactions. Hospital officials said that, in this instance, they were totally above board, particularly with parents and that researchers at the hospital published scientific papers about the incident. Quebec's Health Minister said he was confident that physicians had fully disclosed the causes of death to parents, as is their ethical duty. Reported in the Globe and Mail.

CONSEQUENCES

Iraq had a 150% increase in infant mortality between 1990 and 2005, according to a report by Save the Children, which tracked mortality trends in 60 developing countries that accounted for 94% of child deaths worldwide. Egypt showed a 68% decline in deaths. In Iraq, most reasons for death were pneumonia, diarrhea and newborn disorders. In 2005, 122,000 Iraqi children, one in eight, died before age 5. The countries deemed best for children and mothers were Sweden, Iceland and Norway. The US placed 26th, tied with Hungary. Niger was last.

UH-OH

Doctors reported that expectant mothers with epilepsy who took a commonly prescribed drug to control seizures were at increased risk of having a child with mental deficits. Toddlers who had been exposed in the womb to the drug Depakote, from Abbott Laboratories, scored seven to eight points lower on IQ tests at age 2 than those whose mothers had been taking other epilepsy drugs while pregnant, the study found. They were twice as likely to score in the range associated with mental retardation, according to the authors, who presented the findings at the annual meeting of the American Academy of Neurology in Boston. Researchers at the University of Florida followed 185 children through age 2, using standard IQ measures. Other researchers said the findings should be considered preliminary because IQ measures were less reliable in 2-year-olds than in older children; the study will continue, tracking children through age 6. The report is consistent with several recent studies finding that Depakote is more likely than other anticonvulsant drugs to increase the risk of mental deficits and other birth defects, like neural tube problems. An estimated 24 million American women have taken these drugs, which include Tegretol from Novartis, Lamictal from GlaxoSmithKline and Dilantin from Parke Davis.

SOUTH RISING

The New York Times reports: For decades, Mississippi and neighboring states with large black populations and expanses of enduring poverty made steady progress in reducing infant death. But, in what health experts call an ominous portent, progress has stalled and in recent years the death rate has risen in Mississippi and several other states. To the shock of Mississippi officials, who in 2004 had seen the infant mortality rate fall to 9.7, the rate jumped sharply in 2005, to 11.4. The national average in 2003, the last year for which data have been compiled, was 6.9. Smaller rises also occurred in 2005 in Alabama, North Carolina and Tennessee, and Louisiana and South Carolina reported rises in the previous year. Most striking, here and throughout the country, is the large racial disparity. In Mississippi, infant deaths among blacks rose to 17 per thousand births in 2005 from 14.2 per thousand in 2004, while those among whites rose to 6.6 per thousand from 6.1. (The national average in 2003 was 5.7 for whites and 14.0 for blacks.)

The overall jump in Mississippi meant that 65 more babies died in 2005 than in the previous year, for a total of 481. The main

causes of infant death in poor Southern regions included premature and low-weight births; Sudden Infant Death Syndrome, which is linked to parental smoking, and unsafe sleeping positions as well as unknown causes; congenital defects; and, among poor black teenage mothers in particular, deaths from accidents and disease. Doctors say obesity and its effects are a major cause, because it makes it more difficult to do diagnostic tests, and can lead to hypertension and diabetes, which causes infants to be born undernourished. But social workers say the rise in infant deaths can also be attributed to cuts in social programs and a dearth of transportation, as well as low self esteem. Changes in Medicaid and the children's health insurance program resulted in a decline in the number of non-elderly people, mainly children, covered by these programs. Departments of health have also cut back their system of clinics.

FULL VIEW

Parents-to-be might soon be able to use 3-D glasses in the ultrasound lab to see their developing fetuses in the womb, according to researchers at Duke University's Pratt School of Engineering. The same Duke team that first developed real-time, three-dimensional ultrasound imaging says it has now modified the commercial version of the scanner to produce an even more realistic perception of depth. The researchers created an updated version of the image-viewing software found on clinical ultrasound scanners, making it possible to achieve a stereo display with no additional hardware. This is the first time such images can be observed "live" on a 3-D scanner. The new imaging capability can improve the early diagnosis of certain kinds of birth defects of the face and skull and improve surgeons' depth perception during ultrasound-guided medical procedures, including tumor biopsies and robot-assisted surgeries done through tiny keyhole incisions. For more see the April edition of Ultrasonic Imaging. For a preliminary sample of ultrasound images, go to youtube.com/watch?v=4VSR1H01mzg.

MONKEY BUSINESS

New research from Columbia's Primate Cognition Laboratory has demonstrated for the first time that monkeys could acquire meta-cognitive skills: the ability to reflect about their thoughts and to assess their performance. The study, by researchers at Columbia University, Barnard College and UCLA, was designed to show that a monkey could express confidence in its answers to multiple-choice questions about its memory based on the amount of imaginary currency it was willing to wager. The experiment was derived from the observation that children often make pretend bets to assert that they know the answer to some question. Researchers noted that up to now, the ability to reflect on one's knowledge has always been thought of as exclusively human. The test was designed to determine if a non-human primate could similarly learn to express its confidence about its knowledge by making large or small wagers. In the experiment, two monkeys were trained to play a video game that would test their ability to remember a particular photograph while also allowing them to make a large or a small bet. Ultimately, this wager would reflect the monkey's perception of their memory accuracy. The test used touch-screen technology and a multiple-choice format. Six photographs were presented at the beginning of each trial, one at a time. One photograph was selected at random and then displayed simultaneously with 8 new photographs. The monkey's task was to select the photograph that appeared at the beginning of the trial. The monkey then evaluated the accuracy of its choice by selecting a high and a low-risk icon presented on the screen. The pattern of the monkeys' bets provided clear evidence of their ability to engage in meta-cognition, an ability that is all the more remarkable because monkeys lack language. But the results may have further reaching implications as well, because non-verbal tests of the type used in this and other experiments on animal cognition can be adapted to study cognitive abilities of infants and autistic children.

FROM THE FREEZER SECTION

A California woman has given birth to the first baby conceived in the United States by means of frozen sperm and a frozen egg, according to the fertility firm that sponsored the study in which she took part. The mom, 36, decided to participate in the study by Extend Fertility after being told two years ago her fallopian tubes were blocked. She gave birth to a boy on Wednesday. The mother, who is single, was unable to afford in-vitro fertilization. Egg freezing traditionally has been reserved for women who suffered from illnesses that might leave them infertile and has a low success rate. But there has been recent demand for the procedure by women in their 30s who want to have children in the future but are afraid they will be too old to conceive the traditional way. The low viability of frozen eggs is due, in part, to ice crystals that can damage the egg's structure, though freezing sperm has been done for decades. There have been about 200 documented births from frozen eggs worldwide, but this was the first frozen egg/frozen sperm conception in the US. The Journal of Assisted Reproduction and Genetics reported one case last year in Australia. During the procedure, the mom received shots and pills to stimulate egg production. Fertility personnel harvested the eggs, froze them, and after four months, injected them with thawed donor sperm. A fertilized egg was then placed inside her. Her son was born weighing 8 pounds, 4 ounces.

BIG AND LITTLE

Two premature identical twins, one born only a third the size of his brother, have beaten huge odds to survive. One baby weighed just 1lb 2oz when he was born 11 weeks early along with his big brother, who weighed 3lb 6oz. Doctors at the Royal Hospital for Women in Sydney intervened to deliver the boys when they discovered a relatively rare pregnancy complication: blood was flowing from Lincoln to Byron, putting both in danger. Doctors gave the small baby a one in three chance of survival because he was so small, but despite his very low weight and needing heart surgery after he was born, he is now thriving, as is his brother. The parents conceived through IVF.

THE BIG SCREEN

Newborn screening for cystic fibrosis saves on treatment costs and would offset the actual costs of the screening program, according to a study recently published in Lancet. The new economic evidence suggests that universal newborn screening programs for cystic fibrosis should be adopted internationally. The study also showed that newborn cystic fibrosis screening reduced hospital admissions for invasive therapy. Researchers from the University of East Anglia and the University of Dundee used data from the UK cystic fibrosis database for 2002 to compare the treatment costs of 184 children aged 1-9 years who had cystic fibrosis that was identified by newborn screening with those of 950 children in the same age group, who were identified after clinical presentation of the disease. Patients diagnosed by newborn screening cost significantly less to treat than those who were diagnosed clinically. Patients diagnosed on

the basis of clinical presentation alone received therapy costing an estimated 60-400% more than patients diagnosed by newborn screening. The researchers concluded that newborn screening is associated with lower estimated treatment costs and reduced hospital admissions for invasive therapy, which suggested that indirect costs and disruption to family life would also be less. Furthermore, the potential cost savings to the yearly treatment budget could offset some, if not all, of the costs of a newborn screening service.

NEW OWNERSHIP

Viasys Healthcare Inc has accepted a $1.42 billion takeover offer from Cardinal Health Inc. On news of the takeover, Viasys shares jumped nearly 37%, to an all-time high. Cardinal Health will pay $42.75 per Viasys share, a 3.5.% premium to the stock's closing price on the date of the news was announced. Including debt, the deal is valued at about $1.5 billion. Viasys took in $610 million in revenue in 2006. According to a Goldman Sachs analyst, "The Viasys deal will likely serve to advance Cardinal's long-standing agenda of international expansion, with 40 percent of Viasys revenue coming from international markets, in addition to having a dedicated overseas sales and distribution network." JP Morgan reiterated a "neutral" rating on Viasys shares, and noted that other bids for Viasys could come in at the time we went to press. Reported by the Associated Press.

INHIBITED

If left untreated, approximately 25 percent of newborns exposed to the HIV virus from their infected mothers will become infected themselves and potentially develop AIDS. Antiretroviral drug combinations, which typically include AZT (zidovudine), have reduced the rate of transmission from mother to child to less than 2 percent in infants who are not breast fed. NRTIs work by inhibiting the viral reverse transcriptase and by incorporating into the viral DNA and terminating nascent strands, thus preventing the virus from duplicating. However, previous research has shown that NRTIs also incorporate into the DNA of host cells, causing damage that could have long-term health consequences for those exposed to the drugs. Two new animal studies have examined the cancer-causing effects of transplacental exposure to AZT in mice and rats and found increased rates of tumors and tumors with gene changes that frequently occur in human cancer. In addition, two human studies are the first to observe the induction of mutations and large scale chromosomal damage in red blood cells of newborns exposed to NRTIs in utero.

These, and other, studies were published in April 2007 in a special issue of Environmental and Molecular Mutagenesis that examines the latest research on DNA damage and potential health risks related to the use of NRTIs. Besides the effects of NRTIs on nuclear DNA and cancer risk, the issue also contains recent findings on the toxicity of these drugs toward mitochondrial DNA. Researchers at the Experimental Pathology Laboratories in Herndon, VA, administered AZT in varying doses to female mice and rats during the last 7 days of gestation and examined the tissue of their offspring two years later. They found clear evidence of an AZT-induced increase in the incidence of hemangiosarcoma in male mice and mononuclear cell leukemia in female rats. There was also some evidence of increased liver cancer and reproductive tumors. The carcinogenic effects of AZT were further demonstrated by a study on mice by the National Institute of Environmental Health Sciences, which found mutations in the K-ras and p53 cancer genes that are often mutated in human lung tumors. The development of lung cancer in these mice suggests that the incorporation of AZT or its metabolites into DNA, oxidative stress, and genomic instability may be the contributing factors to the pattern of mutations observed in the study. The cumulative mutagenesis data suggest that infants exposed transplacentally to AZT may be at increased risk for cancer as they age.

In the first of the two human studies, researchers at the University of Pittsburgh measured DNA damage caused by AZT in the blood of newborns. They found increased frequencies of glycophorin A mutations in the red blood cells of newborns who had been exposed to AZT plus lamivudine in utero, and these changes persisted for the most part through one year of age. In the second study involving humans, researchers at the National Institute of Environmental Health Sciences measured the frequency of reticulocytes containing micronuclei, indicators of chromosomal damage, in blood samples of HIV-infected women and their infants exposed to antiretroviral drugs during pregnancy. Most, but not all, of the prenatal treatment regimens in this study included AZT. At birth, the researchers observed ten-fold increases in the frequencies of MN-RET in the women and infants whose prenatal drug regimen included AZT. No increases were detected in the women and infants who did not receive prenatal AZT.

DO IT NOW

Men and women who wait to have babies later in life may increase their children's risk for autism, according to a Kaiser Permanente study featured in the Archives of Pediatrics & Adolescent Medicine. The study investigated 132,844 children born at Kaiser Permanente hospitals in its Northern California region over a five-year period and identified 593 children who had been diagnosed with an autism spectrum disorder (ASD). Study results show that a mother's and father's risk of delivering a child with autism steadily increases as they get older. Women ages 40 and older showed a 30% increase in risk for having a child with autism (1 in 123), when compared to moms between the ages of 25 and 29 (1 in 156). Men ages 40 and older had up to a 50% increased risk of having a child with autism (1 in 116), when compared to their 25- to 29-year-old peers (1 in 176). The advanced age of mothers has been associated with risk of autism in several, but not all earlier studies. The role of a father's age in autism has been less frequently studied, although advanced paternal age has been associated with other adverse reproductive outcomes, including miscarriage, childhood cancers, autoimmune disorders, schizophrenia and other neuro-psychiatric disorders. Children with autism are four more times likely to be male. According to the study, children with the disorder were also more likely to have older, more highly educated and white, non-Hispanic parents. The study data suggest that advanced maternal and paternal age are independently associated with ASD risk. Age effects were found to be independent of birth year and thus not explained by the increasing age of parents that has been observed in recent years. If the relationship between parental age and autism is causal, the fraction of autism in this sample attributable to having a mother or father older than 35 years is 4% to 13%.

GOT BREAST MILK?

A new study published in Lancet suggests that babies born to HIV infected mothers have lower HIV infection risk when fed exclusively on breast milk for at least six months than those

who are raised on alternatives such as baby formula, animal milk or mixed breastfeeding. This study concords with other reports that exclusive breastfeeding confers a significantly lower risk of HIV transmission compared with mixed breastfeeding. The study, by the University of Kwa-Zulu Natal, South Africa, was conducted in 9 antenatal clinics. Every week the mothers were asked questions about what their babies were as being fed, and every month blood samples were taken from mothers and babies. The researchers analyzed the HIV transmission risk at various infant ages up to 6 months, and assessed the influence of other mother and child variables on the risk, such as mothers' immune system health and babies' birth weights. The findings revealed that the HIV infection risk of an exclusively breastfed baby at the age of 6 months who was uninfected at 6 weeks was 4%. However, babies who had formula milk as well being breastfed, before or after 14 weeks old, were almost twice as likely to be infected as exclusively breastfed babies. Moreover, breastfed babies who were also fed with solids were nearly 11 times more likely to become infected compared with exclusively breastfed babies. Researchers suggested that babies who are fed exclusively on breast milk develop a stronger lining in the mucosa of their intestines creating an effective barrier to HIV. Another suggestion was that women who exclusively breastfeed their babies tend to have fewer breast health problems such as mastitis and abscesses which are linked to higher levels of HIV in the breast milk. The survival rate of breastfed babies was also influenced by the status of the mother's immune system. Exclusively breastfed babies of mothers with CD4-cell counts below 200 per microliter were twice as likely to become infected and nearly four times more likely to die before reaching the age of 6 months than babies whose mothers' CD4-cell count was above 500 per microliter.

DON'T MONKEY WITH IT

Researchers at the University of Edinburgh have found that prenatal exposure of nonhuman primate African vervet monkeys to glucocorticoids has long-lasting deleterious effects on cardiovascular, metabolic, and neuroendocrine function. Researchers set out to determine the relevance to human pregnancy of rodent and nonprimate data indicating that prenatal exposure to glucocorticoids, through either the administration of dexamethasone or severe maternal stress, has long-lasting deleterious effects. The study, which appears in the Journal of Clinical Investigation, shows that although the birth weight of offspring born to nonhuman primate African vervet monkeys treated with dexamethasone from mid-gestation onward did not differ from that of offspring born to untreated animals, the high levels of prenatal dexamethasone impaired postnatal growth, impaired glucose-insulin homeostasis, increased blood pressure 12 months after birth, and increased the production of cortisol in response to mild stress. These data suggest that both repeated glucocorticoid therapy and severe maternal stress late in gestation are likely to have long-term deleterious effects on developing human fetuses.

NO HARM DONE

Preemies between 28 and 32 weeks are not harmed by a treatment no longer used to help their lungs mature before birth, according to findings of a study in a recent issue of Pediatrics. Even though previous observational studies suggested that repeated courses of steroids in the womb may result in brain damage, this study shows that the babies' brains are virtually unaffected. Before concerns arose in 2000 about safety of multiple courses of steroids, many mothers in on-and-off preterm labor received several rounds before delivering. Now, when mothers go into preterm labor, obstetricians will often administer only a single course of steroids to help strengthen the baby's lungs upon birth. But if the birth is successfully held off for more than seven days, the mother does not receive another course of medication and the baby's lungs may not be protected. Previous studies showed neurological complications from multiple courses of dexamethasone, a steroid prepared with sulfur. However, clinicians do not commonly use that steroid anymore and have largely switched to sulfur-free steroids, such as betamethasone. This study was based on infants who received betamethasone prior to birth, and they did not show the same adverse effects as previous studies. The study, which was performed by analyzing data collected in the neonatal intensive care unit at Golisano Children's Hospital at Strong between 1996 and 1998, included 174 babies who were born at 28 to 32 weeks. Their brain functioning was measured by ABR. There were no significant differences in the brain's responses to the testing between the 50 babies who received one course of steroids and the 29 who received two or more courses, even when controlled for gestational age, birth weight, race and exposure to illegal drugs. There were also no significant differences between the 51 infants who received no steroids and those who did. The only medical difference between those infants who received one course and those who received more was that the ones who received more were less likely to need mechanical ventilation the day they were born.

NET WORKING

A study in the UK revealed that pregnant women in Africa can reduce their risk of miscarriage or still birth by up to a third by sleeping under insecticide-treated bed nets. The UK scientific research is likely to bolster calls for treated mosquito nets to be made more widely available to pregnant women and children in Africa. When treated nets were used, the number of miscarriages and still-births fell by almost a third. The number of babies born with a low weight also fell by about a quarter.

YET ANOTHER WORRY

Newborns with respiratory distress should be evaluated for primary ciliary dyskinesia, a rare genetic disease that has features similar to cystic fibrosis, said Thomas Ferkol, MD, from Washington University School of Medicine in St Louis, as reported in Medical News Today. He reported finding that about 80% of patients with primary ciliary dyskinesia (PCD) have a history of newborn respiratory distress. Research by Ferkol at the Division of Pediatric Allergy and Pulmonary Medicine at Washington University School of Medicine and St. Louis Children's Hospital, found that neonatal respiratory distress was a common clinical symptom of PCD, a chronic airway disease that affects about 1 in 15,000 children. Their findings appeared in Seminars in Perinatology. Also known as immotile cilia syndrome, ciliary aplasia or Kartagener Syndrome, PCD causes persistent wheezing and cough in children and is associated with recurrent or persistent sinus and ear infections. Half of patients with PCD have reversed internal organs, called situs inversus, and males are usually infertile. In PCD patients, the cilia, tiny hairs that move mucus, bacteria and particulates out of the respiratory tract, including the lungs, middle ear and paranasal sinuses, have abnormal or no motion. As a result, the airways become obstructed and infected, which incites a destructive inflammatory process in those organs. Cilia are also present in the female reproductive system, central nervous

system and gut. Researchers said that physicians often failed to consider PCD, in part because we don't have a great diagnostic test for the disease. Several clinical features of PCD mirror those found in the more-common cystic fibrosis, including chronic sinus and lung disease as well as male infertility. However, chronic ear disease and neonatal respiratory distress are relatively uncommon in cystic fibrosis and should prompt the caregiver to consider PCD, according to the research. Because definitive testing is not always readily available, patients with PCD are often diagnosed late. In addition, treatment of PCD in the community is highly variable, largely because the necessary clinical studies have not been performed.

TAKE IT EASY

The first Gentle Birth World Congress and Gentle Birth and Baby Expo will be held September 27 – 30, 2007, at the Portland, Oregon Convention Center. The Congress will allow maternal care experts from around the world to explore current issues and controversies regarding the care of mothers, infants, and families. Congress sessions topics will include: optimizing the physical, psychological, and emotional outcomes of mother and baby; respecting women's rights to informed consent and informed refusal; addressing the needs of health care providers – physical, financial, and legal; the benefits of water labor and waterbirth for parents and providers; reducing health care costs, liability risk, and high turn-over; medical intervention in birth – a lawyer's perspective; collaboration between health care and allied health care providers; among many others. Contact waterbirthworld.com.

UNDERSTAFFED/OVERSTRETCHED

That's the lot of midwives in some maternity units, a BBC Panorama investigation has discovered. BBC reporter Hayley Cutts tells of the crisis in care she found while working as a volunteer on two large maternity units in the UK. (From the BBC internet wire service): I was beginning to feel uncomfortable about the responsibility I was being given by my third shift as an unpaid volunteer on a joint ante and post natal ward of Barnet Hospital, North London. It included performing the patient observations, such as blood pressure, pulse and heart rate. I told the busy midwives I was untrained and unqualified but they insisted they needed my help. Many parents were demanding attention and needing care on the full unit with no beds but the three midwives on duty were over-stretched. Clearly worried, the midwife in charge said: "We are chocca, we've got labouring women over here, and I've got someone in the bath and another being induced." Another day she confided when wards are full : "We're dangerous." Three hours into this shift a midwife was taken to the delivery ward to look after a lady in labour leaving only two midwives for 23 women on our ward. Then a new mum arrived after giving birth to be told she had no bed. I had to juggle women around so we could squeeze her into the overcrowded and understaffed ward. The only solution, staff devised, was moving another lady, who should have been under midwife supervision, to the unstaffed Transitional Care ward where women who do not need medical care, stay when their babies are on the neonatal ward. I would discover later transitional care was regularly used as a dumping ground when wards were full. The hospital was now closed to new admissions with women told to try a neighbouring hospital or stay at home. However if a woman in labour arrives she should not be turned away, so when a lady in the late stages of labour came to the delivery ward, they sent her to our ward where she was left on a chair in the corridor. Midwives knew she was squirming in pain, and crying but had no bed. For 50 minutes she waited in the corridor without being checked or examined by any staff member. All I could offer was reassurance. I was later given the task of trying to get her into a more private area. Moving women around to other beds, I managed to get a space in the room for antenatal women but there was no bed so she was put on a chair in the middle of the room. When I finally got her a bed she seemed relieved and I was told she delivered a few hours later. I left the ward exhausted and felt there was no control. I had left a woman who had given birth and needed care on a ward not designed for her needs, with no staff. And I had spent the last hour watching helplessly as another in obvious pain, cried and squirmed on a chair in a corridor with no medical help… Another worrying problem at St Mary's was the lack of essential equipment, especially fetal heart monitors. One day, I was sent on a wild goose chase to all the maternity wards to borrow a monitor - we only had one on our ward. I was told women were waiting for them on the other wards too. St Mary's has told us since it has acquired six new monitors. I was also left to monitor a baby's heart even though I was an untrained volunteer.

IT'S NO DIET

While breastfeeding has many benefits, it won't prevent a child from becoming fat as an adult, says a new study that challenges dogma from US health officials. The research is the largest study to date on breast-feeding and its effect on adult obesity. The Harvard study, published in the International Journal of Obesity, involved nearly 14,500 women who were breast fed as infants and more than 21,000 who were not.

In 1989, the women were asked their height and weight and what those measurements were when they were children and at age 18. Every two years, through 2001, they were asked to update their weight information. The surveyed women were all between 25 and 42 at the time of the 1989 questionnaires. In 2001, the mothers of these women were sent a questionnaire asking if their daughters had been breast-fed and for how long. Women who were breast fed for at least a week had a risk of being overweight or obese that was nearly identical to that of women who were bottle-fed, the study found. And duration of breast-feeding didn't seem to make a difference. The women who had been breast-fed for more than nine months had a risk of becoming overweight or obese similar to that of women breast-fed less than one week.

The study involved only women, but the researchers believe the results are equally true for men, Michels said. Researchers said that one reason previous studies might have been misleading about breastfeeding's effects on weight gain is that many of those studies failed to properly account for socioeconomic factors that also may have had an influence. Reported by CNN.

PRODUCT NEWS

OXIMETRY PRODUCT UPDATE

Twelve clinical presentations at two recent, major pediatric conferences spotlighted how near-infrared spectroscopy (NIRS) technology, specifically cerebral/somatic oximetry via the INVOS System, enhances pediatric patient assessment and is a growing standard of care in the pediatric operating room and intensive care unit. The presentations took place at the Cardiology 2007 Annual Update on Pediatric Cardiovascular

Disease and Society of Pediatric Anesthesia (SPA) Winter Meeting, where physicians and nurses from leading medical centers nationwide discussed how noninvasive monitoring of blood oxygen levels in the brain and body can help improve patient care. Dr Jonathan Kaufman at Denver Children's Hospital was awarded "Outstanding Investigator of Cardiology 2007" by the conference faculty for his groundbreaking study demonstrating the ability of the INVOS System to determine when a patient in the Pediatric CICU is ready to feed. Determining the proper time for feedings can be challenging, and incorrect timing can exacerbate ischemic issues or other complications in the gut area. By placing an INVOS System sensor on the patient's abdomen, Kaufman compared the blood oxygen saturation values with more traditional gut perfusion indicators, correlating "stomach NIRS" and gut tonometry, lactate levels and sVO_2. Dr. Kaufman concluded that abdominal-site NIRS may be very useful in monitoring for early gut ischemia and determining readiness to feed in the congenital cardiac population so as to not tax the gut and other systems. Several other presentations at Cardiology 2007 focused on the unique value of cerebral/somatic oximetry to detect low cardiac output syndrome, a challenging complication largely associated with infants undergoing surgery to correct congenital heart defects. Clinicians from Children's Hospital of Wisconsin discussed the impact of low cardiac output after the Stage One Norwood procedure, while clinicians from Miami Children's Hospital and Phoenix Children's Hospital addressed the causes and better management of low cardiac output. Neuroprotection and NIRS was a prime focus at the SPA Winter Meeting. Here, Dr. Dean Andropoulos of Texas Children's Hospital & Baylor College of Medicine, called for a change in the way neuromonitoring, cardiopulmonary bypass and follow-up is performed on infants and neonates. He raised the issue that new modalities, including cerebral/somatic oximetry, should be used to monitor oxygen levels in the brain to help identify potential complications as early as possible. With a sensor placed directly on the forehead, the INVOS System provides real-time brain oxygenation that can help surgical and critical care teams to intervene and potentially lessen or avoid neuro-complications. The INVOS system uses visible and near infrared spectroscopy to "reflect the color of life" by identifying both total and oxygenated hemoglobin molecules within red blood cells, and measuring the relative amounts of each. The resulting regional oxygen saturation (rSO_2) is a vital sign that helps critical care teams detect and correct site-specific blood oxygenation issues that can lead to complications and poor outcomes.

NEW FROM DRAEGER

The **Oxylog 3000**, which recently received FDA clearance, is Draeger Medical's newest emergency and transport ventilator. It provides high level, ICU-like transport ventilation by including standard oxygenation and inspiration hold, for use during X-ray imaging. The Oxylog 3000's tidal volume begins at just 50ml so it can be used for small children and adults alike. And its patented blender permits oxygen concentration adjustments between 40% and 100 percent with greater precision and range than previously possible. Designed and manufactured with the same attention to detail and performance as Draeger's high-end Evita ICU ventilators, the Oxylog 3000 represents a significant advance in emergency and transport ventilation systems. The company's **Carina*home*** ventilator is designed to support both invasive and noninvasive ventilation modes and offers smart features like Volume Guarantee and Autoslope. A technical breakthrough known as SyncPlus enables the patient to stay in sync with the ventilator – even with mask ventilation. Intuitive to operate, compact in size and extremely quiet, this advanced ventilator delivers the right therapy while maximizing your patient's comfort and safety. The Carina*home*, with its pressure- and volume-oriented modes, has proven equally effective in and out of the clinical environment, and presents both professional and non-medical caregivers with their own interfaces. This unique user interface concept means that while a full-access interface is available, showing both pressure and flow curves, a dedicated patient-friendly screen enables patients to adjust pre-determined settings according to personal needs. This newest ventilator for the home environment also features low noise levels during operation, an autodimming screen and energy-saving capabilities. Optional accessories, such as a DC input, further increase a patient's freedom and allow Carina*home* to be used in the car. Contact draeger.com.

GOING UP

Viasys Healthcare announced that for the 10th sequential quarter its adjusted operating results were achieved. The total revenue in the first quarter exceeded the prior years quarter by 19%, while adjusted net income increased by over 40%. With strong revenue performances in their core businesses resulted in a growth of 16%, which was complemented by a contribution from their strategic acquisitions in its sleep division, that accounted for the remaining 3% of revenue growth.

SPOTLIGHT ON MONITORING

SMARTEN UP

The **SmartMonitor 2 PS** multi-parameter monitor from Children's Medical Ventures provides health care professionals with detailed information about a patient's heart rate, respiration and oxygen saturation. Features include Masimo SET technology, large memory capacity, 15 hours of portable operation and a bright digital readout. In addition, an easy-to-understand interface incorporates universally recognized symbols that help reduce potential language barriers. Pediatric and adult clearances make the SmartMonitor 2 PS ideal for documenting patient response to conscious sedation, patient-controlled analgesia and general floor monitoring. Diagnostic quality waveforms can be captured and reviewed through the Synergy-E software. The **SmartMonitor 2 PSL** allows healthcare professionals to monitor heart and respiration activity of infants through adults. SmartMonitor 2 PSL captures the data and, with the use of Synergy-E Event Software, creates detailed reports. The "Light" designation refers to the PSL's ability to provide high-quality, cost-effective heart and respiration monitoring parameters without integrated pulse oximetry. SmartMonitor 2 PSL is ideal for documenting patient response to conscious sedation, patient controlled analgesia, and general floor monitoring. It also features an easy-to-use interface; and incorporates universally recognized symbols that simplify operation and reduce potential language barriers. The **SmartRecorder Multi-Channel Recording System** is a versatile diagnostic recording system that can be used for infants and adults in the hospital or homecare setting. It offers the same dependability and superior performance as our other SmartMonitor family of products and is loaded with powerful features such as seven internal channels, Masimo oximetry technology, built-in modem and PCMCIA memory card technology.

A GOOD BLEND

Maxtec, Inc, Salt Lake City, UT is a proud manufacturer of the **MaxBlend** Low Flow oxygen/air blender for monitoring blended gas to NICU patients. The MaxBlend combines the great Bird blender and the globally acclaimed Maxtec oxygen monitor, providing the accuracy of having a "knob and a number all in one place." The built-in manifold system offers an oxygen sensor port to reduce the risk of cross-contamination, while helping to eliminate temperature, pressure and humidity factors which could cause unstable readings. Contact a Maxtec representative for additional information today, at maxtecinc.com, (866) 4-MAXTEC.

NONINVASIVE

The **USCOM** noninvasive hemodynamic monitor uses continuous wave Doppler to accurately measure cardiac output through either the aortic valve or the pulmonary valve to assess both left and right heart hemodynamics. The operator simply places the transducer in the suprasternal notch to access the aortic valve and at the left parasternal edge to access the pulmonary valve. The patient may be awake, sedated or ventilated, facilitating examination in a variety of settings. Weighing twelve pounds, USCOM is highly portable and is designed to be operated by paramedical staff; all measurements are automatically stored and trended for subsequent review by clinicians. The USCOM has been validated against flow probes in animals, the pulmonary artery catheter, echo, artificial hearts and transesophageal Doppler in children and adults. It may be applied to patients of any size or weight. Applications include trauma, burns and sepsis, patient transport and preclinical evaluation in primary rescue, optimization of hemodynamics in potential organ donors, and management of post-op cardiac surgery patients.

QUICK AND COMFORTING

When caring for a baby in the NICU, it is critical for the medical staff to be able to attach monitoring leads and other lifesaving equipment quickly and in a most comforting manner. The **HALO SleepSack** wearable blanket is designed to allow nurses as well as parents to care for babies quickly and easily. The inverted zipper is not only a convenience for diaper changes, but in the NICU, it is also the best path for attaching monitor leads. And, since HALO products, the only brand to carry the First Candle/SIDS Alliance gold seal — are so widely available, parents can continue to care for baby safely at home.

TAKE A LOOK

The **RetCam** family of products has expanded. RetCam II Wide-Field Digital Imaging System with Fluorescein Angiography option provides 130-degree FOV imaging for pediatric retinal and adult anterior segment pathologies. The new RetCam Shuttle enables RetCam imaging with a convenient, mobile system that can be easily maneuvered in tight spaces and transported to affiliate hospitals. RetCam Review Software allows in-depth comparison and analysis of RetCam images from any networked location. Contact claritymsi.com.

Editorial…Continued from 5

major goals: 1. Identifying acute HIV infection during pregnancy, in women who present with clinical syndrome compatible with acute HIV infection, with HIV RNA testing in addition to HIV antibody testing; 2. HIV testing in the third trimester, preferably at 34-36 weeks GA for high risk women whose test was negative in early trimester; 3. Point of care rapid HIV testing in delivery settings with the result available within an hour, and initiation of immediate treatment of positive mother during labor or of the infant within 12 hours of birth; 4. Assuring that access to care and support services are linked to case management in order to provide support many babies would need.

In a recent report, the United States Preventive Services Task Force (USPSTF), American College of Obstetricians and Gynecologists (ACOG), American Academy of Pediatrics (AAP), and Centers for Disease Control (CDC) recommended universal screening of pregnant women, with HIV testing as a part of routine laboratory work, with an "opt-out" approach. The near-elimination of pediatric AIDS in the USA is a public health success story in the more than 25 years of the HIV epidemic. This success is due to education and funding by public health, pregnancy counseling and testing, and the availability of highly effective anti-retroviral drugs. The treatment of the mother and baby with combination of anti-retroviral drugs has significantly decreased morbidity and mortality, with a productive long line of survival. As they say, "an ounce of prevention is worth a pound of cure," and we can hope that pediatric AIDS will soon be a thing of the past and not as the death sentence it once was. However, AIDS is still a social stigma, and as a result, many avoid seeking early medical care. Hopefully, an effective vaccine will be made available in the future to help prevent HIV infection, like we prevent any other childhood infectious disease. It will be particularly helpful for the developing world where death and disease is still rampant.

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Clinician's Dilemma: Aerosol Delivery to Neonates

James B. Fink, MS, RRT, FAARC

Introduction

Aerosol delivery to the neonate has long been an area of controversy, with strong division in clinician opinions based on a sparseness of evidence. The practice of aerosol administration to neonates and small infants largely evolved based on anecdotal evidence and attempts to achieve observed therapeutic or adverse effect. The delivery efficiency of aerosol from pMDIs and jet nebulizers has been demonstrated to be so small, and the inconvenience of integrating these devices into the ventilator circuit so great, that many clinicians avoid delivering aerosols to neonates requiring mechanical ventilatory support.[1]

Because of the difficulties of using radiation with small infants, only one study has quantified aerosol delivery in infants less than 4 kg, on and off the ventilator. As this study had similar results as animal models under similar conditions, we have been left to rely on in vitro models and animal studies to quantify the impact of variable upon aerosol delivery during infant ventilation. These studies suggest that selection of appropriate technology may improve efficiency and consistency of aerosol drug delivery to neonates. This promise of improved efficiency with newer technology must be tempered by the clinician's responsibility to carefully titrate doses to desired effect, with close monitoring to avoid administration of potentially toxic local and systemic levels of drugs. In addition, attention to a few key issues can substantially reduce the risk of aerosol delivery to the neonate.

Why is the Neonate Different

The neonate typically has a fully defined conducting airway at birth; however, the size of those airways and the number of alveoli increase dramatically in the first year of life. The low tidal volume, vital capacity, functional residual capacity, and short respiratory cycles of neonates result in limited amounts of aerosol inhaled with low residence time for small particles in the lung, resulting in a further decrease in pulmonary deposition. Resting respiratory rate decreases with age as tidal volume and minute ventilation increase, resulting in a 5-10-fold increase in aerosol deposition by age 6 years.[2-4]

Many variables have been shown to impact aerosol delivery to the neonate (Table 1).[5] Because of the small tidal volumes and high respiratory rates required, ventilators designed to support the neonate are often time or pressure cycled, with a continuous flow of gas circulating through the ventilator circuit. This flow tends to dilute aerosols and sweep them past the patient and into the expiratory limb of the ventilator circuit.

Data regarding inhaled particle mass, lung deposition, and regional distribution of aerosols in neonates is limited. Pulmonary deposition of medical aerosol from either a jet nebulizer or pMDIs to neonates may be 0.5 - 1% of the nominal dose,[3] compared to 8-22% in older children and adults.[4,5] With the absence of data in infants, we have had to rely on in vitro and animal models to assess the impact of various technologies and delivery variables for aerosol delivery efficiency (Table 2). These studies show that while pMDI and jet nebulizers deliver less than 1% of dose to the lung of a neonate size animal, that ultrasonic nebulizers may deliver up to 3%,[10] and vibrating mesh nebulizers can deliver up to 12.9%.[12] While increased efficiency of aerosol delivery to the neonate may offer new opportunities, the use of such technologies must be tempered with caution by the clinician to assure the patient's safety.

Should dosing be reduced for neonates?

I recall that in the first Neonatal Pediatric Specialty (NPS) exam offered by the National Board of Respiratory Care (NBRC), no less than four questions concerned how to reduce the dose of terbutaline for administration to infants based on body weight. The assumption that smaller patients need smaller doses of aerosol may be intuitive, but is not supported by any firm evidence.

In the case of the neonate receiving a standard unit dose of

The author is Fellow, Respiratory Science, Nektar, Inc, San Carlos, CA. He discloses that he was previously an employee of Aerogen, Inc, and involved in the development of the Aeroneb vibrating mesh technology and its use in critical care settings.

albuterol sulfate (2500 µg) with a deposition efficiency of 0.5%, the lung dose of 12.5 µg in a 4 kg infant would be 3.1 µg/kg. In contrast, typical 10% deposition (250 µg) in a 70 kg adult would provide a similar 3.6 µg/kg.[7] It appears that the low efficiency of deposition in neonates may effectively produce a similar dose per kg. Consequently, reduction of the dose based on some arbitrary basis may have substantially reduced delivery below a therapeutic threshold.

Anecdotally, this low deposition in neonates appears to provide a comparable safety and efficacy profile similar to that in adults. Consequently, rationales to reduce doses for infants and small children with beta-adrenergic bronchodilators that have not been well substantiated in the literature should not form the basis of institutional practice.

That said, in the absence of empirically based dosing guidelines for neonates, the AARC clinical practice guidelines recommended that any bronchodilator administered by aerosol to a neonate be titrated to effect, with close monitoring.[13] This is especially relevant when adopting aerosol technology with potentially greater efficiency than the commonly used standard jet nebulizer or pMDI.

Nebulizer placement

Standard jet nebulizers, ultrasonic nebulizers and pMDI spacers may have internal volumes ranging from 15-130 mL. Due to the low volumes being administered to neonates (5-15 mL), placement of these devices at the airway would result in the infant rebreathing through greatly increased mechanical deadspace and being at high risk of becoming hypercarbic. Consequently, nebulizers are typically placed in the inspiratory limb of the ventilator circuit. Due to the size and weight of the nebulizers, they are placed at least 10 cm away from the patient wye, and on some occasions back near the ventilator. While there is some evidence in adult ventilator circuits that placement of jet nebulizers near the ventilator may improve delivery,[14] there is little rationale or evidence to suggest similar placement may increase delivery to the neonate. In adult ventilator circuits, with an internal volume of 500-600 mL, a jet nebulizer can charge the inspiratory limb so that a bolus, rich in aerosol, can be inhaled with a typical 500 mL breath. Even though an infant ventilator circuit has a smaller internal volume (< 200mL), tidal breaths are less than 10% of that internal volume. Consequently, placement of the nebulizer at around 10-20 cm from the wye may offer a more appropriate volume for supplying an aerosol rich bolus with each breath.

Table 1: Factors that Alter Aerosol Delivery in the Ventilated Neonate

Ventilator type
- Pressure vs Volume Limited
- Continuous flow of gas through circuit
- Respiratory rate
- Tidal volume
- Inspiratory flow rate
- I:E ratio

Circuit type
- Diameter
- Length
- Adapters

Airway
- Size
- Type

Nebulizer
- Type
- Fill Volume
- Particle size
- Aerosol Output rate
- Gas flow rate
- Position in the ventilator circuit

pMDI
- Adapter/spacer used
- Timing of actuation
- Position in the ventilator circuit

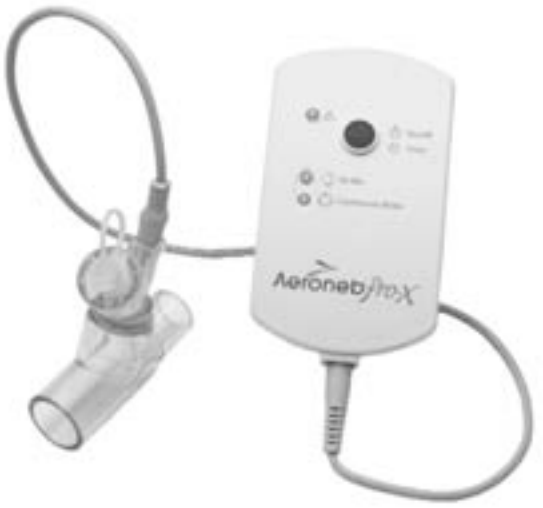

Figure 1: The Aeroneb Solo (Aerogen) is a vibrating mesh nebulizer designed for use with intermittent (up to 30 minutes treatments) and continuous nebulization.

Continuous nebulization

One method to compensate for low aerosol delivery efficiency has been to use a continuous feed through an infusion set into a nebulizer. This method can allow dosing of aerosol at different rates, by adjusting the flow of drug/unit of time into the nebulizer. Researchers have reported using continuous nebulization to deliver drugs ranging from bronchodilators to prostacyclins.

Continuous nebulization options have long been available with jet and ultrasonic nebulizers. Recently, a vibrating mesh nebulizer (Figure 1) has been introduced with this capability.

Care must be taken to assure that the drug is not loaded into the nebulizer faster than it leaves the nebulizer as aerosol. Overflowing the nebulizer reservoir can reduce aerosol efficiency and increase the amount of unwanted fluid in the ventilator circuit.

Potential for contamination during nebulization

Aerosol delivery has been associated with increased incidence of pulmonary infection in the adult ICU. Although no reports have established that relationship with neonates, the clinician should be aware of a few obvious but common practices that may place their patients at risk.

Evidence suggests that patients manage to contaminate their ventilator circuit within a matter of minutes or hours. Any

Table 2: Deposition Efficiency of Animal Models

1986	Flavin (6)	Rabbit	Nebulizer	0.19 – 1.96%
1991	Cameron (7)	Rabbit	Nebulizer	0.05 – 0.11%
1992	Everard (8)	Rabbit	pMDI	1.5 – 2.0%
1992	OCallaghan (9)	Rabbit	pMDI	1.2 – 1.9%
1997	Fok (10)	Rabbit	pMDI	0.23 – 0.5%
1997	Fok (11)	Rabbit	pMDI, Nebulizer	0.22 – 3.05%
2002	Dubus (12)	Monkey	Nebulizer	0.5 – 13.9%

condensate that forms in the ventilator circuit can be contaminated. Even in well controlled heated wire circuits, the gas source used to drive a jet nebulizer is not heated, resulting in cooling of the gas mixing with aerosol in the ventilator circuit, which results in some level of condensate formation. Fluid in ventilator circuits tends to collect in the lowest point of the circuit. Unfortunately, the lowest point in the inspiratory limb of an infant vent circuit may be the medication reservoir of the nebulizer. Jet and ultrasonic nebulizers are placed below the lumen of the ventilator circuit. In addition to creating aerosol, these nebulizers may act as a gravity-dependent water trap, collecting contaminated condensate and even secretions that enter the inspiratory limb. Even with unit dose of medication, it is not uncommon for clinicians to come back to the bedside after 15-30 minutes of nebulization to find more fluid in the nebulizer than when they started. It is difficult to rationalize that this is a good thing for the patient. Aerosolizing potentially contaminated condensate during mechanical ventilation would appear to present a hazard to the mechanically ventilated neonate. This hazard can be avoided with the use of pMDIs or vibrating mesh nebulizers. In both cases, the medication reservoir is a superior position to the lumen of the ventilator circuit, and separated from ventilator circuit. Gravity is much less likely to bring condensate in contact with the aerosol generator. Even if it does, the medication is less likely to be contaminated with condensate or secretions prior to nebulization.

It is incumbent upon clinicians to base their practice on a combination of the best available science and good common sense. As technology improves the ability to deliver aerosols to patients, we must use our best judgment tempered with close monitoring to assure safe and effective respiratory care.

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Development of Fetal Senses: Implications in Intrauterine and Postnatal Life

Muhammad Aslam, MD; Musaddaq Inayat, MD

Introduction

Fetal senses are developed in an orderly fashion during intrauterine life and represent different phases of adaptation to the intrauterine environment. Most of them have a considerable overlap but the sequence of their development remains constant. Touch is the first sense to develop followed by taste, smell, hearing and sight. Premature human infants may be at risk of "executive dysfunction" and hearing loss when sensory systems have been stimulated out of order. The following review represents the intrauterine journey of the fetus with an emphasis on fetal senses. Postnatal adaptation occurs similarly; premature infants have varied responses as compared with mature infants.

Touch[1,2,3]

Touch is the first sensory system to develop in the fetus. It is very important in the overall development and coordination during intrauterine and postnatal life. The receptors start developing at 12 weeks of gestation and by 14 weeks the fetus has a functional tactile system. The areas of the fetus which are highly sensitive include mouth and extremities; both are important in intrauterine well being.

Premature infants are very sensitive to touch and different levels of tactile stimulation can be perceived as pleasant or painful. A painful touch can result in agitation, irritability, tachycardia, tachypnea and poor neurodevelopment. One study has demonstrated that an infant admitted to a neonatal intensive care unit is handled approximately 150 times per day.[4] Certain patient care measures can be used to make NICU experiences less traumatic for these infants. Containment and facilitated tuck are methods where an infant is bundled and flexed during a procedure. Clustering of care is a method where a number of care-giving activities are scheduled at one time to minimize painful stimulation.[5, 6]

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Kangaroo care is defined as skin-to-skin contact between an infant placed on the mother's lap. Bogota, Colombia was one of the pioneers where kangaroo care was initiated and one study has demonstrated that it has decreased infant mortality significantly.[7] Infants who receive kangaroo care demonstrate an improved growth, better breast-feeding rates, and a reduction in nosocomial infections.[8] In 2002, 82% of NICUs were practicing kangaroo care in the United States.[9]

Pain[1,2,3]

Sensory receptors are first developed around the perioral area around eighth week of gestation. They are present in all cutaneous and mucous surfaces by the twentieth week of gestation. Synapses between peripheral sensory afferents and dorsal horn neurons in the spinal cord first appear at 6 weeks of gestation. By 16-18 weeks of development, specific hemodynamic and neuroendocrine responses to noxious stimuli are demonstrated in the fetus. By 20 weeks of gestation, the thalamocortical connections are present allowing painful stimuli to reach the somatosensory cortex.

Pain threshold increases progressively during late gestation and in the postnatal period.

Preterm neonates have much greater response to pain than term neonates, and they manifest prolonged hyperalgesia after tissue injury.[10] An infant's response to pain can be physiologic (vital sign changes) as well as behavioral (tremors, crying) and varies with the behavioral stage at the time of the stimulus.[11] Infant states of behavioral organization are classified as follows from state 1-6.[11] The threshold for pain increases with the behavioral state and is at its maximum in state 6. These are:

- State 1: Deep sleep
- State 2: Light sleep
- State 3: Dozing
- State 4: Quiet awake
- State 5: Active awake
- State 6: Crying

Neonates admitted to a NICU are often exposed to painful stimulation from a variety of sources. These sources include but are not limited to postoperative pain resulting from surgery such as hernia repairs, patent ductus arteriosus ligation, and circumcision. Other acute sources of pain include repeated heelsticks, venipunctures, tracheal suctioning, lumbar

punctures, and chest tubes. Prolonged or chronic pain can result from necrotizing enterocolitis, meningitis, birth trauma, or ventilation. Even routine care procedures like diaper changes, daily weights, removal of adhesive tape, and rectal stimulation can be perceived as painful.[12]

Premature infants have a greater sensitivity to pain than term infants. However all neonates feel pain, and one must effectively deal with the potential for pain during any procedure performed during the neonatal period. Pain scales may not be as useful because responses to pain by infants may be dampened or may not be identified by caregivers.[13] Nonpharmacologic treatments to reduce pain and stress in infants include behavioral and environmental strategies such as non-nutritive sucking, administration of sucrose, swaddling and containment, attention to sound and light, limiting environmental stressors such as clustering of care and allowing for rest periods.[14] Pharmacologic treatments include narcotic and non-narcotic analgesics, sedatives and in extreme circumstances paralytic agents.

Taste[1,2,3]

Taste buds appear at 8-9 weeks' gestation with chemoreceptors fully present by 16-18 weeks. Taste buds of the infant prefer sweet tastes and withdraw from bitter tastes. Taste buds are very important in the initiation of a coordinated suck and swallow response and their underdevelopment is associated with a delayed initiation of oral feedings especially in premature infants.

Smell[1,2,3]

The olfactory system develops early and is thought to be functioning in a fetus at 16-18 weeks' gestation. It is very important in infant-mother bonding and also helps coordinate the proper functionality of other senses.

Sound[1,2,3]

A fetus is capable of responding to sound by 25 weeks' gestation. Both cortical and brain stem auditory-evoked responses can be elicited at 24-28 weeks' gestation. Preterm infants generally have a hearing frequency range of 500-1000 Hz compared with term infants, who have a frequency range of 500-4000 Hz. The adult hearing frequency range is 30-20,000 Hz. Sound in the amniotic fluid is 70-85 dB and less than 1000 Hz. In the NICU, the intensity increases to >90 dB and the frequency ranges from 500-10,000 Hz.[15] Common sounds in the NICU include:

- Intravenous pump alarms (61-78 dB)
- Writing on tops of incubators (59-64 dB)
- Vacuum sounds (70 dB)
- Bottles being placed on top of incubators (96 dB)
- Metal door cabinet of incubator opening and closing (96 dB)
- Telephones ringing (80dB).

Sound levels of >55 dB arouse an infant from light sleep and levels >70 dB are incompatible with sleep in term infants. Preterm infants are at risk for sensorineural hearing loss, which occurs at a rate of 10% compared with 0.5% for term infants.[16] Increased hearing loss has been reported in school-aged children whose mothers were exposed to noise levels of 65-85 dB approximately 8 hours per day during pregnancy.

The American Academy of Pediatrics (AAP) recommends that NICU sound levels should be <45 dB with minimization of levels of >80 dB to less than 10-minute durations.[17] Sound levels should be measured from time to time in the NICU and appropriate measures to decrease levels to less than 45 db should be instated. Incubator covers decrease noise levels inside the incubator. Soft ear plugs/covers have been found to increase oxygen saturation, decrease behavioral state changes, and increase quiet sleep time.[18] Easily preventable and cost effective measures include rounding away from the bedside, setting beepers to vibration mode, and placing signs to remind staff/families to be quiet. Removing radios and cell phones from the NICU and padding garbage cans are also helpful.[19]

Sight[1,2,3]

Vision is the last sensory system to develop and all visual structures and pathways are developed by 24 weeks of gestation. Visual evoked responses (VERs) can be elicited as early as 24 weeks' gestation, and by 36 weeks' gestation VER is similar to that of an infant carried to term. At birth the newborn has at least 20/150 vision, while color vision develops at 2 months of age.

Bright lights are stressful for neonates as intrauterine environment is dim with minimal light. NICU overhead light (80-90 fc) is much brighter than the intrauterine environment or light at home (50-60 fc). A premature infant is unable to guard against light exposure and needs shielding from the common sources of light in the NICU. At least 38% of white light can penetrate the eyelids and excess light exposure at 32-40 weeks' gestational age may lead to sensory interference.[20]

Constant high-intensity light in the NICU can interfere with the natural circadian rhythms.[21] Cycling low (1 fc) and normal light levels (60 fc) in the NICU can help develop normal day and night rhythms. Cycling is associated with lower heart and respiratory rates, increased behavioral organization, faster weight gain, and decreased length of hospitalization and ventilator days in infants.[22]

The AAP recommends maintaining light levels at 1-60 fc by day and 0.5 fc at night. NICU staff should be educated regarding the impact of light on infant outcome. Protective covers over the infant's eyes during examination and repositioning should be utilized. Windows and overhead lights are the two most common sources of increased light intensity. Incubator covers help to avoid direct natural/sunlight that may come from windows. Individual light source controls and dimmers are effective in minimizing overhead light. Overhead light intensity should be minimized and individualized for each infant.

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Antiviral Therapy in Neonatal Cholestatic Cytomegalovirus Hepatitis

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Abstract

Background: Neonatal hepatitis refers to a heterogeneous group of disorders, caused by many factors including cytomegalovirus infection, revealing similar morphologic changes in the liver of an infant less than 3 months of age. Approximately 40% of cholestasis in infants is due to neonatal hepatitis. It may cause latent or acute cholestatic or chronic hepatitis, including cirrhosis in immunocompetant infant.

Methods: Twelve infants diagnosed with neonatal cytomegalovirus hepatitis in the last one year were included in the study. Group 1 consisted of seven babies treated with ganciclovir for 21 days. Group 2 included five cases who did not receive antiviral treatment. Physical examination, biochemical, serologic and virologic tests were done for both groups at the time of diagnosis and in the third month.

Results: Initial levels of total bilirubin, aminotransferases, gamma glutamyl transpeptidase, and alkaline phosphatase revealed a significant decrease after the treatment in Group 1 ($p < 0.05$) when compared with Group 2. This study revealed that ganciclovir treatment is safe and effective in cases with cholestatic hepatitis. Similarly, all the patients in the treatment group had evidence of improvement serologically and virologically, while the comparison group did not reveal any significant change ($p < 0.01$).

Conclusion: The clinical spectrum of perinatal infection varies from an asymptomatic infection or a mild disease to a severe systemic involvement, including central nervous system. The treatment in the early period of infection improved serologic markers and cholestatic parameters significantly. Further studies will lead us to clarify the efficacy of ganciclovir treatment in the early period of cytomegalovirus hepatitis, and the preventive role of anti-viral therapy on progressive liver disease due to cholestasis and hepatitis in neonatal cytomegalovirus infection.

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Background

Neonatal hepatitis is a specific type of hepatitis seen in the first months of life. Hepatitis A-E viruses and other hepatotrophic viruses (Epstein-Barr virus(EBV), herpes viruses, adenoviruses and parvovirus) are known to be the main causes of the disease. It is obvious that A-E hepatotrophic viruses are the main causes of etiology in 10% of acute viral hepatitis cases without immunosuppression. Cytomegalovirus (CMV) is a member of herpes virus family, and although it is known that CMV and other herpes viruses can cause significant pathologies (particularly in immunodeficient patients), they can also affect individuals with normal immune system. Typical acute unicteric hepatitis, as a part of systemic infection, is one of these pathologies.[1]

Approximately 20% of children less than 15 years of age and 50–60% of individuals younger than 25–30 years of age are infected with CMV. It is known that virus replicates in both hepatocytes and cholangiocytes during infection. However, controversy exists about the pathogenesis of hepatic disease whether related to the direct cytopathic effect of the virus or the immune response of the host. In addition, the hepatocyte damage in latent infections has not yet been well explained. Besides this, it is obvious that patients with chronic viral hepatitis and cirrhosis may have more sensitivity to acute CMV infections resulting in additional hepatic damage.[2-4]

In severe cases, ganciclovir or foscarnet treatment may be effective. Although ganciclovir treatment reported to be effective in CMV retinitis, esophagitis, hepatitis and pneumonia in adults, there is insufficient research in children. It is mentioned that ganciclovir may be used effectively in symptomatic congenital or neonatal CMV infections but its side effects are of concern.[3]

In the current study, the objective was to evaluate efficacy of ganciclovir in cholestasis of neonatal CMV hepatitis, which is an important step for prevention of chronic CMV hepatitis.

Table 1.The Demographic Characteristics of the Groups

Groups (n=number of cases)	Age (months) Mean±SD Median	Sex		Weight (kg) Mean±SD Median
		M	F	
Group 1 (n=7)	*3.7±2.4 3	** 3	4	△5.05±1.6 4.7
Group 2 (n=5)	*6.6±2.2 7	** 4	1	△5.97±2 5.9

*, **, △ NS

Table 2. The Comparison of the Physical Examination Findings of the Groups

Groups		Jaundice (n)	Hepatomegaly (n)
Group 1 (n=7)	Initial	*3	**5
	Posttreatment	2	2
Group2 (n=5)	Initial	*1	**2
	Control	2	2

*, ** NS

Methods

Twelve infants diagnosed with neonatal cytomegalovirus hepatitis in the last one year were included in the study. Local ethics committee (Abant Izzet Baysal University, Duzce Medical Faculty Ethics Committee) approved the study and the written informed consent obtained from the parents of the patients. The babies (n: 7) whose parents accepted ganciclovir therapy formed the treatment group(Group1), while the other five babies without ganciclovir therapy formed the comparison group (Group 2) (Table 1). One baby with ileal atresia (because he may have had additional enterohepatic circulation disorder) and another one with myoclonic convulsions receiving anticonvulsant therapy (because he may have had additional toxic hepatitis) were excluded before the study groups were chosen. Liver biopsy was performed in babies with unexplained hypertransaminasemia icterus and/or hepatomegaly, in order to reveal idiopathic neonatal hepatitis, extrahepatic bilier atresia, immune insufficiency and metabolic hepatic disorders (such as ·1antityripsine deficiency, storage disorders) which were also among exclusion criteria. Convulsions, petechia, purpura, chorioretinitis, microcephaly, neuromuscular dysfunction, cerebral calcifications, and/or severe disease that may be seen in congenital CMV infections were not observed in any patient.

Children in Group 1 were treated with ganciclovir (10 mg/kg/day, in two doses) for 21 days. Antipruritic treatment for cholestasis, calcium, vitamin D, and other lipophilic vitamin supplementation were given to both groups.

All the patients' clinical and laboratory parameters (age, icterus, organomegaly, ALT, AST, ALP, GGT, T. Bil., D. Bil., CMV Ig G and CMV Ig M antibody, CMV avidity and CMV-DNA) were evaluated initially and at the third month of the study. Anti-CMV IgG and IgM ab titers were measured with ELISA method and CMV-DNA was detected with PCR. CMV-DNA was purified with QIAmp DNA Blood Mini Kit (Qiagen, Hamburg). Quantitative PCR analysis was performed by RealArt CMV RG PCR Kit used with Rotor-Gene 2000/3000. The quantitation standards were defined as copies/µl. An equation was used to convert the values determined using the standard curve into copies/ml of sample material:

$$\text{Result (copies/ml)}: \frac{\text{(Result (copies/µl) x Elution volume (µl))}}{\text{Sample volume (ml)}}$$

For preparation of PCR assay, a standard volume (20 µl), of sample DNA was mixed with 30 µl of CMV RG Master. Data analyses were performed with Rotor-Gene software according to the manufacturer's manual.

Statistical analysis was performed using Mann-Whitney U Test for comparison of the initial and the third month changes of weight and CMV-DNA PCR, Fisher's Chi square exact test for the variants such as sex, organomegaly, jaundice and CMV antibody titers, and Wilcoxon Test was used for the comparison of individuals among each group (SPSS 13.0 version).

Results

The mean age of seven babies (four female, three male) in Group 1 and five babies (one female, four male) in Group 2 was 3.7 ± 2.4 months and 6.6. ± 2.2 months, respectively. One baby in Group 1 and two babies in Group 2 had low weight percentile at the initial evaluation. There was no significant statistical difference between groups regarding to age, sex and weight (NS, NS, NS respectively).

In the physical examination, five babies in Group 1 and two in Group 2 had hepatomegaly (liver was palpated >2 cm below the last rib) at the first evaluation (NS). One baby in each group had palpable spleen evaluated as a normal variation.

Liver biopsy was performed for 7/7 babies in Group 1 and for 4/5 babies in Group 2. Although hepatic inclusion bodies are rarely found in the histopathologic examination of pediatric cases, it was detected in one baby in Group 1. Granulomatous changes and findings related to cholestasis were determined in four babies in the treatment group and two babies in the comparison group. Nonspecific histopathological findings of

Table 3. The Comparison of the Biochemical Values of the Groups

Groups		T.billirubin mean±sd median	D.Billirubin mean±sd median	ALT mean±sd median	AST mean±sd median	ALP mean±sd median	GGT mean±sd median
Group 1 n=7	Initial	*4.6±3.2 4.6	*3.9±2.5 4	*119.4±56.4 80	*167±68.4 197	*1148±300 750	♦4414±186.3 110
	Posttreatment	1.29±0.82 2.5	0.53±0.27 0.3	53±18.5 54	75±28.1 58	556±196.5 324	150.7±61.5 71
Group 2 n=5	Initial	**2.52±1.07 1.45	**1.42±0.45 0.25	**172.7±57.6 92	**155.2±68 93	**393.5±44.7 381	♦♦67.7±25 49
	Control	4.37±2.21 0.3	2.97±1.75 0.1	123.2±18.5 98	152.7±47 116.5	435.7±37.5 311	73.2±24.6 51

Comparison of initial and post treatment values among Group 1
♦ $p<0.01$
* $p<0.05$

Comparison of initial and control values among Group 2
**, ♦♦ NS

Table 4;The Comparison of serological CMV markers in Groups

Groups		◊ CMV IgM (+) patient no/total	CMV IgG avidity >0,8 patient no	* Ψ CMV DNA copy/ml
Group 1 (n=7)	Initial	7/7	5	2230(166-9240)
	Posttreatment	0/7	3	14 (8-1930)
Group 2 (n=5)	Initial	3/5	3	2178(158-2917)
	Control	3/5	1	1915(656-2900)

◊ The ratio of patients, in each group, having affirmative results in the second evaluation ($p<0.01$)
* Median (minimum-maximum)
Ψ The comparison of value changes between first and second evaluation ($p<0.05$)

CMV hepatitis as lymphomonocytic cell infiltration, hydrophic degeneration, mild steatosis, perisinusoidal fibrosis, and Kuppfer cell hyperplasia were found in all babies.

At the initial evaluation, three babies in Group 1 and one baby in Group 2 had icterus. They were still icteric at the third month (NS) (Table 2, 3). In comparison with Group 2, initial levels of total bilirubin, AST, ALT, GGT, and ALP revealed a significant decrease in Group 1 after the treatment($p < 0.05$) The differences of initial and third month values were statistically significant among the babies in Group 1 (Table 3). No significant change was observed in the comparison group at the third month regarding to initial values (NS) (Table 3). The serological evaluation for CMV revealed that all the babies were CMV IgG (+) and CMV IgM antibody was found in five and three babies in the treatment and comparison groups, respectively. CMV avidity test was not available for the whole group. The avidity value indicating infection longer than 3 months (avidity index >0.8) was determined in 60% and 33% of the evaluated babies in the treatment and the comparison group, respectively (Table 4). The confirmative serological changes were defined as the decrease in CMV IgG antibody or avidity titers, or loss of CMV-IgM antibody at the third month's evaluation. While all the patients in the treatment group had evidence of serologic improvement ($p < 0.01$), the comparison group did not reveal any significant change (NS). Similarly, CMV-DNA PCR values decreased to desirable levels following the treatment in Group 1 ($p = 0.05$). However, the changes in the comparison group were inconsiderable (Table 4).

Discussion

Neonatal hepatitis refers to a group of pathologies causing similar morphologic changes in the liver of the babies less than three months of age. It is blamed for 40% of cholestatic situations in the neonates after exclusion of extrahepatic biliary atresia. It affects males more frequently than females, and similar results were found in the present study. As the term "idiopathic neonatal hepatitis" refers to the neonatal hepatitis of unknown (but probably multifactorial) etiology, "neonatal hepatitis" is caused by a group of well defined etiologic factors, so treatment should be considered.[1,3,5]

Neonatal cytomegalovirus infection may occur due to either intrauterine or perinatal exposure to CMV infected cervicovaginal secretion and breast milk. The clinical spectrum of perinatal infection varies from an asymptomatic infection or a mild disease to severe systemic involvement, including central nervous system.[6]

The clinical presentation of acute neonatal CMV infection resembles the mononucleosis of the Epstein-Barr virus seen in neonates and immunodeficient individuals with fever, malaise, and cervical lymphadenopathy. Severe jaundice and granulomatous hepatitis also have been established due to

neonatal CMV infection.[1,3] Physical examination may reveal minimal hepatomegaly and mild jaundice, in addition to slightly increased serum aminotranspherases (less than threefold of normal values).[4]

CMV infection is unlikely to be a cause of massive hepatocellular necrosis in a normal host. Previous studies reported that transaminases reached the highest levels (<200 U) in the second or third week of infection, decreasing to normal values by the fifth week.[4] In our study, transaminases increased moderately in both groups, but a significant decrease at the third month was observed only in the treatment group.

The laboratory tests used for serologic diagnosis of CMV hepatitis are CMV-IgM ab, CMV early antigen (in tissue or blood), CMV-DNA PCR and virus cultures.[8,12] We could not obtain viral cultures or early antigen titers of the babies in our study, but the liver biopsy evaluations suggested CMV hepatitis. In the histopathologic examination of liver, the presence of cytomegalic cells and inclusion bodies refers to the intensive immune activation against viral attack. The liver damage in an immunocompetant individual is mostly due to the primary immune response of the host, whereas cytopathic damage of the virus has priority in patients suffering from immune deficiency.[1]

Chang et al recently evaluated the existence of CMV-DNA in liver biopsy samples of healthy neonates in comparison to the neonates with neonatal hepatitis. He reported that CMV DNA was detected in 46% of babies with neonatal hepatitis (n: 50) whereas none of the healthy group had viral DNA (n: 30). Thus, he suggested that CMV could play a major role in the pathogenesis of neonatal hepatitis.[9] Although it has been reported that hepatomegaly might regress spontaneously in the first year of life in babies with congenital CMV infection, portal hypertension may occur without the evidence of cirrhosis.[10,11] In the current study, one patient in the comparison group died of abundant upper gastrointestinal haemorrhage at the age of 18 months as a result of portal hypertension without cirrhosis. Two patients in the same group also progressed to chronic hepatitis.

The necessity of treatment is controversial in neonatal CMV infection, as spontaneous recovery is expected in most cases unless severe systemic disease occurs.[3,12] However, as in the present study, an increasing number of studies indicate the necessity of treatment, especially in cases with symptoms of acute or chronic cholestatic hepatitis or proven histopathological findings.[3,13-17] A new study from Lanari et al. demonstrated the importance of high CMV-DNA titer on development of sequelaes. Furthermore, they suggested that the CMV-DNA quantity could be useful for identifying the patients who will benefit highly from antiviral therapy.[18]

Ganciclovir is recommended as a first step antiviral agent for the management of congenital CMV infection. Most common adverse effects of ganciclovir treatment include dose-dependent neutropenia and blood counts including absolute neutrophil count. Therefore, leukocyte counts should be monitored closely during treatment. In our treatment group, we have not seen any severe adverse effects requiring the cessation of the treatment.[3,6]

Conclusion

We suggest that ganciclovir therapy significantly improves the clinical course of neonatal cholestatic CMV hepatitis. Currently the number of studies of neonatal cholestatic CMV hepatitis is insufficient. New and extensive research will lead us to clarify the efficacy of ganciclovir treatment in the early period of CMV hepatitis, and the preventive role of anti-viral therapy on progressive liver disease due to cholestasis and hepatitis in neonatal CMV infection.

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Benefits and Challenges of Transitioning Preterm Infants to At-Breast Feedings

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Abstract

Upon hospital discharge it is not unusual for mothers of preterm infants to continue to meet all or most of their infants' nutritional needs through bottle feedings of expressed breast milk (EBM) because of infants' physiological immaturity and maternal concerns with an inadequacy of milk supply. Although for some mothers the challenge of transitioning the infant to feeding at the breast may be beyond their ability and resources, for others it appears to be based on a conscious choice. Mothers are often unaware of the advantages of breastfeeding at the breast. The purpose of this article is to examine some of the factors that may contribute to the inability and resistance of mothers to transition their preterm infants, and to report on the potential short and long-term advantages associated with feeding at the breast as opposed to feeding bottles of EBM.

Review

Breast milk for preterm infants has been found to reduce the health risks associated with feeding infant formula including a higher incidence of infections and necrotizing enterocolitis,[1,2] lower scores on cognitive and developmental tests,[3-5] and decreased visual development.[6] However, preterm infants encounter a number of barriers to breastfeeding due to their immature physiological and neurodevelopmental systems. Mothers desiring to breastfeed their preterm infants are often initially encouraged to express breast milk by hand or breast pump; the expressed breast milk (EBM) is then given to the infant by gavage or bottle. Later some mothers are able to transition from gavage feeding to exclusive feeding at the breast in a short period of time without problems. Others take more extended time and experience this process as a trial and error period fraught with challenges.

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In a qualitative study of mothers' experiences with breastfeeding their infants in a neonatal unit in Sweden, mothers found the process of feeding their infants at the breast to be closely regulated with strict routines including scheduled times, limits on the amount of time at the breast, and pre and post test-weighings.[7] When the mothers were successful feeding at the breast, they described feelings of pride and security. However, when their attempts were not productive, mothers expressed feelings of disappointment, frustration, rejection, shame and inadequacy, which interfered with the mother-infant relationship.[7]

Upon hospital discharge, it is not unusual for mothers to continue to meet all or most of their infants' nutritional needs through bottle feedings of EBM or commercial infant formula because of their infants' weaker, less coordinated suck, problems staying alert during feedings, and difficulty in giving clear cues for hunger and satiety.[8,9] Rather than being transitioned to at-breast feedings, preterm infants are often gradually weaned from bottles of EBM to infant formula, as the mother decreases her pumping frequency leading to a diminishing supply of breast milk. In the US breastfeeding rates of preterm infants receiving mother's milk exclusively at-breast upon discharge have been found to range from 18–32% at discharge from the hospital, increasing only slightly to 23–38% by four weeks post-discharge.[9,10]

The advantages of transitioning the infant to feeding at-breast may be poorly understood by some mothers and health professionals. Mothers have raised questions about at-breast feedings, such as, "Why should I try to breastfeed at the breast? Isn't the baby getting all that is needed from my pumped breast milk?" or "What are the advantages of breastfeeding at the breast as opposed to feeding bottles of breast milk? Does it really make a difference to the baby's health, growth or development?" In some cases, the mothers' inability or reluctance to transition to at-breast feedings may be due lack of knowledgeable and consistent support, teaching and assistance by the health care team. Being aware of the clear advantages of at-breast feedings may also be helpful to health care providers

in providing support and information for these mothers. The purpose of this article is to discuss some of the factors that may contribute to mothers' need for support and information in transitioning to full at-breast feedings and to examine the potential short and long-term advantages associated with feeding at-breast as opposed to feeding bottles of EBM.

Impediments toward transitioning

To effectively counsel and support mothers in transitioning to full at-breast feedings, it is important for nursing and medical staff to have an understanding of the factors that may contribute to mothers' inability or resistance toward this process (Table 1). A central factor in determining the exclusivity and duration of breastfeeding for the preterm mother-infant couple is the volume of milk production. Early initiation of frequent and efficient milk expression has been found to be a key factor in adequacy of milk supply, considered by some experts to be greater than 500 ml per day.[11-14] It is likely that inadequate levels of breast milk production not only impair the infant's ability to access breast milk, but also burden the mother with "triple feeding" (feeding at the breast followed by supplementation with a bottle, then by pumping), leading mothers to abandon their efforts early.

Even when mothers are able to pump more than adequate milk volumes for their preterm infant, they may continue to report feelings of vulnerability related to breastfeeding in the early postpartum period.[15,16] These concerns may be promoted by the inability of some preterm infants to consume enough of the available milk because of their immature feeding behaviors. Jain and others found that preterm infants not only feed more slowly than full-term infants, but also consume lower volumes per suck.[17] This may be due to the infants' relatively low suction pressures and irregular sucking bursts.[18] Meier and Brown report that upon hospital discharge some preterm infants require complementation of breastfeeding with a bottle, supplemental nursing system, nipple shield or other breastfeeding device until the infant's gestational age reached full-term, corrected age and adequate intake of breast milk at-breast is achieved.[8]

Assuming that an infant is physiologically ready for feedings at the breast, there may be more personal reasons that contribute to a mother's discomfort or reluctance toward transitioning. A mother's initial reasons for supplying breast milk during hospitalization may play a role in her decision. The choice to breastfeed or provide breast milk for a premature infant is affected by factors other than those that influence decisions of mothers of full-term infants.[19] Mothers of preterm infants may experience feelings of anxiety, vulnerability, depression and guilt surrounding the birth of the infant.[20] In response to these feelings and the information that mothers receive from nurses and physicians in the neonatal intensive care unit (NICU), some mothers change from their initial decision to formula feed to providing EBM for their infants. One of the primary extrinsic factors affecting this decision is mothers' learning of the superiority of breast milk in terms of infant growth and reduced infection rates.[21] Mothers described the offering of their breast milk to their preterm infants as a unique contribution that was likely to have a positive impact on their infants' outcome.[19] In a study of mothers of very low birth weight (VLBW) premature infants, several sociodemographic characteristics influenced breastfeeding decisions. Older white mothers who were married with higher levels of education, previous breastfeeding experience, and carried private insurance or that of a health maintenance organization were not only more likely to express breast milk initially for feedings, but also to progress to feedings at the breast.[22] Although some mothers agree to express milk with a breast pump for a short-term basis, they may have strong personal needs or reasons for not wishing to continue by feeding their infant at breast.[18]

Table 1: Contributing factors to mothers' inability or resistance to at-breast feedings

- Inadequate breast milk supply
- Maternal feelings of vulnerability and lack of confidence
- Infants' immature feeding behaviors
- Lack of commitment or desire to breastfeeding prior to the birth
- Personal choice
- Bottle feeding more convenient
- Ability of father or other family members to participate in feedings
- Avoidance of embarrassment of feeding in public
- Ease of pumping and storing breast milk
- Maternal lack of confidence
- Parental need to quantify intake
- Lack of informational and emotional support

Mothers' feeding preferences for their preterm infant may be similar to those found in mothers of full-term infants, who choose to bottle feed infant formula. Bottle feeding has been reported by mothers to be more convenient, especially considering that fathers or other family members may be able to feed the infant allowing the mother more freedom in being able to leave the infant for longer periods of time.[23] The participation of the father in feeding is seen by some mothers as a good way of involving fathers in the care for the baby.[24] Bottle feeding allows some mothers to avoid the perceived embarrassment of breastfeeding in public.[23]The portability and convenience of using breast pumps may also contribute to these choices.[25] Mothers who plan on returning to work may view the pumping as needed.

Mothers' reluctance to feed the preterm infant at-breast may also be due to a maternal lack of confidence in having enough breast milk. Wooldridge and Hall studied a group of preterm infants between 30–35 weeks gestation, without any facial or gastrointestinal anomalies or identified syndromes, over a four-week period following hospital discharge.[9] They found that mothers who were able to breastfeed exclusively or feed at-breast more than half of the time had significantly higher levels of confidence than those who were giving breast milk and infant formula.[9]

Another factor that may play a role in a mother's desire to continue pumping and feeding EBM is a parental need to carefully quantify the intake of her infant. In a study of mothers' concerns about breastfeeding preterm infants after discharge, the researchers reported the mothers' feelings of vulnerability were not "unreasonable, given that volume intake was measured to the nearest millimeter throughout the infants' hospital stay" [15, p30]. In response to these feelings of vulnerability, mothers may become preoccupied with schedules, times, routines and careful quantification of the infant's intake. Although several observational tools have been developed to assess effectiveness of breastfeeding, there is a lack of reliable and valid tools that can be used by mothers to visually determine milk intake for their preterm and low birth weight (LBW) infants.[26] The clinical

Table 2: Benefits of feeding at-breast as opposed to bottle feeding expressed breast milk (EBM)

Benefits to infant	
Improved oxygenation and temperature regulation during feedings	• Higher oxygen saturation • Better coordinated sucking, swallowing, breathing pattern • Increased body temperature • Fewer episodes of apnea and bradycardia
Advantages of skin-to-skin contact	• Increased breast milk volume • Greater production of maternal milk antibodies to pathogens in infant's environment
Enhanced nutritional and immunological properties of breast milk	• Superior nutritional content lost by freezing, thawing and reheating EBM • Lower risk of bacterial contamination and growth due to handling
Better oral development	• Optimal mandibular development • Strengthening of the jaw muscles • Increased nasal cavity space • Improved future teeth alignment and decrease in malocclusions • Greater breathing efficiency
More efficient emptying of the breast	• Greater milk volume in same amount of time as breast pump • Increase in milk volume over time
Benefits to mother	
Reduced risk of breast trauma	• Less risk of mastitis with ineffective emptying of breast • Lower risk of damage to nipple from breast pump
Reduced risks to mothers' health	• Decreased incidence of type 2 diabetes • Reduced risk of breast cancer
Psychological effects	• Potential reduction in perceived stress and negative mood after feedings
Practical advantages	• Less time in preparing EBM for feeding and cleaning of supplies • Breast milk at optimal temperature without preparation • Cost savings in not renting or buying an electric breast pump

indicators of estimating milk intake that are often used for mothers of term infants, such as changes in breast fullness after feeding and audible swallowing, have not been found to be useful in measuring adequate intake for preterm infants. A more accurate measure of milk intake at-breast has been established by pre and post test-weighings.[16] However, some clinicians are concerned that test-weighings are mechanical and unnecessary, and this concentration on numbers may interfere with breastfeeding.[16,27] The use of test-weighings varies between settings.

Finally, in some cases the inability of mothers to transition to the breast is not due to resistance on the part of the mother, but due to a lack of knowledgeable and consistent support to the mother and family. The lack of informational and emotional support by those counseling the breastfeeding mother may contribute to the reluctance of mothers to transition to breastfeeding. With shorter hospital stays in the United States, fewer preterm infants are entirely feeding at-breast prior to discharge as compared to Canada and European countries.[11] In these countries the funding of health care and cultural differences, such as extended paid maternity leave, may affect the acceptance of breastfeeding. For example, significant compensation leave benefits from employment for parents are guaranteed in Sweden after childbirth to ensure a long period of breastfeeding.

If infants are discharged prior to their full-term corrected age, it is likely that they may not be ready to fully transition to the breast. This may leave mothers in a position of finding the resources to undertake this endeavor on their own. In the US, home health agencies may have physician orders and insurance reimbursement for a few visits, but these infants are generally discharged from home care by one to two weeks post hospital discharge. Further, the expertise needed in helping a mother transition to the breast often requires an expert in lactation. In a case study of transitioning a 36-week-old premature infant to the breast after hospital discharge, Drosten describes the difficulty and time involved for a mother, who had a routine of pumping six times per day as well as attempting to slowly breastfeed her infant before every bottle feeding.[28] She gives recommendations that included special positioning of the infant for feedings, using breastfeeding devices for supplementation, developing a realistic but adequate pumping schedule with an increased frequency of up to eight times a day, and monitoring feeding schedules and weight gains. Once an infant is discharged from the hospital, these services may be unavailable to mothers who cannot afford a private lactation consultant in the US.

Benefits of at-breast feedings

Although the advantages of breastfeeding have been well described in the literature, the focus of this section is on the specific advantages of feeding at the breast as opposed to bottle feedings of EBM. Mothers, who are expressing breast milk for their preterm infants and feeding it by bottle, might benefit from the knowledge of the advantages of feeding at the breast in order to make the decision whether or not to move to the next level of breastfeeding. Feeding an infant at the breast has been found to provide physiological benefits to the infant, as well as physical, psychological and pragmatic benefits to the mother (Table 2). Some of these advantages appear to be short-term, whereas others become more evident over longer periods of time.

Physiological benefits for infants

The primary short-term benefits of an infant receiving breast milk at the breast are physiological. In studies conducted by Chen and others, the researchers found that in comparison to

bottle-feeding events, preterm infants tend to have higher oxygen saturations when they were directly breastfed, which may be due to more coordinated sucking, swallowing and breathing during breastfeeding.[29] They also found the breastfed infants' body temperatures were higher during feedings despite the bottle feeding infants being fed inside the incubator. The researchers propose that this finding may be related to the infants' position during breastfeeding, the skin-to-skin contact with the mother, and the temperature of the breast milk. Preterm infants have also been found to have less variation from baseline in heart rate, respiratory rate and oxygen saturation, and fewer episodes of apnea and bradycardia during breastfeeding when compared to bottle-feeding.[30-32] These findings may be due to infants' ability to breathe easier during sucking bursts and to regulate their breathing pattern during sucking pauses while breastfeeding. Breast milk not only helps the infant nutritionally, but taken at-breast appears to benefit the infant physiologically.

Skin-to-skin contact

Feeding an infant at-breast necessitates some skin-to-skin contact between the infant and mother. Mothers who hold their premature infants skin-to-skin (also known as kangaroo care) often experience an increase in breast milk volume and possibly a greater production of maternal milk antibodies to specific pathogens in the infant's surroundings.[33] Therefore, it is feasible that some of the benefits experienced with skin-to-skin care may also emerge through breastfeeding at the breast.

Nutritional & immunological benefits

Taking breast milk at the breast rather than from a bottle offers other advantages to the infant. Breast milk loses some of its nutritional and immunological properties by freezing, thawing and reheating in the process of expressing the breast milk prior to feeding it with a bottle, which reduces the protective benefits offered by breast milk.[18] Rapid heating, especially in a microwave oven, and at high temperatures contributes to an even greater loss of beneficial components. For example, ascorbic acid levels decrease significantly when stored at low temperatures, and have been found to drop 40% when reheating.[34] Further, there may be risks of bacterial contamination and growth, if the breast milk is not expressed and handled appropriately.

Infant oral developmental effects

In addition to the potential physiological, nutritional, immunological and more efficient advantages offered by receiving breast milk at-breast, infants may benefit from fewer dental problems later in life. According to Palmer, breastfeeding at-breast has a positive effect on the development of an infant's oral cavity including optimal mandibular development, strengthening of the jaw muscles, and increased nasal cavity space.[35] During breastfeeding, the tongue, lower lip and mandible move in concert to draw the milk into the mouth by a stripping action, gently shaping the infant's hard palate. This process leads to an enhanced formation of the hard palate producing improved future teeth alignment and a decrease in malocclusions. Whereas the shape of the breast-nipple is in a geometric form consistent with the infant's mouth, the artificial nipple in bottle-feeding hinders the formation of the jaw muscles. Palmer also proposes that the increase in nasal space may have a significant effect on the person's breathing efficiency, reducing later problems with snoring and obstructive sleep apnea.[35]

Efficiency of feeding

Another potential advantage of feeding at the breast for infants who have reached term is related to the infant's efficiency of feeding. Zoppou, Barry and Mercer used a computer model to compare the differences between breastfeeding and breast pumps.[36] The pump relies on suction to remove milk, whereas the infant uses a massaging motion of the tongue and jaw to apply a peristaltic force through compression of the nipple and most of the areola at a particular time during the suction cycle. This peristaltic force acts as a stripping mechanism of the milk from the breast. The amount and timing of the peristaltic force is crucial in increasing the amount of milk volume obtained. In comparison to breast pumps that only apply suction, the researchers were able to demonstrate an increase of 15% in milk volume, when they altered the speed of the peristaltic force and the time it was utilized in the suction cycle. The data suggest that once infants reach term and have an appropriate strong, coordinated suck, they may get more milk volume in the same amount of time as a breast pump, and that the suction and compression seen in breastfeeding are mutually dependent during suckling. Hill and others recently compared the milk output of mothers of preterm and term infants.[37] They found that whereas the milk output increased for the mothers of term infants over time, it remained stable or declined for the mothers of the preterm infants, who were using regular mechanical expression.[37]

Reduced risk of breast trauma

Although electric breast pumps have been crucial for the milk supply of many mothers of preterm infants, they also offer some potential disadvantages. Problems with breast pumps may be overlooked and contribute to ineffective emptying of the breast, especially if they are underpowered or poor fitting.[38] Some researchers have suggested that the breast pump's reduced physiologic mechanism may negatively affect emptying, especially in the periphery of the breast and may be a contributing factor to the association between pump use and mastitis.[39] Another disadvantage of breast pumps is that they work primarily on suction, and may be ineffective if set at too low a level (<150 mmHg) or cause damage to the nipple skin if set too high (>200 mmHg).[36]

Lack of breastfeeding is a risk to mothers' health

It is reasonable that when mothers are successful breastfeeding at the breast, they are more likely to continue breastfeeding longer, and reduce the health risks of not breastfeeding. Breastfeeding reduces mothers' risk of developing type 2 diabetes later in life.[40] In an analysis of data from 47 epidemiological studies in 30 countries, breastfeeding was also found to reduce the relative risk of breast cancer by 4.3% for every year of a woman's life spent breastfeeding.[41]

Psychological effects of breastfeeding

The act of breastfeeding has also been associated with positive psychological effects for the mother in respect to mood and stress. Mezzacappa and Katkin conducted a study among 28 mothers who were both breastfeeding and bottle feeding.[42] After a breastfeeding session, the mothers were found to have a reduction in perceived stress and negative mood relative to what was found after a bottle feeding. In contrast, bottle feeding appeared to decrease positive mood. The researchers suggested that the higher levels of the hormone oxytocin released by breastfeeding contributed to the decrease in negative mood.[42] The authors also speculated that over time breastfeeding may

condition the mother to regard her infant positively leading to greater mother-infant attachment, and the decrease in negative mood and stress associated with breastfeeding may reduce the risk of postpartum depression.[42] These findings are consistent with those found by Shepherd and others, who reported a higher maternal contentment level and a positive emotional experience in women who breastfed their infants.[24]

Practical advantages for mothers

Finally, there are the practical advantages for a mother, who transitions to at-breast feedings rather than continuing to feed EBM. One benefit is the savings in time and effort of feeding. Hours of the mothers' time, which were previously spent in expressing breast milk and later preparing it for refeeding and cleaning bottles and breast pump equipment, are saved. The milk is always available in the breast at an ideal temperature. The time and effort spent in pumping and refeeding around the clock has clear advantages for the infant with immature sucking skills, but once the infant is able to efficiently feed at-breast, these efforts may become overwhelming for the mother leading to early weaning to infant formula. There may also be a considerable cost savings to the mother in not having to rent or buy an electric breast pump.

Breastfeeding advice falling short

Some neonatal units are more successful than others in transitioning infants to at-breast feedings prior to discharge. In a study of interventions for VLBW infants, Miracle and others reported that one of the primary reasons for the high rates of lactation in the unit they studied was due to the encouragement the mothers received from the NICU nurses and physicians.[19] Mothers wanted the care providers to discuss the benefits of human milk feeding in order that they could make an informed decision.[19]

Even in NICUs where mothers are encouraged by health care professionals to provide breast milk to their preterm infants, is the advice falling short? Hurst and Meier suggest that mothers who did not intend prenatally to breastfeed their preterm infants may be reluctant to begin breast milk expression for their infant in the NICU if they have to make a commitment for several months.[18] Further, they recommend that health care professionals should not encourage mothers to feel that an alternative to long-term exclusive breastfeeding is "second best." While the message in the NICU may be to get the baby off to the "best start" and to postpone other breastfeeding decisions, there are potential risks of not providing mothers prior to hospital discharge with the opportunity and clear benefits of eventually transitioning to feeding at-breast as opposed to only pumping and feeding EBM.

One of the primary factors contributing to early termination of breastfeeding in mothers of preterm infants is the failure to transition from breast milk to at-breast feedings. In a study of mothers of VLBW infants, the mothers who lactated the longest were those who were expressing at least five times a day and had put the infant to breast by 35 weeks corrected age.[12] In another study of low-birth-weight (LBW) infants in a Swedish neonatal unit, mothers were encouraged to initiate breastfeeding as soon as their infants were clinically stable rather than a standard based on weight or gestational age.[11] This practice combined with progressing from tube to breastfeeding and extended mother-infant exposure through kangaroo care resulted in 93% of the 70 LBW infants receiving their mothers' milk at discharge, and 95% of them at the breast.[11] Although the decision to transition the infant to at-breast feedings may not carry the same "life and death" risks as compared to feeding a preterm infant EBM at earlier stages of development, the extended immune protection of breastfeeding could have a major impact on the length of time the infant receives any breast milk as well as the infant's overall health and development.

Implications for education and practice

Health care providers should have a sound understanding of the factors that impede mothers from transitioning to at-breast feedings in order to address mothers' primary concerns and to keep their perspectives in mind during discussions about feedings. For example, if a mother's major concern is the need to quantify intake, this could be addressed with assisting her in obtaining an electronic scale for infant pre and post test-weighings, and giving clear parameters on how to transition to the breast. Although the message should not contain value statements about the right or wrong way of feeding infants, mothers need factual evidence-based information about the nature of maternal concerns regarding transitioning to the breast and the potential returns of at-breast feedings in order to make an informed choice.

Conclusion

Preterm infants who receive expressed breast milk rather than formula have fewer infections and necrotizing enterocolitis, as well as better cognitive, neurological and visual development. However, an optimal outcome would be for the preterm infant to transition to at-breast feedings prior to or shortly after hospital discharge. But with earlier discharges and limited home health care follow-up, mothers may not receive the informational and emotional support to transition to the breast. Health professionals and mothers may benefit from a clear understanding of the factors that impede mothers of preterm infants from transitioning to at-breast feedings, and their potential outcomes.

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Emergence of Physiological Rhythmicity in Term and Preterm Neonates in a Neonatal Intensive Care Unit

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Abstract

Background: Biological rhythmicity, particularly circadian rhythmicity, is considered to be a key mechanism in the maintenance of physiological function. Very little is known, however, about biological rhythmicity pattern in preterm and term neonates in neonatal intensive care units (NICU). In this study, we investigated whether term and preterm neonates admitted to NICU exhibit biological rhythmicity during the neonatal period.

Methods: Twenty-four-hour continuous recording of four physiological variables (heart rate: HR recorded by electrocardiogram; pulse rate: PR recorded by pulse oxymetry; respiratory rate: RR; and oxygen saturation of pulse oxymetry: SpO_2) was conducted on 187 neonates in NICU during 0–21 days of postnatal age (PNA). Rhythmicity was analyzed by spectral analysis (SPSS procedure Spectra). The Fisher test was performed to test the statistical significance of the cycles. The cycle with the largest peak of the periodogram intensities was determined as dominant cycle and confirmed by Fourier analysis. The amplitudes and amplitude indexes for each dominant cycle were calculated.

Results: Circadian cycles were observed among 23.8% neonates in HR, 20% in PR, 27.8% in RR and 16% in SpO_2 in 0–3 days of PNA. Percentages of circadian cycles were the highest (40%) at <28 wks of gestational age (GA), decreasing with GA, and the lowest (14.3%) at >= 37 wks GA within 3 days of PNA in PR and were decreased in the later PNA. An increase of the amplitude with GA was observed in PR, and significant group differences were present in all periods. Amplitudes and amplitude indexes were positively correlated with postconceptional age (PCA) in PR ($p < 0.001$). Among clinical parameters, oxygen administration showed significant association ($p < 0.05$) with circadian rhythms of PR in the first 3 days of life.

Conclusion: Whereas circadian rhythmicity in neonates may result from maternal influence, the increase of amplitude indexes in PR with PCA may be related to physiological maturity. Further studies are needed to elucidate the effect of oxygenation on physiological rhythmicity in neonates.

Background

Preterm neonates hospitalized in a neonatal intensive care unit (NICU) face many challenges to adapt to the new environment. Heat loss,[1] weight loss,[2] respiratory distress and cardiac instability[3] are very common features for them. An artificial environment in NICU is mandatory to support these neonates; however, external influences such as constant light, noise, and medical intervention may be stressful. Further, neonates are deprived of maternal influences, which is essential for their development. It has been thought that this environmental condition may influence the development of biological rhythm in preterm neonates.[4-6]

Circadian rhythms are generated endogenously by a biological clock, which is located in the anterior hypothalamic suprachiasmatic nuclei (SCN),[7,8] and are modulated by exogenous factors.[9,10] Many physiological processes are now known to be cyclically organized.[11] They show different cycles: circadian cycles last approximately 24 hours, ultradian cycles shorter than 24 hours, and infradian cycles longer than 24 hours.[12] These rhythms interact mutually as well as with the outside fluctuating environment under the control of feedback systems providing an orderly function that enables life.[11]

Circadian rhythms have been described in the human fetus[13-16] and have been attributed either to the maternal environment or

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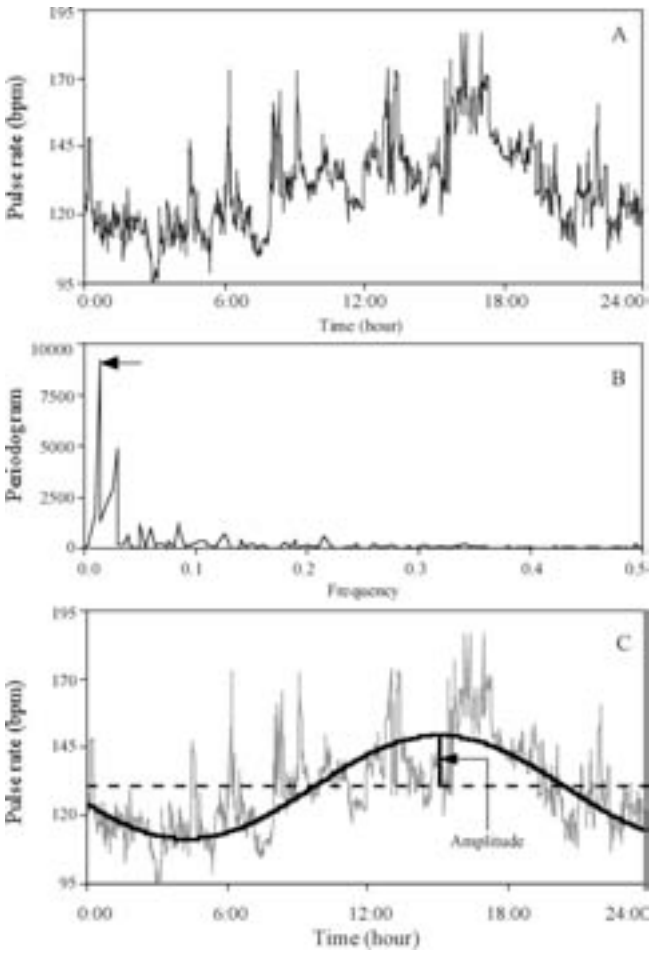

Figure 1
Brief description of steps to determine the dominant cycle using spectral analysis. ***A***: Plot of original data for pulse rate (PR). PR was measured once every 10 seconds and averaged into 1 minute time block for 1440 minutes; N = 1440 observation. ***B***: Periodogram intensities for PR (plotted on linear scale). The largest peak of the periodogram was selected (arrow) as representative cyclic component that represent the largest amount of variance. ***C***: The corresponding cycle of the largest peak in the periodogram intensities was reconstructed from the FFT coefficient to fit the sinusoidal function: $\chi_t =$ + Acos(ωt) + Bsin(ωt). The bold line is the detected cycle (period: 1440 minutes = 24 hours) superimposed on the original data.

to the maturation of the fetal nervous system.[13,17,18] The SCN has been detected as early as 18–20 weeks of gestational age,[19] and primate studies indicated that the SCN is responsive to light at 24 weeks of gestational age.[20] In term neonates, circadian rhythms have been reported to be present immediately after birth but to eventually disappear,[4,21] not being detected again until 3 to 4 weeks of postnatal life.[22] Some studies showed that circadian rhythms are predominant in preterm neonates,[4,21,23] while others showed ultradian rhythms to be dominant in preterm neonates.[22,24-27] To elucidate the developmental process of physiological rhythmicities, we studied four physiological variables in preterm and term neonates.

Methods

Subjects and data collection: From January 2004 to March 2006, 520 neonates were admitted to the NICU at Miechuo Medical Center. All of them were monitored with electrocardiogram (ECG) for heart rate (HR), respiration rate (RR), and with pulse oxymetry on the wrist or the feet for saturation of pulse oxymetry oxygen (SpO2) and pulse rate (PR) throughout their stay in the NICU. Monitored physiological information was transformed as measurement variables at 10-second intervals by the Wave Achieving System (WAS-J; Philips Electronics Japan, Tokyo, Japan) through the local area network in the NICU. The data were recorded for 24 hours for the following postnatal periods: Period 1: days 0–3; Period 2: days 4–6; Period 3: days 7–13; and Period 4: days 14–21. Subjects with continuously disrupted data for more than 1 minute were excluded from the study. A total of 187 neonates (114 boys and 73 girls) were recorded from period 1 to period 4.

The NICU was maintained under a light-dark cycle. The light was dimmed (less than 30 lux) during the night from 21:00 pm to 07:00 am, while it was maintained at a higher level (300–580 lux) during the daytime. NICU staff also varied according to time of day: the number of attendants at night was one third that of attendants during daytime hours. Parent's visitations were allowed three times a day (11:00 to 12:00 in the morning, 14:00 to 15:00 in the afternoon, and 17:00 to 21:00 in the evening). Bathing and measurement of body weight were conducted daily in the morning. Medical examinations, such as blood sampling, radiography, or ultrasonography, were mostly provided in the morning if necessary.

Written informed consent was obtained from the parents, and the study was approved by the ethical committee of the institute. Demographics and health status information were obtained from the medical records.

Analysis of rhythms: Physiological rhythmicity was analyzed for HR, PR, RR and SpO_2 with spectral analysis (periodogram) with SPSS 11.5 software (SPSS Inc Chicago, IL), as previously

Table 1: Demographic characteristics of 187 preterm and term neonates.

Variables/Categories	*n (%)*
Gender (boys/Girls)	114 (61)/73 (39)
Gestational age (wks), median (range)	34 (23–42)
< 28	17 (9.1)
28–32	49 (26.2)
33–36	58 (31)
≥37	63 (33.7)
Birth Weight (g), median (range)	1968 (454–4132)
< 1000	27 (14.4)
1000–1499	31 (16.6)
1500–1999	38 (20.3)
≥2000	91 (48.7)
Apgar score 1 min/5 min, median (range)	8 (0–10)/9 (2–10)
Age at hospitalization (day), median (range)	0 (0–9)
Hospitalization (day), median (range)	32 (5–182)
Caesarian Section	96 (51.3)
Multiple gestation	4 (2.3)
Intubation	111(59.4)
Oxygenation	72 (38.5)
Birth asphyxia	27 (14.4)
Intrauterine growth retardation	23 (12.3)
Respiratory distress syndrome	31 (16.6)
Transient tachypnea of the newborn	38 (20.3)

Data are expressed as mean ± SD or n (%).

Table 2: Descriptive profiles for significant cycles of HR, PR, RR and SpO_2.

Period		Period 1	Period 2	Period 3	Period 4
Sampling		(0–3)	(4–6)	(7–13)	(14–21)
n		116	114	125	106
Eligible sample*	HR	82 (70.7)	64 (56.1)	91 (72.8)	67 (63.2)
	PR	101 (87.1)	88 (77.2)	106 (84.8)	84 (79.2)
	RR	99 (85.3)	85 (74.6)	104 (83.2)	84 (79.2)
	SpO2	103 (88.8)	89 (78.1)	106 (84.8)	85 (80.2)
Significant cycle**	HR	80 (98)	64 (100)	89 (98)	67 (100)
	PR	100 (99)	87 (99)	104 (98.1)	83 (99)
	RR	90 (91)	84 (99)	97 (93.3)	79 (94)
	SpO2	94 (91.3)	86 (97)	103 (97)	78 (92)
Circadian cycle***	HR	19 (23.8)	11 (17.2)	20 (22.5)	13(19.4)
	PR	20 (20)	16 (18.4)	20 (19.2)	16 (19.3)
	RR	25 (27.8)	28 (33.3)	21 (21.6)	11 (13.9)
	SpO2	15 (16)	10 (11.6)	17 (16.5)	15 (19.2)

Data are shown in n (%). Parentheses are percentages of * eligible samples in all samples, ** significant cycles in all eligible samples, and *** circadian cycles in significant cycles.

reported.[28] Briefly, 24 hours sessions were run in 10-second intervals and were aggregated into 1-minute time blocks. Periodogram analysis was performed with a time series of 1440 minutes (N = 1440 observations). The Fisher test was used to test the statistical significance of the cyclic components (N = 1440, · = 0.05).[28,29] Among the significant cycles, the cycle with the largest peak in the periodogram was considered to be the dominant cycle for each time series data and was used for further analysis.[28] All dominant cycles were confirmed by Fourier analysis, and further circadian cycles were confirmed by cosinor analysis with a significance of $p < 0.05$ by least square analysis (Figure 1). The amplitude, the distance between mesor and the highest value of the cosine curve, was calculated for each dominant cycle. In addition, an amplitude index was calculated as follows: Amplitude index = amplitude ÷ mean of variables × 100.

Statistical analysis: Data were analyzed with SPSS and Statview. ANOVA was used to evaluate the differences between gestational age groups. The Pearson correlation coefficient was used to analyze the relationships between postconceptional age (PCA) and rhythmicity parameters. Univariate analysis using Mann-Whitney U-test for continuous variables or Fisher's exact test for categorical variables was used to compare clinical variables according to the development of physiological rhythmicity. A multiple logistic regression analysis was performed using a step-wise approach to determine the independent relationship of significant variables found in the univariate analysis.

Results

Sample characteristics: The demographics of neonates are shown in Table 1. The median gestational age (GA) was 34 weeks (range: 23–42 weeks), and the median birth weight was 1968 g (range: 454–4132 g). Among these neonates, 9.1% were born at < 28 weeks of gestation age and 14.4% had birth weight of less than 1000 g. The median age at hospitalization was 0 day (range: 0–9 day) and the median duration of hospitalization was 32 days (range: 5–182 days). One hundred eleven neonates (59.4%) were intubated and 72 neonates (38.5%) received oxygen.

Rhythmicity analysis: Results of the analyses of rhythmicity are summarized in Table 2. To ensure the accuracy of rhythmicity analysis, parameters missing more than 7% of total data were excluded from the analysis in each study. Among 461 time series recorded for each parameter, eligible samples were obtained in 304 for HR, 379 for PR, 372 for RR, and 383 for SpO_2 within the

Table 3: Distribution of circadian cycles according to gestational age groups in each period.

	Gestational age		Period 1		Period 2		Period 3		Period 4
	Groups	n	(0–3 d)	n	(4–6 d)	n	(7–13 d)	n	(14–21 d)
PR	<28 wks	10	4 (40)	12	3 (25)	12	5 (41.7)	13	4 (30.8)
	28–32 wks	26	6 (23.1)	22	6 (27.3)	42	11 (26.2)	39	9 (23.1)
	33–36 wks	29	5 (17.2)	26	5 (19.2)	31	2 (6.5)	23	3 (13.0)
	≥37 wks	35	5 (14.3)	27	2 (7.4)	19	2 (10.5)	8	0 (0)
RR	< 28 wks	7	1 (14.3)	11	1(9.1)	13	5 (38.5)	13	0 (0)
	28–32 wks	24	8 (33.3)	20	9 (45)	38	9 (23.7)	36	8 (22.2)
	33–36 wks	25	8 (32)	27	9 (33.3)	28	3 (10.7)	22	2 (9.1)
	≥37 wks	34	8 (23.5)	26	9 (34.6)	18	4 (22.2)	8	1(12.5)
SpO2	< 28 wks	10	0 (0)	12	3 (25)	12	3 (25)	13	2 (15.4)
	28–32 wks	25	5 (20)	20	3 (15)	40	7 (17.5)	37	9 (24.3)
	33–36 wks	26	5 (19.2)	25	5 (20)	32	4 (12.5)	20	3 (15)
	≥37 wks	33	5 (15.2)	29	4 (13.8)	19	3 (15.8)	8	1 (12.5)

Data are shown in n (%).

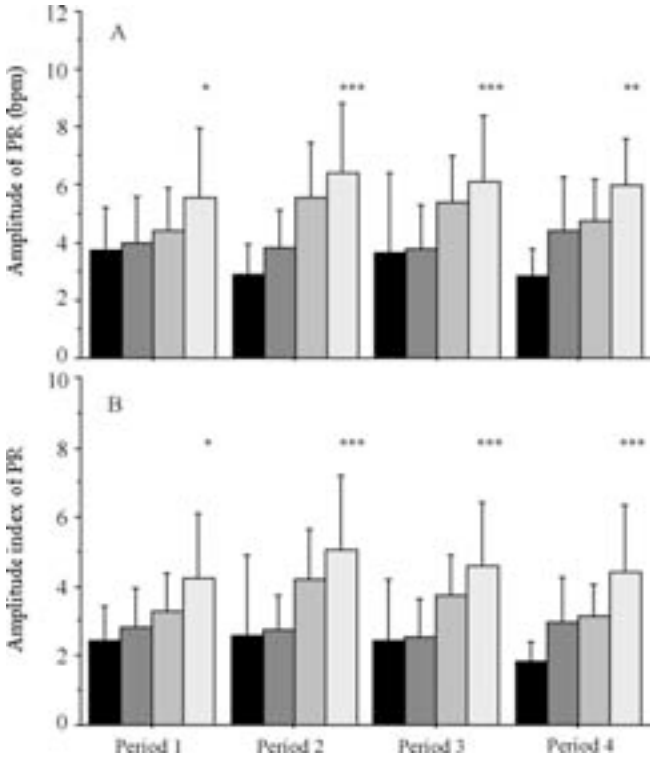

Figure 2
Amplitudes (*A*) and amplitude indexes (*B*) of all detected cycle of PR over the 4 periods for 4 gestational age groups infants. Data are shown in Mean ± SD. The dark bar is for < 28 wks, the gray bar is for 28–32 wks, the light gray bar is for 33–36 wks, and white bar is for ≥ 37 wks. * $p < 0.01$, ** $p < 0.001$, *** $p < 0.0001$, according to ANOVA. The sample size for each gestational age group is shown in Table 2.

4 periods. Among eligible samples, rhythmicity was observed in more than 90% of neonates in each period for HR, PR, RR and SpO_2 (Table 2). The percentage was not much lower (HR: 89%, PR: 90%, RR: 79%, SpO_2: 76%) after Bonferroni correction for multiple testing ($p < 0.0001$).

Without correction for multiple testing, circadian cycle (1440 minutes) was observed among 23.8% neonates in HR, 20% in PR, 27.8% in RR and 16% in SpO_2 in Period 1. Because many samples were excluded from HR analysis, and the percentage of eligible samples was consistently lower than for PR, further analysis of cardiac rhythmicity used PR instead of HR.

Rhythmicity and gestational age: Rhythmicity was analyzed in four gestational age groups: < 28 wks, 28–32 wks, 33–36 wks, ≤ 37 wks. The distribution of circadian cycles in each gestational age groups and periods is summarized in Table 3. In PR, the percentage of circadian cycles was highest (40%) at <28 wks of GA, decreasing with GA, and lowest (14.3%) at ≤ 37 wks of GA in Period 1. A similar tendency was observed in each period in PR; however, there was no consistent tendency in percentages of circadian cycle in RR and SpO_2.

Amplitudes and amplitude indexes of all detected cycles in PR in each period are shown in Figure 2. An increase of circadian amplitude with gestational age was observed in PR. and significant differences were present among gestational age groups in all periods (Figure 2A). These changes were not observed in RR and SpO_2 (data not shown). Amplitude indexes showed similar tendency to amplitudes in PR (Figure 2B). There were no significant associations between cycles and amplitudes in any parameter in each period (data not shown).

Relationship between rhythmicity and postconceptional age: In examining the relationship with postconceptional age (PCA), correlation of coefficient was performed using amplitudes and amplitude indexes in each period for all parameters. Amplitudes and amplitude indexes of PR were positively correlated with PCA in all four periods (Figure 3).

Clinical conditions associated with rhythmicity: To determine whether clinical conditions may affect the emergence and development of rhythmicity, clinical factors were determined according to cycle length with circadian cycles (1440 minutes) or ultradian cycles (≤ 720 minutes). On univariate analyses in Period 1, circadian cycle (1440 minutes) was significantly associated ($p < 0.05$) only with oxygen administration at data sampling in PR (Table 4), while there were no significant associations in RR or SpO_2 (data not shown). In Periods 3 and 4

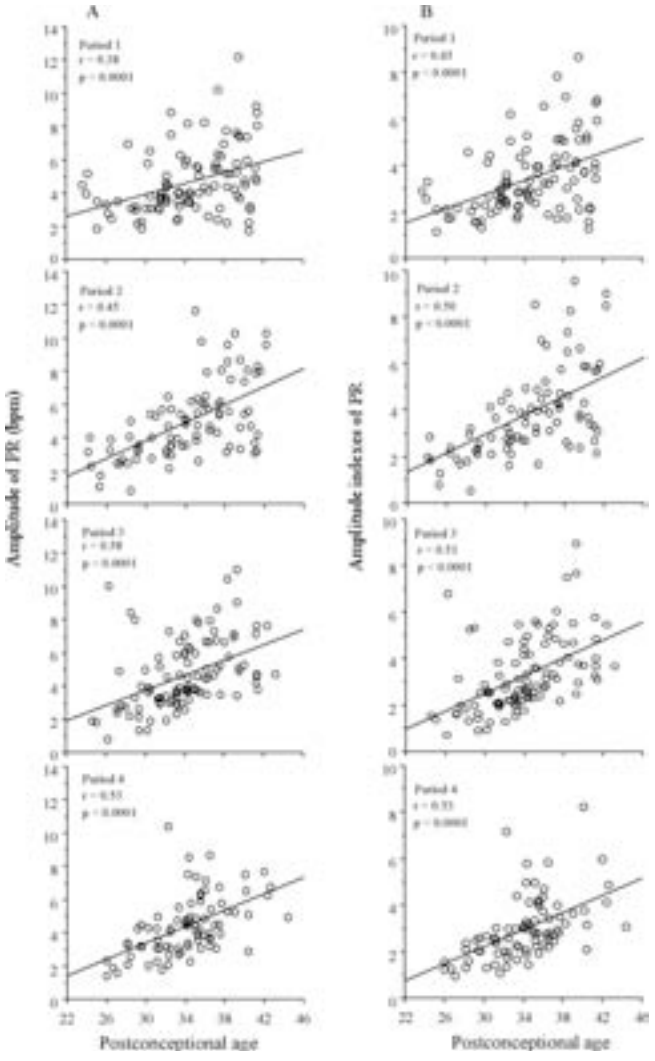

Figure 3
Linear regression (and coefficients of correlation) for amplitudes and amplitude indexes of PR as functions of postconceptional age. A significant increase in amplitudes and amplitude indexes with postconceptional age is present in all period in PR.

Table 4: Univariate analysis for association of clinical parameters with existence of circadian rhythmicities in PR in Period 1.

Clinical variables	Cycle 1440 (n = 20)	≤ 720 (n = 80)	p
Gestational age (wks)	32.7 ± 4.9	34.2 ± 4.6	NS
Birth weight (g)	1930 ± 983	2077 ± 900	NS
Apgar Score < 6 (5 min)	1 (5)	10 (12.7)	NS
Asphyxia	4 (20)	17 (21.3)	NS
RDS	4 (20)	14 (17.3)	NS
IUGR	3 (15)	6 (7.5)	NS
Mean of variables			
Mean PR (/min)	140.2 ± 8.6	135.5 ± 12.8	NS
Mean RR (/min)	45.7 ± 8.5	43.0 ± 8.5	NS
Mean SpO2 (%)	97.9 ± 1.1	97.9 ± 1.3	NS
Treatment of data sampling			
Oxygenation	18 (90)	46 (57.5)	0.02
Intubation	10 (50)	25 (31.3)	NS
Aminophylline	1 (5)	4 (5)	NS
Phenobarbital	0 (0)	1 (1.3)	NS
Midazolam	3 (15)	6 (7.5)	NS

Data are expressed as mean ± SD or n (%). Mann-Whitney U test was performed for continuous variables and Fisher's exact test was performed for categorical variables.

in PR, gestational age was found to be significantly associated with circadian cycle ($p < 0.01$) as well as with oxygen administration ($p < 0.05$). Neither gestational age nor oxygen administration qualified as an independent factor for existence of circadian cycle in multivariate logistic regression models. Clinical parameters were not associated with the existence of significant cycles in amplitude or amplitude index.

Discussion

Rhythmicity has been previously studied in preterm and term infants for various physiological variables, such as body temperature,[24,30] blood pressure,[21] heart rate,[18] sleep-wake pattern,[24] rest-activity pattern,[26] melatonin secretion,[31] and electroencephalogram.[32] In this study, we have investigated rhythmicity in PR, RR, and SpO_2. All of these are important parameters in the regulation of human physiology, and yet little is known about rhythmicity of these variables in neonates. We have shown that most of the analyzed neonates had individual rhythmicity for these parameters with variable cycles after birth, even in extremely immature infants.

Emergence of circadian rhythmicity has been reported to be associated with brain maturation of preterm infants.[33,34] In term neonates, circadian cycles are detected immediately after birth and subsequently disappear and are not detectable until 3 to 4 weeks of postnatal life.[22] It has been suggested that circadian cycles in the early neonatal period are due to maternal influence in utero and that endogenous rhythmicity appears only later.[13,17,18] However, conclusive studies are limited by subject number because of the difficulty in collecting continuous data in NICU. Our sample size of 187 neonates is larger than that of previous studies. As a result, circadian cycles were confirmed in early neonatal period for all parameters either in preterm or term neonates. In PR, comparatively higher percentages of circadian cycles were observed during early neonatal period in preterm neonates and persisted through the later neonatal period, especially in extremely immature infants, while percentages of circadian cycles decreased through the later period in term neonates. These results partially support the previous studies.[4,21,23] The fact that environmental conditions were rhythmic in our study (ie, presence of a light-dark cycle, of a cycle of NICU staffing, of a cycle of bathing, etc.) prevents us from making inferences about the endogenous or exogenous nature of biological rhythmicity in our subjects.

Although exact factors for the development of rhythmicity are still unclear, it has been suggested that physiological complications may play a role.[35] Among clinical parameters, disease conditions such as respiratory problems or asphyxia, and therapeutic drugs such as phenobarbital or aminophylline, were not associated with emergence of circadian cycles. Only oxygen administration revealed significant association with emergence of circadian cycles in PR within 3 days of birth. Disruption of circadian rhythmicity by reduction of oxygen supply, and restoration by re-oxygenation, has been demonstrated in rats.[36,37] Reduced oxygen activates hypoxia-inducible factor 1(HIF-1),[38] which is involved in oxygen homeostasis. Chilov and colleagues also indicated that oxygen supply modulates the circadian clock at the molecular levels via HIF-1 in the mouse brain.[39] Our observations support these experimental results and suggested that oxygen supply may also influence rhythmicity in humans. Further analyses are required to explore the influencing mechanisms on emergence of rhythmicities in neonates.

Conclusion

Preterm neonates are at great risk of life-threatening events such as infection, respiratory distress or circulatory failure. As shown in this study, co-existence of circadian cycles with low amplitude in preterm neonates may complementarily support immature homeostasis and function against unstable physiological condition. Our results should aid further research on physiological rhythmicity in neonates.

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Nurse Staffing in Relation to Risk-Adjusted Mortality in Neonatal Care

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Objective: To assess whether risk-adjusted mortality in very low birthweight or preterm infants is associated with levels of nursing provision.

Design: Prospective study of risk-adjusted mortality in infants admitted to a random sample of neonatal units.

Setting: Fifty four UK neonatal intensive care units stratified by: patient volume; consultant availability; nurse:cot ratios.

Patients: A group of 2585 very low birthweight (birthweight,1500 g) or preterm (31 weeks gestation) infants.

Main Outcome Measure: Death before discharge or planned deaths at home, excluding lethal malformations, after adjusting for initial risk 12 hours after birth using gestation at birth and measures of illness severity in relation to nursing provision calculated for each baby's neonatal unit stay.

Results: A total of 57% of nursing shifts were understaffed, with greater shortages at weekends. Risk- adjusted mortality was inversely related to the provision of nurses with specialist neonatal qualifications (OR 0.67; 95% CI 0.42 to 0.97). Increasing the ratio of nurses with neonatal qualifications to intensive care and high dependency infants to 1:1 was associated with a decrease in risk-adjusted mortality of 48% (OR: 0.52, 95% CI: 0.33, 0.83).

Conclusions: Risk-adjusted mortality did not differ across neonatal units. However, survival in neonatal care for very low birthweight or preterm infants was related to proportion of nurses with neonatal qualifications per shift. The findings could be used to support specific standards of specialist nursing provision in neonatal and other areas of intensive and high dependency care.

Health care in the United Kingdom, in common with many developed countries, is subject to continuing nurse shortages.[1,2] Concerns have been raised about the impact of such shortages on the quality of health care and links made between inadequate nursing provision, increased workload and poor patient outcomes.[3-7] While these views have been echoed in neonatal care, there is little evidence of the impact of nursing levels on infant outcomes. Rather, a number of studies have reported declining mortality in low birthweight and preterm infants associated with technical advances in intensive care and improved obstetric management,[8-10] while others have evidenced increasing demands for neonatal intensive care services.[11-15]

A few studies have attempted to empirically test the relationship between staffing and neonatal outcomes, but they provide us with inconclusive evidence. One study conducted in seven Scottish and two Australian neonatal units suggested that riskadjusted mortality is independently related to infant:nurse ratios in the first three days after birth, with a 79% increase in odds of mortality when more than 1.7 infants were assigned per nurse per shift.[16] However, another Australian study, based in one neonatal unit, reported a decline in risk-adjusted mortality associated with fewer nurses caring for high-risk infants.[17] These counterintuitive findings have been interpreted cautiously and differences in study design and the Australian and UK models of care have been emphasized.[18] In the absence of less equivocal evidence, the relationship between neonatal outcomes and nurse staffing warrants further investigation.

Despite the lack of outcome evaluation, the need for more skilled medical and nursing staff has dominated neonatal organizational debates. Several reviews have reported high infant:nurse ratios, variable skill utilisation, diverse nurse

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Table 1 Nurse staffing per shift by unit organisational type

	Registered nurses	Nurse provision ratio	Specialist nurse provision ratio
	Median (IQ range)	Median (IQ range)	Median (IQ range)
Total	4 (2)	0.92 (0.36)	1.33 (1.0)
Unit Volume Type			
High	6 (2)	0.93 (0.34)	1.33 (1.0)
Medium	4 (2)	0.92 (0.35)	1.33 (1.0)
Low	3 (2)	0.91 (0.36)	1.20 (1.2)
	p⩽0.001*	p⩽0.001*	p⩽0.01*
Unit Consultant Availability			
High	4 (3)	0.93 (0.36)	1.33 (1.1)
Low	3 (1)	0.91 (0.36)	1.33 (1.0)
	p⩽0.001†	p⩽0.001†	P=0.06†
Unit Nursing Establishment			
High	4 (2)	0.96 (0.36)	1.33 (1.0)
Low	4 (2)	0.89 (0.33)	1.33 (1.0)
	p⩽0.001†	p⩽0.001†	P=0.07†

Statistical Test: * Kruskal Wallis Test, †Mann Whitney U Test

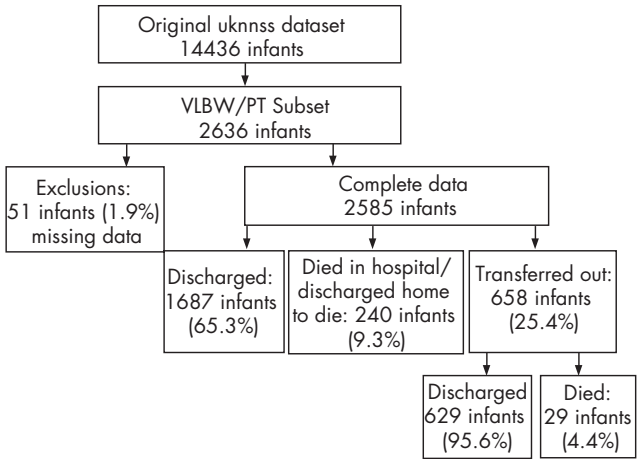

Figure 1 Very Low Birthweight/Preterm Infant Data Selection.

Table 2 Number of shifts where nursing provision ratio is less than 1.0

	Type of shift			
Understaffing	Week day n (%)	Weekend day n (%)	Week night n (%)	Weekend night n (%)
Nurse Provision Ratio <1	6026 (47)	2765 (54)	8239 (64)	3349 (66)
Specialist Nurse Provision <1	2366 (19)	1129 (22)	3502 (27)	1408 (28)

staffing policies unrelated to unit size or type and under-provision of nurses, specifically those with specialist neonatal nursing qualifications.[12,15,19,20] In acknowledging the changing case-mix of infants and increasing technological demands, standards have been produced for neonatal staffing in the UK.[21-23] The most recent used nursing activity studies to recommend nursing levels responsive to infant volume and dependency.[20,22-24] These recommendations were used to assess the adequacy of staffing in neonatal care in this study.

Objective: To examine the relationship between nurse staffing input and risk-adjusted mortality in very low birthweight or preterm infants in 54 neonatal intensive care units randomly sampled from all such units in the UK.

Methods: The study population is a subset of the UK Neonatal Staffing Study (UKNNSS), details of which are given elsewhere.[25] Data collection took place between 1st March 1998 and 2nd April 1999. Workload logs were compiled at each of the 54 selected units twice daily, providing 35,877 shift records of staffing and infants. Data were simultaneously recorded on the characteristics of 13,515 babies admitted (gestational age, gender, birth weight and mortality risk). Of the 35,880 records from the workload logs, information was incomplete or erroneous in 229 records (0.6%) which were coded as missing data. The remaining 35,651 records were used to compute the following nursing indices

- Total number of registered nurses per shift.
- Nursing provision ratio per shift. A responsive measure of nursing input based on the extent to which a shift meets the recommended minimum number of registered nurses for the number of babies requiring care. The expected number of nurses was defined as a function of the number of babies admitted during the shift (calculated as one half of the intensive care and high dependency babies plus one quarter of the low dependency babies plus one).[23]
- Specialist nursing provision ratio per shift. A responsive index of skilled nursing provision based on the actual and recommended number of nurses with specialist neonatal qualifications (qualified in speciality, QIS) required to care for intensive care and high dependency infants. Specialist neonatal qualifications included neonatal nursing courses such as ENB "405," "904"or equivalent. It was calculated as one half of the intensive care and high dependency babies plus one.[23]

A value less than 1 indicates that nursing levels are below the recommended nurse staffing guideline.[23]

Table 3 Indicators of infant illness severity and infant nurse staffing for duration of unit stay by unit organisational type

	Birthweight mean (SD)	Gestation mean (SD)	Predicted mortality score median (IQ range)	Registered nurses median (IQ range)	Nurse provision ratio median (IQ range)	Specialist nurse provision ratio median (IQ range)
Cohort	1231.7 (359)	29.3 (2.6)	0.98 (0.08)	4.6 (2.5)	0.92 (2.5)	1.35 (0.6)
Unit volume type						
High	1176.4 (344)	29 (2.6)	0.98 (0.12)	6 (1.1)	0.93 (0.21)	1.41 (0.47)
Medium	1257.3 (356)	29.3 (2.5)	0.99 (0.06)	4.3 (2.3)	0.94 (0.22)	1.33 (0.75)
Low	1270.5 (373)	29.5 (2.5)	0.99 (0.06)	3.5 (1.4)	0.87 (0.23)	1.26 (0.63)
	p⩽0.01*	p⩽0.01*	p⩽0.01*	p⩽0.001*	p⩽0.001*	P⩽0.001*
Unit consultant availability						
High	1228.9 (351)	29.2 (2.6)	0.99 (0.05)	5.5 (2.6)	0.94 (0.22)	1.35 (0.62)
Low	1234.6 (368)	29.3 (2.6)	0.98 (0.08)	4 (2.2)	0.89 (0.25)	1.35 (0.58)
	p=0.69*	p=0.82*	p=0.29†	p⩽0.001†	p⩽0.001†	p=0.42†
Unit nursing establishment						
High	1230 (355)	29.3 (2.6)	0.99 (0.08)	4.8 (2.8)	0.95 (0.21)	1.32 (0.55)
Low	1234 (364)	29.3 (2.6)	0.98 (0.09)	4.4 (2.2)	0.87 (0.21)	1.39 (0.67)
	p=0.78*	p=0.72*	p=0.83†	p⩽0.001†	p⩽0.001†	p⩽0.01†

Statistical tests: *one way ANOVA, Kruskal Wallis, †Mann Whitney U test

Units were categorised using three organisational measures from a previous neonatal census.[26] These were: unit volume (high >57, medium 35–57, and low <35 low birthweight infants admitted per year); neonatal consultant availability (greater [high] or less than/equal to [low] the median of 2 clinical pediatricians with more than a 50% commitment in neonatal care) and nursing establishment (similarly defined as being above or less than/equal to the median of 0.84 nurse to cot ratio).

Patients: From the original UKNNSS cohort of 14,436 infants, data on 2636 infants were selected using the inclusion criteria of birthweight ≤1500 g and/or ≤ gestation (31 weeks [fig 1]). Observed mortality was defined as in-hospital death or discharged home to die and included all deaths (excluding lethal malformations and deaths post specialist surgery). For risk-adjustment we used a predicted mortality score, derived from the original UKNNSS cohort for 14,436 infants, which incorporated diagnostic information obtained at 12 hours of birth (gestation, size of infant for gestation, sex, mode of delivery, diagnostic category, maternal treatment with antenatal steroids, admission temperature, most extreme partial pressure of carbon dioxide ($PaCO_2$), mean appropriate fraction of inspired oxygen (FiO_2), and lowest base excess).[25] The riskadjustment model demonstrated good discriminatory power for mortality with the area (SE) under the Receiver Operating Curve of 0.92 (0.009) as compared to 0.88 (0.013) for gestation alone.[27] The predicted mortality derived from this model ranges from 0–1, where a higher value indicates a higher chance of survival.

Statistical analyses: Statistical analysis was carried out using SPSS version 10 Software.[28] Individual profiles for each infant were compiled using the nursing variables for each shift that the infant was cared for in the unit from admission to discharge, death or transfer. These were averaged to give three mean nursing provision variables for each infant representing their NICU stay. These were then fitted as potential explanatory variables, along with unit organisational type, with risk-adjusted mortality as the dependent variable and the infant as the unit of analysis using logistic regression techniques on multivariate analysis.

Results

Nurse staffing: Data describing characteristics of the nursing shifts are shown in table 1. The overall median nursing provision ratio was 0.92 (mean, 0.96; SD 0.31) indicating that the average shift was understaffed. In total 20,380 shifts (57%) were understaffed and 35 units (65%) had an average ratio of less than one. Each unit had understaffed shifts, ranging from 90% shifts in the "worst" staffed to 13.4% in the "best" staffed units (both large units). The median specialist nursing provision ratio was 1.3 (mean, 1.42; SD 0.78). Eight (14.8%) units had an average specialist nursing provision ratio less than one. In total

Table 4 Observed and risk-adjusted mortality by unit organisational type

		Crude mortality		Risk-adjusted mortality	
Unit type	Died n (%)	p Value	OR (95% CI*)	p Value	OR (95% CI*)
Unit volume type					
High	111 (11.7)	Referent category		Referent category	
Medium	93 (11.2)	0.73	0.95 (0.71 to 1.27)	0.44	1.18 (0.77, 1.8)
Low	65 (8.1)	0.01	0.66 (0.48 to 0.91)	0.63	0.89 (0.56 to 1.41)
Unit consultant availability					
High	146 (11.1)	Referent category		Referent category	
Low	123 (9.7)	0.22	0.85 (0.66 to 1.10)	0.43	0.86 (0.6 to 1.24)
Unit nursing establishment					
High	133 (9.7)	Referent category		Referent category	
Low	136 (11.3)	0.19	1.18 (0.92 to 1.52)	0.16	1.3 (0.9 to 1.9)

*The odds ratios and 95% confidence intervals are derived using logistic regression modelling with an odds ratio <1 indicating a decrease in odds relative to high volume/consultant/nursing units.

8405 (23.6%) shifts were understaffed for specialist nurse provision with wide variation ranging from 0.7% in the "highest" to 65.1% in the "lowest" staffed neonatal unit. For nursing and specialist nursing ratios, the frequency of understaffed shifts increased for night shifts (table 2).

Infant variables: Table 3 shows the descriptive data for the infant cohort according to unit organizational type. Larger units had significantly smaller and more immature infants. Predicted mortality scores ranged from 0.002 to 0.998 and were skewed to the right with a mean of 0.89 (SD 0.206; median 0.98), indicating that on average the infants had an 89% chance of survival according to variables measured at 12 hours of age. Infants who died had a mean mortality score of 0.513 (SD 0.31) versus 0.939 (SD 0.13) for those who survived. Predicted mortality differed significantly across neonatal units grouped by size, with the larger units treating sicker infants than medium and low volume units (table 3).

The nurse provision calculated for each infant for the duration of their unit stay (table 3) shows that in each group infants in the higher volume category had more registered nurses than those in the lower volume category units. The median nurse provision ratio for the infant cohort was 0.91 and 69% (n=1784) of infants had an understaffed nurse provision ratio for their neonatal stay. The median specialist nurse provision ratio/shift for each infant's neonatal stay was 1.3 (mean 1.4; SD 0.49). However, 19% of the cohort infants (n=497) had a specialist nurse provision ratio less than one.

Infant mortality: Observed mortality was 10.4% (n=269) and was significantly lower for infants treated in low compared to high volume units (table 4). Risk-adjusted mortality (using the predicted mortality scores) is also shown by unit organizational type, relative to the high category units, with no difference across these categories.

On multivariate analysis, a stepwise model was fitted for each infant (table 5). The criteria for inclusion in this conditional model was set at a significance level of ≤ 0.05. Birthweight, unit organisational characteristics (size, consultant availability, nursing establishment levels), number of nurses per shift and nurse provision ratio per shift were excluded in the final risk-adjusted mortality model. Mortality was significantly related to gestation, predicted mortality and the specialist nurse provision ratio aggregated for each infants' unit stay (OR 0.63; 95% CI 0.42 to 0.96).

In order to determine linearity of the relationship between risk-adjusted mortality and specialist nursing, four categories of ratio were entered into a logistic regression model (table 6).

There was no difference in risk-adjusted mortality for infants with a specialist nurse provision ratio between 1.0 and 1.2 compared to those with a ratio less than one (understaffed). The median specialist nursing provision ratio for this cohort was 1.3 and the odds of mortality decreased by 48% (odds ratio: 0.52, 95%CI: 0.33,0.83) when the ratio was increased from <1 to ≤1.3.The predictive accuracy of the combined probabilities from the regression model (risk-adjusted mortality and qualified in speciality nurse provision) is represented by the area under the Receiver Operating Curve (SE) which was 0.92 (0.01).

Table 5 Multivariate analysis of infant mortality

Variables	p Value	Odds Ratio (95% CI)
Gestation	<0.001	0.745 (0.67 to 0.83)
Predicted mortality	<0.001	0.008 (0.003 to 0.019)
Specialist nurse provision ratio/shift	0.031	0.63 (0.42 to 0.96)

Table 6 Risk-adjusted mortality and specialist nurse provision ratio categories

Specialist nurse provision ratio	p Value	Odds Ratio (95% C.I.*)
<1.0	0.03	Referent Category
1.0–1.2	0.105	0.63 (0.37 to 1.10)
1.3–1.8	0.006	0.52 (0.33 to 0.83)
>1.8	0.08	0.57 (0.31 to 1.08)

*The odds ratios and 95% confidence intervals are derived using logistic regression modelling with an odds ratio <1 indicating a decrease in odds relative to high volume/consultant/nursing units.

Discussion

Specific recommendations for nurse staffing enabled comparisons between units and an examination of levels of nursing provision in relation to risk-adjusted mortality in neonatal care.

Adjustment was made for infant illness severity using gestational age and a 12 hour probability model.[25] Although larger units tended to have more immature and sicker infants than smaller units, risk-adjusted mortality was not related to the size or type of neonatal unit. Other studies, including the UKNNSS have detected no difference in risk-adjusted outcomes by unit size.[11,25,29,30]

Over half of the nursing shifts were understaffed, while nearly a quarter did not have the minimum number of nurses with specialist neonatal nurse qualifications to care for intensive care and high dependency infants. There was wide variation in nursing provision, consistent with previous studies of neonatal nurse staffing.[19,20,26] Similarly variation in staffing levels by time of day and day of week corroborates the findings of an earlier UK survey.[19]

Using logistic regression specialist nursing provision was inversely related to risk-adjusted mortality and subgroup analysis indicated that increasing the ratio to greater than 1.2 decreased the probability of mortality by 48%. In other words, providing more than the minimum recommended number of nurses with specialist neonatal qualifications significantly increased the chance of survival in this cohort.

The possibility that the relationship between risk-adjusted mortality and specialist nursing provision could be attributed to confounding variables that were not examined in this study cannot be excluded. However, the probability is small as the approach included two primary methods of stratification not previously utilised. The first included organisational stratification by unit type and thus an attempt was made to separate the relative contributions of unit size and staff interaction. Secondly, analysis was based on infant profiles using individually determined risks, initially of illness severity and subsequently of workload demands and nurse provision representative of that infant's neonatal stay.

An important consideration is the omission of the neonatal unit as a predictive variable in the regression equation, and the independence of workload variables, calculated for each infant, which could potentially overestimate the significance of the association between specialist nurse provision and risk-adjusted mortality. This possible effect could be determined by modelling for the 54 neonatal units. However, the ability to do so was limited by the raw event rate, which, in 15% of units, was zero. Conversely, by using data for the whole duration of infant stay, not simply the most critical period of intensive or high dependency care, it could be argued that there was a dilution of the effects of inadequate staffing.

The method for adjusting for illness severity used a probability model based on twelve-hour data from birth, which is independent of subsequent therapeutic decisions. Although closely related to the validated and widely used CRIB score, the logistic model derivation process is designed to maximize predictive power, but runs the risk of over-fitting the idiosyncrasies of this dataset. Thus both the probability model and the final model of risk-adjusted mortality and specialist nurse provision, while having a good discriminatory power, lack support from independent validation.[25,29,30] Adjustment for clustering, for example by use of generalised estimating equations, may have increased the confidence interval around the observed estimates of risk adjusted mortality, but is unlikely to have changed the direction of apparent effect.

This study used recommendations published in 1996 to measure adequacy of nursing levels. More recent recommendations in the UK suggest higher ratios of nursing staff for intensive care and high dependency infants.[22,31] However, a survey of UK neonatal units conducted in 2005 showed that of 143 neonatal units, only three (2%) met the new recommendations for nurse staffing establishments and 20% were below those made earlier.[23,32] Thus the analysis using earlier recommendations is appropriate.

The measure of specialist nursing used in this study is the ratio of nurses who have undergone specialist neonatal training, in relation to the number of intensive care and high dependency infants. It reflects the ability to meet the demands for trained neonatal nursing and supports claims that quality of care may be impaired if the availability of trained staff is too low.[15] In the current nursing shortage, increasing nurse: patient ratios will be difficult. In America and Australia, one controversial initiative has been to mandate ratios for adult and pediatric care.[33,34] Optimization of workload planning, by developing improved workload predictors from patient characteristics is also possible.[35,36] In neonatal care, mechanisms that allow more efficient staffing, that is the ability to flex up and flex down in the face of volume changes, are also key in addressing variable demand.[37] This study adds weight to previous calls for the collection of more detailed nurse staffing data in conjunction with more reliable measures of patient acuity to better match nurse staffing and patient need.[38,39] More effective workforce planning, perhaps involving networked care, are crucial to ensure that nursing levels match infant demands.

Conclusion

Reports of nursing in neonatal care have created an image of a workforce stretched by excessive infant volume workloads and technical demands of highly dependent infants with a possible deleterious effect on outcomes. The study devised a model to explore this issue, by investigating whether exposure of small and premature infants to different levels of nurse provision, aggregated for each infant for the duration of neonatal care, is related to survival, after adjusting for initial illness severity. The results show nurse understaffing in relation to infant demands across all neonatal units and an inverse relationship between risk-adjusted mortality and provision of nurses with specialist neonatal qualifications for this population of babies.

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Periodontal Disease and Spontaneous Preterm Birth: A Case Control Study

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Abstract

Background: Several studies have suggested an association between periodontal disease and prematurity but this finding has not been consistently observed.

Methods: Case control study. Cases (n=50) were women who had delivered after spontaneous preterm labor at <35 weeks gestation. Two groups of controls (n=101) were recruited: women who were undelivered but at a preterm gestation and women who delivered at term. A standard, clinical, periodontal examination was performed and gingival crevicular fluid was obtained from standardized locations and tested for neutrophil elastase along with the bacterial enzymes gingipain and dipeptidylpeptidase. Data were analyzed with Fisher's exact tests, ANOVA and multivariate logistic regression.

Results: There was no difference in the proportion of sites with significant attachment loss (≥3 mm): Cases-3.2%, Controls-2.2% p = 0.21. The gingival crevicular fluid concentrations of elastase and gingipain were elevated in cases vs. control 238.8 uU/ul vs. 159.6 uU/ul p = .007 and 2.70 uU/ul vs. 1.56 uU/ul p = 0.01. On multivariate analysis, the mean log concentration of elastase, but not of gingipain, remained a significant predictor of preterm labor p = 0.015.

Conclusion: We found no evidence that clinical periodontal disease is associated with spontaneous preterm birth. Elevated gingival crevicular fluid levels of elastase were associated with preterm birth but further research is needed before this can be assumed to be a causal relationship.

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Preterm birth remains the most important cause of perinatal mortality and morbidity. Despite considerable research, the pathogenesis of preterm delivery is not well understood and no effective preventative therapy is available. Several recent studies have suggested a relationship between preterm delivery and periodontal disease. Offenbacher et al reported a strong association, OR = 7.9, between periodontal disease as either premature delivery or low birth weight in North Carolina.[1] Similar results were reported in studies of other US populations by Jeffcoat et al and in further work by Offenbacher et al.[2,3] However, this association has not been consistently observed. In fact, Davenport et al found that the risk of having a preterm infant was actually reduced in women with periodontitis in the United Kingdom.[4]

One concern with these studies is that confounding, especially by socioeconomic status, has not been consistently controlled for. Socioeconomic status has been associated consistently with spontaneous preterm birth and may also be associated with poor dental care, particularly in jurisdictions where it is not publicly funded. As well, no studies of which we are aware, related to spontaneous premature birth, have evaluated biochemical measures of active periodontal disease in addition to standard clinical examination. Since periodontal disease is characterized by a relapsing/remitting pattern, identifying active disease may be an important factor in establishing associations with other disease states such as preterm labor. The population from which the subjects were recruited is also high risk for premature delivery. The city where this study was performed has one of the highest rates of preterm birth in Canada with 10% of births in 2004 occurring before 37 weeks (unpublished local data). The population is predominately Caucasian (81%) with Chinese (6%), South Asian (4%), Aboriginal (2%) and Black (1.5%) comprising the other main ethnic groups.[5] In addition, and in contrast to the studies published to date, our investigation restricted the outcome to only spontaneous preterm birth <35 weeks gestation.

Periodontitis is an inflammatory process initiated by bacterial plaque involving the supporting structures of the tooth which include the gingival, the junctional epithelium, root cementum,

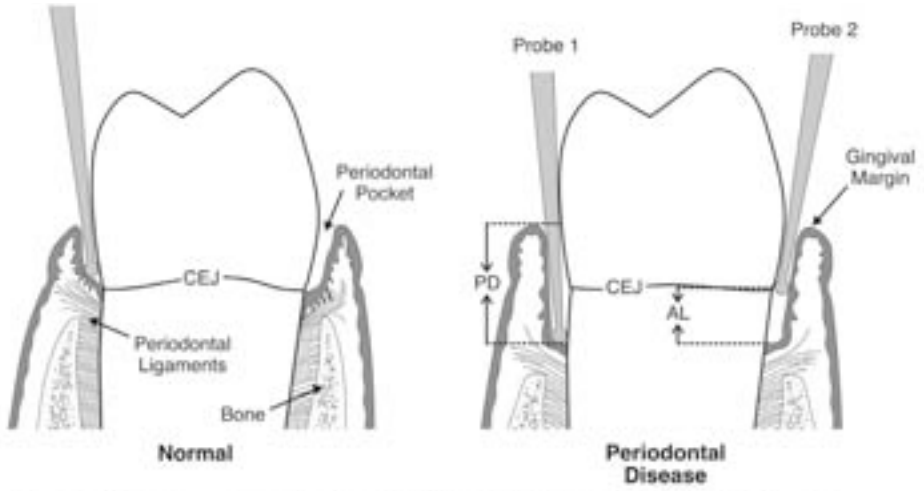

Figure 1
Clinical Examination for Periodontal Disease.

periodontal ligament, and alveolar bone.[6] These structures are responsible for maintaining the attachment of the teeth to the upper and lower jaws. Their destruction leads to loss of attachment between the tooth and the alveolar bone and ultimately, to excess mobility, infection, and loss of the tooth. Periodontitis is diagnosed clinically by measuring a deepening of the space (pocket) between the root of the tooth and the gingival tissue (Figure 1). Attachment loss is an accurate measure of disease severity and is defined as the distance, in mm, between the cemento-enamel junction and the base of the periodontal pocket. As periodontitis is episodic in nature, probing alone cannot determine whether the disease is active or quiescent. Several tests have been developed to assess substances in the gingival crevicular fluid (GCF) which can be obtained from periodontal pockets. One of these tests, which measures neutrophil elastase, has been shown to be highly predictive of eventual attachment loss. Armitage et al demonstrated that sites with high neutrophil elastase levels are at significantly greater risk for progressive bone loss over the next 6 months.[7] Using the same elastase substrate in fully quantitative assays, two of the present authors (SC and BE), in a two year longitudinal study, found that enzyme activity above a critical value had very high sensitivity and specificity for future attachment loss.[8] Further tests based on the two bacterial enzymes dipeptidylpeptidase and gingipain have proved to be of almost equal diagnostic value.[9,10]

This case control study was designed to assess the possible relationship between periodontal disease and spontaneous preterm delivery using both clinical examination and the assessment of neutrophil elastase, bacterial gingipain and dipeptidylpeptidase in gingival crevicular fluid.

Methods

Cases were women with singleton pregnancies who delivered at or before 35 weeks gestation, either after spontaneous labor or induction of labor for preterm premature rupture of membranes. The subjects all had access to universally funded prenatal care but not to publicly funded dental care. Two groups of controls were recruited: a group of postpartum women who delivered at term and the other, undelivered women who were assessed between 22 and 35 weeks gestation. Women were recruited in one hospital following delivery and in the hospital antenatal clinics.

Consenting subjects had a full periodontal examination in a standard, well-equipped, dental office maintained by one of the co-investigators, an experienced periodontist (AF). The dental examination was performed between 2 days and 28 days following delivery for the post partum subjects. Clinical examination was carried out by one highly experienced periodontal hygienist (SN). The intra-person variability in clinical examination by the hygienist was assessed by one of the investigators (AF) in a pilot period, using five volunteers, and was found to be acceptably low (mean .34 mm SD .5 mm). Clinical examination included assessment of oral hygiene with a standardized index (Oral Hygiene Index Simplified, OHI-S)[11] and probing for attachment loss. Probing depth and attachment level were measured with a standard probe (UNC-15) for all teeth in 6 locations (disto-lingual, mid-point lingual, mesio-lingual, disto-buccal, midpoint buccal, and mesio-buccal). The number and location of points which bled on probing were noted and a whole mouth bleeding index was calculated as the percentage of all sites. The hygienist was unaware whether the women had delivered prematurely or at term. Samples of gingival crevicular fluid for enzyme analysis were obtained in all subjects except those who had had a course of antibiotics lasting more than one week prior to delivery. This group was excluded because antibiotics could have affected the subgingival microflora and reduced the concentrations of bacterial enzymes. Subjects who had had antibiotics for short courses only during labor were included. The gingival crevicular fluid samples were taken before clinical assessments with 12 x 1.5 mm Whatman chromatography paper #1 with markings every 2 mm. The areas sampled were the typically high risk areas for periodontitis, the mesio-buccal gingival crevices of the two molars and premolars in each quadrant (total of 16 per subject). The supragingival plaque was removed and the sites isolated with cotton wool rolls and air dried. The strips were inserted gently and left in place for 30 seconds. The volume of gingival crevicular fluid

Table 1: Characteristics of study population.

	Preterm Cases n = 50	Undelivered Controls n = 51	Postpartum term Controls n = 50	p value
Age (years)	30.6 +/- 5.9	30.0 +/- 5.2	32.1 +/- 4.0	0.2*
Nulliparity	20 (40%)	28 (55%)	24 (48%)	0.3*
Post secondary education (years)	2.3 +/- 2.0	4.1 +/- 2.9	4.3 +/- 2.7	<.001*
Gross family income ≤ $20,000.	9 (18%)	4 (8%)	3 (6%)	0.15§
Smoker during pregnancy	13 (26%)	5 (10%)	3 (6%)	0.01§
Last dental cleaning ≤ 6 months	13 (26%)	21 (41%)	21 (42%)	0.12§

Value expressed as mean +/- SD or number (percentage)
*ANOVA §Fisher's exact.

was assessed by visually comparing the degree of strip wetting with that produced by known amounts of serum. Although less accurate than electronic measurement,[8,9] for the very low volumes of fluid expected from non-inflamed gingivae, visual assessment was considered adequate for the present investigation. This is because local site data were combined for subject mean values in the case-control statistical analysis and the great majority of women (117 of 129 sampled) had fluid volumes >0.1 Ìl at more than half the sites. Each strip was labeled and placed into 300 ul of 50 mM 2-(N-morpholino)-ethane-sulphonic acid (MES) buffer, PH 5.5, with 0.1 mM dithiothreitol (DTT), 0.15 M NaCl and 0.1% v/v Triton X-100. After 1 hour, with occasional agitation at 4°C, the strips were removed and the eluates were frozen with dry ice. The samples were maintained at -20-70°C and transported for analysis in the laboratory of two of the co-investigators (BE, SC). Enzyme activities were determined using selective peptide substrates for neutrophil elastase (MeOSuc-Ala-Ala-Pro-Val-AFC), bacterial gingipain (Z-Val-Lys-Lys-Arg-AFC) and dipeptidylpeptidase (Ala-Pro-AFC). Assay procedures and conditions were as described previously for each enzyme.[8,9] Concentrations of liberated 7-amino-4-trifluormethyl coumarin (AFC) were measured after 5 hours with a Perkin Elmer LS30 fluorimeter and enzyme activities were calculated in terms of uUnits pmoles of substrate hydrolysed per minute. Laboratory personnel and the co-investigators performing these analyses were not aware of the subjects' group. Standardized questionnaires were used to obtain data relating to medical-dental history and socioeconomic status.

Two control groups were used in this study as a previous investigation of periodontal disease in pregnancy had documented decreases in probing depth at term compared to preterm gestations.[12] Therefore, comparisons between postpartum preterm cases and term controls could lead to the observation of a spurious difference. Analysis was planned to examine the control groups separately and only combine them if no obvious difference in attachment loss was observed between these two groups.

Univariate analysis was planned to evaluate mean attachment loss and the frequency of significant attachment loss, (3 mm), between the cases and controls. Final analysis with logistic regression was planned to include possible confounding factors such as smoking, income, and education. Univariate analysis of the log mean enzyme concentrations was also planned as well as a comparison of the number of subjects who had concentrations over critical enzyme levels as this previously had been shown to predict attachment loss:[8,9] neutrophil elastase >400 uU/ul, bacterial dipeptidylpeptidase >30 uU/ul and gingipain >30 uU/ul. Analysis was performed with Stata version 8. A sample size of 50 cases and at least 50 controls was estimated to have at least 80% power to detect an association between clinical periodontitis and preterm birth of the magnitude of an odds ratio equal to 4. The sample size calculation was also based on an estimate of a 13% prevalence of periodontal disease.[13]

Results

During the study, we recruited 151 women, 50 cases, 51 undelivered controls and 50 postpartum term controls. One of the undelivered controls delivered preterm, two weeks after her dental examination, so she was reassigned as a case. The remainder of the undelivered controls all subsequently delivered at term.

The 50 cases delivered after spontaneous preterm labor between 22 and 35 weeks gestation (mean = 30.8 +/-3.7 weeks). The mean gestational age of the undelivered controls on examination was 29.2 +/-4.2 weeks. The post partum controls

Table 2: Full mouth examination data.

	Preterm Cases n = 50	Undelivered Controls n = 51	Postpartum term Controls n = 50	p value
Probing depth (mm)	2.11 +/- .33	2.17 +/- .26	2.14 +/- .21	.68†
Attachment loss (mm)	.86 +/-.32	.89 +/-.26	.87 +/- .18	.93†
Attachment loss ≥ 3 mm (mean %)	3.2 +/- .06	2.5 +/- .04	1.9 +/- .02	.33§
Extent Severity Score (3,5) *	9 (18%)	10 (20%)	4 (8%)	.22§
Debris Score	3.6 +/- 2.6	3.0 +/- 2.1	2.9 +/- 1.7	.42†
Calculus Score	4.5 +/- 3.6	5.1 +/- 3.7	3.9 +/- 2.8	.19†
Bleeding Index (% sites with bleeding)	24 +/- 15	24 +/- 15	20 +/- 11	.41†

Value expressed as mean +/- SD or number (percentage)
* Extent Severity Score (3,5) indicates subjects with = 3 mm of attachment loss at 5% or more of sites probed. † ANOVA §Fisher's exact.

Table 3: Gingival crevicular fluid enzyme levels.

	Preterm Cases n = 40	Undelivered Controls n = 46	Postpartum term Controls n = 43	p value *
Neutrophil elastase				
Concentration in GCF. Median (intraquartile range) (uU/*u*l)	261.0 (160.6, 383.1)	180.8 (81.5, 241.6)	169.7 (117.0, 285.4)	0.018
# of subjects with ≥ 1 site with >400 *u*U/*u*l	33	30	32	
Gingipain				
Concentration in GCF. Median (intraquartile range) (uU/*u*l)	2.24 (1.38, 3.48)	1.73 (1.01, 2.54)	1.60 (1.0, 2.47)	0.005
# of subjects with ≥ 1 site with >30 *u*U/*u*l	6	3	1	
Bacterial dipeptidylpeptidase				
Concentration in GCF. Median (intraquartile range) (uU/*u*l)	1.91 (1.17, 3.40)	2.08 (1.15,2.86)	1.16 (.70, 2.40)	0.192
# of subjects with ≥ 1 site with >30 *u*U/*u*l	5	5	4	

* ANOVA based on differences in mean log concentrations.

delivered at a mean gestational age of 39.4 +/-1.1 weeks. Additional characteristics of the subjects are described in Table 1. The Oral Hygiene Index scores for calculus and debris as well as the bleeding index (% of sites with bleeding on probing) were similar amongst the three groups (Table 2). There was also no difference between the preterm cases and undelivered or postpartum controls in mean attachment loss: 0.86 mm, 0.89 mm, and 0.87 mm respectively, p = .93. The mean percentage of sites probed with ≥ 3 mm of attachment loss was similar amongst the three groups: 3.2% of preterm cases, 2.5% of undelivered controls and 1.9% of postpartum controls, p = 0.33 (Table 2).

Initial analysis of the attachment loss of the two control groups revealed no significant differences so, as planned, for the final analysis, they were combined. The percentage of sites with attachment loss ≥ 3 mm was 2.2% in the combined control group compared to 3.2% in the preterm cases p = 0.21. It was originally intended to dichotomize the subjects with an extent severity score of (3,60), which was used by Offenbacher.[1] This would characterize all subjects as having periodontal disease if they were found to have 3 mm or more attachment loss in at least 60% of the sites probed. However, we had no subjects with this degree of periodontal disease. Therefore, as a much lower incidence of periodontitis was encountered, subjects were dichotomized using an extent severity score of (3,5). This characterized the women as having periodontitis if they showed attachment loss ≥ 3 mm in at least 5% of the sites probed, with the threshold corresponding to a moderate level of disease. This lower threshold was also adopted in a recent study.[14] An extent severity score of (3,5) was not associated with preterm labor in the crude analysis OR = 1.36 (0.54, 3.41). Univariate analysis also identified several other factors that were associated with preterm birth: gross family income, education and smoking during pregnancy. Logistic regression analysis was then performed with a model incorporating variables for age, income, smoking during pregnancy, education, dental cleaning within 6 months and periodontal disease defined by an extent severity score of (3,5) or greater. Controlling for a previous preterm birth was considered since it is a well known risk factor for premature birth. However, only one control subject and 7 cases had a previous preterm birth, so it was neither possible nor meaningful to control for this variable. Again, after adjusted analysis, no association between clinical periodontal disease and premature delivery was demonstrated OR = .56 (0.13, 2.37) p = .43. The analysis was repeated for the two control groups separately and again, there was no association with spontaneous premature labor (data not shown).

Gingival crevicular fluid samples were obtained from sixteen standard sites in 40 of 50 cases, 46 of 51 undelivered controls and 43 of 50 postpartum controls. Mean log concentrations of neutrophil elastase were significantly higher in the cases compared to undelivered and postpartum controls, p = .018 (Table 3). Of the cases, 33 had at least one site with a concentration of neutrophil elastase over the critical value of 400 uU/ul (range 1-11, median = 3), compared to 30 undelivered controls (range 1-10, median 2) and 32 postpartum controls (range 1-10, median = 2). Mean log concentrations of gingipain were higher in the cases compared to undelivered and postpartum controls, p = .005 (Table 3). Critical gingipain levels (> 30 uU/ul) were observed in 6 preterm cases, three subjects with one high enzyme site, one subject with two and two subjects with three high enzyme sites. Three undelivered controls and one postpartum control subject had one site each with high gingipain levels. There was no significant difference in the mean log concentration of bacterial dipeptidylpeptidase or in the frequency of sites with critical levels between the cases and controls (Table 3). The frequency of gingival crevicular fluid enzyme levels over the critical thresholds for neutrophil elastase and gingipain in cases vs. controls are illustrated in Figure 2.

Logistic regression analysis was then performed with a model incorporating terms for mean log enzyme levels, age, gross family income, education, smoking during pregnancy and dental cleaning in the last 6 months. In the adjusted analysis, the association between neutrophil elastase concentration and spontaneous premature birth remained significant: OR = 1.93(1.13, 3.28) p = 0.015, but the association with gingipain concentration did not: OR = 3.06 (0.68, 13.8) p = .15. The multivariate analysis was also performed replacing enzyme concentration with a variable for the number of sites with high enzyme levels. The number of high elastase sites was significantly associated with spontaneous preterm birth OR = 1.25 (1.03, 1.52), p = 0.021. The number of high gingipain sites was also positively associated with premature birth but, again, did not reach statistical significance OR = 1.43 (0.36, 5.62), p = 0.61. Although the lack of dental cleaning within 6 months of delivery had an association with premature birth in univariate analysis, the association was no longer statistically significant in the final model OR = 1.15 (0.54, 4.26), p = 0.43. Further analysis was performed to determine if high neutrophil elastase was associated with dental history. It appeared that having a dental cleaning within 6 months and not smoking during pregnancy were highly associated with lower gingival crevicular fluid elastase concentrations (ANOVA, p = .02 and p = .025 respectively). Additional regression analysis was also performed

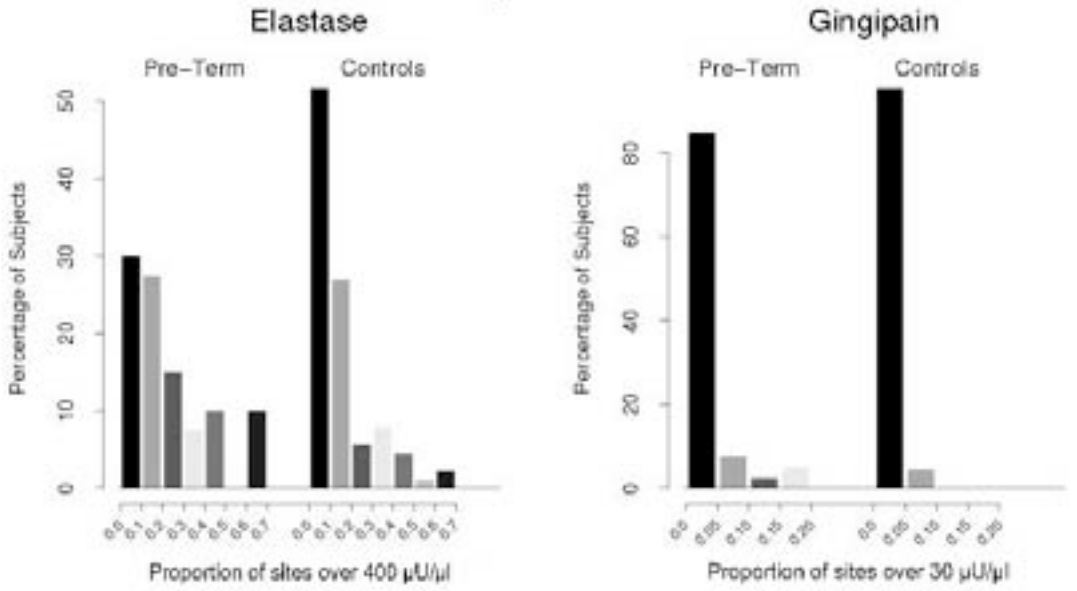

Figure 2
Proportion of subjects by percentage of sites over critical thresholds for gingival crevicular fluid Neutrophil Elastase and Gingipain. Cases vs. combined postpartum and antepartum controls.

to confirm that the time from delivery to dental examination was not associated with neutrophil elastase levels p = .28.

Discussion and Conclusion

Our study did not find an association between clinical periodontitis, measured by attachment loss, and spontaneous preterm birth. This is in contrast to several of the studies to date[1,2,15,16] but is consistent with the reports of Davenport and Moore et al.[17,18] One reason for these discrepancies may be our strict definition of preterm birth to include only those subjects with a preterm birth after spontaneous labor or induced labor due to preterm premature rupture of membranes. Several previous studies have used definitions of outcome that included intrauterine growth restriction or early second trimester miscarriage or iatrogenic preterm birth rather than spontaneous preterm birth alone.[1-3,19] As there is no indication that these diverse problems have a common pathogenesis, the amalgamation of these outcomes for analysis is methodologically questionable. Differences in disease severity between study population and access to prenatal care may also have led to different findings amongst studies. However, this lack of consistency raises the possibility that the associations observed in previous studies are non-causal.

Another explanation for a negative finding in any observational study is measurement error. We consider it quite unlikely that this could be responsible for our findings as we used only one, highly trained, blinded examiner to assess all the patients. This consistency in examination should reduce variability in measurement and any tendency to bias the results to a null finding. Finally, limited power could be an explanation for our findings. Although our study was relatively small, the degree of attachment loss was almost identical amongst the three groups. In order to detect a statistically significant difference, of the magnitude we observed, we would have required over 8000 subjects. Our study was also more than adequately powered to detect the strong associations that have been reported in the literature to date, especially if our study had observed a similar frequency of severe periodontal disease as those studies. The fact that we did not find the same frequency of disease does not invalidate our findings and suggests that an association between clinically measured periodontal disease and prematurity may not be evident in all populations. However, we do recognize that, given the relatively small size of our study, inadequate power is always a possible explanation for a null finding.

However, we do report an association between a marker of active periodontitis, gingival crevicular fluid neutrophil elastase, and premature delivery. It is difficult to fully evaluate the significance of this finding, especially as we did not find an association between premature delivery and standard clinical measurements of periodontitis. In our study, the gingival crevicular fluid enzymes were measured after delivery. It may be that following a preterm delivery, women are under increased stress and may neglect their dental hygiene. As neutrophil elastase may rise in gingival crevicular fluid with the development of gingivitis, this may be all that is reflected in our data. However, analysis of the Oral Hygiene Index scores between the case and control groups suggested only a slight, non-significant increase in only the debris scores, but not in the calculus scores, in the preterm group. The possibility of selection bias should also be considered in the evaluation of the results of any case control study. However, none of our patients had symptomatic periodontal disease. Therefore, it seems difficult to conceptualize how patients or study nurses could have perceived factors associated with elevated gingival crevicular fluid enzyme levels and have let this influence the probability of enrolment. One explanation for the inconsistency between the clinical and enzyme data is that high elastase levels reflect active periodontal inflammation and this, rather than past attachment loss, is the more important risk factor. If so, it may be that, in our minimally diseased population, the subjects have not had time to develop clinically apparent disease. Based on our data, such a conclusion is reasonable and would be consistent with a recent publication documenting an increased risk of preterm birth with progression of attachment loss during pregnancy.[20] Furthermore, our data suggest that simple treatments such as dental cleaning and avoidance of smoking

during pregnancy are associated with lower gingival crevicular fluid elastase and other enzymes with dental cleaning has been recently reported by Figueredo.[21] Therefore, if a causal relationship between early periodontal disease and premature labor is ultimately proven, this may lead to effective preventative strategies.

It is also possible that previous studies and our own enzyme findings have simply detected a yet to be defined generalized susceptibility to infection in women who deliver preterm. This could place women at increased risk for a variety of infections including periodontal disease and ascending chorioamnionitis leading to premature labor. On the other hand, one possible basis of share risk, cytokine gene polymorphisms, does not appear to be a common factor in preterm birth and periodontitis.[14]

In conclusion, in contrast to other authors, we did not find an association between clinical periodontal disease, measured by attachment loss, and spontaneous premature delivery. We did find an association between gingival crevicular fluid enzyme levels and premature delivery, possibly indicating an association between active periodontal disease and spontaneous premature delivery. However, given the lack of agreement between the analysis of the clinical and enzyme data, we feel it would be premature to conclude that a causal relationship exists. Ultimately, because of the difficulty in proving a temporal relationship between exposure and disease, a case control study can rarely, in and of itself, prove causality. Therefore, at this time a recommendation for screening and treatment of periodontal disease in pregnant women, with the aim of preventing premature birth, cannot be made until further research is completed. Of course, it is still recommended that women who are pregnant or planning to become pregnant continue to maintain optimum periodontal health with professional cleanings and meticulous oral hygiene to prevent periodontal disease. Based on our results, future investigations in this area should also consider measuring markers of active periodontal disease and not rely solely on clinical examination.

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Somatic and Cerebral Oximetry Aids Detection of Low Cardiac Output After Stage One Palliation of Hypoplastic Left Heart Syndrome

L. Eliot May

Neonates with hypoplastic left heart syndrome (HLHS) have unique post-operative needs following the Norwood stage one palliation (S1P) procedure typically performed in the first 7-10 days of life. When treating these infants with diminished cardiac reserve and little room for luxuriant cardiac output that exceeds demand, it is crucial to minimize oxygen demand while optimizing oxygen supply to the brain and other vital organs of the body. Near-infrared spectroscopy (NIRS) is used as a dual-site, noninvasive regional oximetry to simultaneously monitor somatic and cerebral tissue oxyhemoglobin saturations. This technology provides real-time information regarding the tissue oxygen economy, indirectly reflecting the adequacy of cardiac output and allows practitioners to institute corrective actions before anaerobic metabolism and acidosis promote a downward spiral.

A Little History

Just over two decades ago, diagnosis of HLHS was considered lethal even with attempted palliation. During the early 1980s innovative surgical interventions evolved to what is now regarded as the Norwood procedure, and marked the start of an era where infants with HLHS could be successfully palliated. Over the next two decades, modifications in surgery, cardiopulmonary bypass, pharmacology and monitoring resulted in improved survival for infants with HLHS and other forms of complex single ventricle disease.

Advances in the perioperative approach, increased understanding of cardiovascular physiology, and the advanced application of that knowledge to the care of neonates with HLHS have also contributed to improved survival rates in major centers to >90% following S1P. However, these infants are still at great risk for low cardiac output in the post-operative period. HLHS is marked by the inherent inefficiency of parallel circulation that is dependent on the right ventricle, an inferior power source. Additional perioperative insult is incurred from ischemia and a systemic inflammatory response from cardiopulmonary bypass. Postoperatively, diastolic dysfunction and autonomic dysfunction, along with increased metabolic demand, may contribute to inadequate systemic oxygen delivery even with balanced systemic and pulmonary flow.

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Newer Technologies

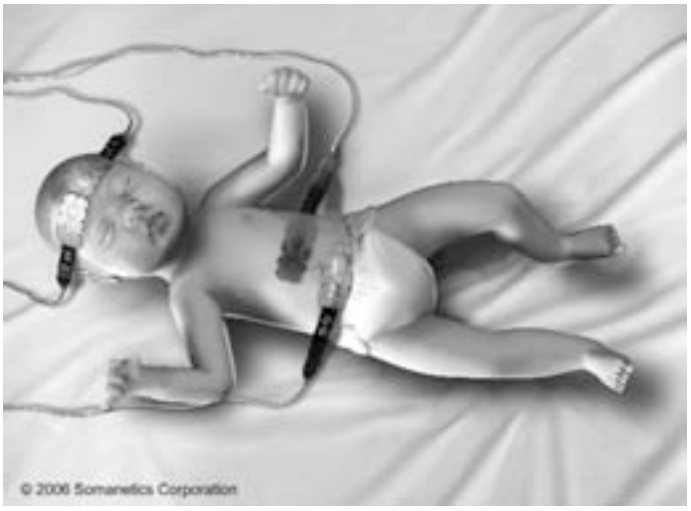
Post-operative management of infants following S1P is designed to achieve and maintain adequate (ideally, excessive) oxygen delivery to the tissues of the body in order to meet metabolic needs and promote healing while allowing for cardiac reserve. The approach is two-fold: maximize efficient distribution of cardiac output and minimize unnecessary resistors and wasted cardiac reserve.

Traditionally, cardiac output is assessed by physical exam, blood pressure, filling pressures, pulse oximetry, end tidal CO_2, ECG, lab values such as arterial blood gas and lactate levels, and urine output. Newer technologies that measure systemic venous oxygen saturation (SVO_2) and regional oxygen saturation (rSO_2) provide more timely data and trending information reflective of cardiac output. As such, they empower clinicians with an ever-changing picture of tissue oxygenation.

Systemic Venous Oxygen Saturation

SVO_2 monitoring involves insertion of a 4 French oximetric catheter into the superior vena cava (SVC), and serves as a surrogate for mixed venous oximetry which is only obtainable in the pulmonary artery when there is absence of an intracardiac shunt. Normally, the body uses approximately 25% of the oxygen in arterial blood, resulting in an SVO2 value of roughly 75% for normal subjects. The faster the blood travels through the circulation, the less oxygen is extracted. When cardiac output is poor, extraction occurs over a longer period of time and is more complete. The end result: SVO_2 is lower in low cardiac output states, and higher in higher cardiac output states.

SVO_2 monitoring allows for approximation of the pulmonary to systemic blood flow ratio (Qp/Qs) and reflects real-time changes in cardiac output and blood distribution. Changes in SVO_2 occur



before changes in traditional systemic measures such as blood pressure and arterial oxygen saturation (SaO_2), allowing for more timely identification and correction of problems. SVO_2 values between 55-65% have been shown to reduce morbidity and mortality after S1P, while a value below 45% can be associated with ischemic brain injury. Through derivation of the Fick Equation, Qp/Qs can be calculated as [SaO_2 – SVO_2] [assumed PvO_2 (95-100) – SaO_2], and 1.4:1 has shown to be optimal.

Unfortunately, SVO_2 monitoring has some disadvantages in the clinical setting. It's invasive, with a potential for bleeding or tamponade when the catheter is removed, and theoretically increases the risk for SVC thrombosis or infection. Readings can be positional, requiring frequent readjustments of the patient and/or equipment. Perhaps most importantly, SVO_2 doesn't take into account regional vasoconstriction in splanchnic-mesenteric beds, as seen in shock states secondary to low cardiac output.

Tissue oxyhemoglobin saturation as detected by NIRS (rSO_2) monitoring has emerged as an effective surrogate for SVO_2 monitoring in neonates following S1P. Regional oximetry enables noninvasive, two-site (cerebral and somatic) monitoring that delivers continuous readings, allowing derivation of oxyhemoglobin saturation in the tissues 2.5-3 cm below the skin.

Regional Oximetry

At Children's Hospital of Wisconsin, practitioners have adopted a strategy of universal rSO_2 monitoring with the Somanetics INVOS System in all children undergoing cardiac surgery. The system gathers information through light-emitting diodes (LEDs) placed on the forehead and over the kidney area in the lower back, emitting at least two wavelengths of near-infrared light that penetrate the skin and bone to the underlying tissues.

The amount and spectrum of light absorbed by hemoglobin in the blood varies depending upon the degree of oxygenation. Photodetectors spaced 2-3 cm from the LEDs measure the amount of reflected light, factoring in the energy absorbed by skin and skull. Employing a process known as spatial resolution, regional oximetry selectively measures oxygenation of the brain (cerebral oximetry) or region of the body (somatic oximetry) as a ratio of oxyhemoglobin to total hemoglobin. By reviewing simultaneous rSO2 from cerebral and somatic sensors, practitioners can differentiate between the adequacy of oxygenation in the brain compared to the peripheral organs.

Regional oximetry identifies significant trends in oxygenation levels reflecting real-time fluctuations in cerebral and somatic oxygenation. These trends reflect the evolving hemodynamic status of the neonate through the pre-, peri- and post-operative periods, identifying unpredictable cerebral and somatic desaturation events in their early stages. With real-time data in hand, clinicians can make timely decisions and initiate tailored corrective interventions to reduce hypoxic risks. Clinicians can also assess the impact of and patient response to interventions by observing corresponding changes in rSO_2 values.

Aggressive Postoperative Management

Cerebral and somatic oximetry readings are expressed as rSO2 values ranging from 0 to 100 percent. Following S1P, cerebral rSO_2 values >50% and somatic values > 60% have generally proven to predict better outcomes. It's important not only to monitor the readings themselves, but to follow trends as well.

The benefits of rSO_2 monitoring are well validated. It is a noninvasive, patient-friendly method that alleviates risks associated with invasive catheters. It also serves as a valuable adjunct to blood pressure and pulse oximetry, traditional measures of blood oxygenation saturation that rely on systemic values to infer cerebral oxygenation. Further, rSO_2 values are not affected by variations in pulse, blood pressure or body temperature, making it particularly valuable following cardiovascular procedures that purposefully or inadvertently compromise regional blood flow and limit the applications of traditional vital signs.

Aggressive postoperative management that includes detecting and correcting low cerebral and somatic oxygen saturation may reduce the incidence of postoperative ischemia and associated neurological or organ deficits. At Children's Hospital of Wisconsin, regional oximetry contributes significantly to the rapid assessment of cardiac output following S1P and is a standard of care that includes:

- SaO_2 values between >78%
- SVO_2 values between 55-65% (arterio-venous difference <25 %)
- Cerebral rSO_2 values >50% (arterio-cerebral difference <30 %)
- Somatic rSO_2 values > 60% (arterio-somatic difference <20 %)
- Diasotolic Blood Pressure > 30 mmHg
- Mean Blood Pressure > 40 mmHg
- Filling pressures at a level that maximize cardiac output
- ECG readings to reflect normal sinus rhythm with a heart rate that maximizes cardiac output
- Hematocrit at 45% or greater
- Urine output greater than 1 cc/kg/hr

Collectively, this approach has enabled tighter, more tailored and more rapid assessment and management of low cardiac output in HLHS patients. The result is enhanced ability to address their unique clinical needs and improve outcomes, while also increasing our patient-friendly care approach.

Intrauterine Testicular Torsion: A Case Report

Muhammad Aslam, MD; Stacey L. Valentine, MD; Musaddaq Inayat, MD

Abstract
A newborn male presented at birth with findings consistent with right testicular torsion. Preoperative ultrasound demonstrated no flow to the right testicle, and he underwent surgery, during which right extravaginal testicular torsion was confirmed. The right testicle was grossly necrotic and orchidectomy was performed, whereas the left testicle was normal and underwent orchiopexy. He was discharged home in stable condition and was doing well on follow up evaluations.

Keywords: Intrauterine testicular torsion, Doppler ultrasound, Hydrocele, Inguinal hernia, Orchiectomy, Orchiopexy.

Case
A full term male infant was born at 40 weeks' gestation by spontaneous vaginal delivery to a 27 year old primigravid mother. Her prenatal screen was as follows: blood type A positive, direct antibody test negative, HBsAg negative, Rubella immune, RPR non-reactive, and GBS negative. The pregnancy was complicated by preterm labor at 26 weeks' gestation treated with Terbutaline. She had rupture of membranes 12 hours prior to delivery. Loose nuchal cord was noted at delivery with no respiratory effort. He was given BMV with 100% FiO_2 for one minute. APGAR was 2, 6, and 9 at one, five and ten minutes respectively. He was transferred to the special care nursery (SCN) for further care. In the SCN, detailed physical examination was significant for a large left hydrocele and a firm right testicle with darkened and adherent scrotal skin. Scrotal ultrasound with Doppler demonstrated no venous or arterial flow to the right testes and normal flow to left testes. A consultation with Pediatric Urology was obtained and he was transferred to a tertiary care neonatal intensive care unit (NICU) for immediate surgery.

At the NICU an immediate scrotal ultrasound with Doppler was performed. The right testicle was noted to be heterogeneous in echogenicity with no flow on color Doppler examination. The epididymis was also enlarged and heterogeneous with a thickening of the scrotum. The left testicle was noted to have a "bell clapper" deformity, but with normal echogenicity and color Doppler flow. There was a large left hydrocele as well (Figures 1 & 2). He was immediately taken for surgery and underwent a right orchiectomy and left orchiopexy. He remained stable postoperatively and was discharged home without any complications. The pathology demonstrated a hemorrhagic ischemic infarction of the right testes with no evidence of tumor.

Discussion
Intrauterine testicular torsion (IUTT), aka spermatic cord torsion, is usually seen in infants within the first 30 days of life. There are some case reports of testicular torsion seen in older infants, but exact association to an intrauterine etiology has not been well established.[1] Five percent of all torsions occur before or soon after birth. Of these, 72% occur prenatally and 28% postnatally. Twenty one percent are bilateral and 3% are asynchronous bilateral. Different theories have been proposed regarding the mechanism of IUTT but exact intrauterine or peripartum process remains undetermined.[2,3] The most convincing theory to date relies on the hypothesis of rapid testicular descent through the spermatic canal with insufficient contact time between testes and scrotal wall resulting in lack of firm anchoring. IUTT is mostly extravaginal though few cases of intravaginal torsion have been reported.[4,5]

IUTT can take place over a varied time period, leading to diverse clinical presentation.[1,6,7,8] If the torsion takes place several months before birth, testes may be absent or present as nubbin testes. If it occurs days or weeks before birth, the testes may be palpable as painless, firm mass in the scrotal region. It does not transilluminate, a feature used to differentiate it from hernia or hydrocele. When torsion occurs few days or hours before birth, there are obvious classic signs of scrotal inflammation.[5] These include bluish discoloration, swelling with no transillumination, erythema, elevated testes and painful cord.[9,10,11] The cremasteric reflex is usually absent. When torsion takes place in the newborn period, the infant is usually asymptomatic at birth and will develop signs of inflammation during the first month of life.[7,8]

Differential diagnoses include benign and malignant tumors of the testes and epididymis, torsion of the appendix of the testes or epididymis, inguinal hernia with or without incarceration, hydrocele, hematocele, epididymo-orchitis, idiopathic infarction of the testes, meconium peritonitis and ectopic splenic or adrenal rests.[7,8,12,13] Prenatal diagnosis is technically not possible at present. Some cases of prenatal hydrocele were found to be torsion retrospectively at postnatal evaluation. The best diagnostic modality is Color Doppler ultrasonography that has a sensitivity of more than 95% in different studies.[4,11,14,15] Demonstration of a diminished arterial flow in the symptomatic testes as compared with normal flow in the asymptomatic testes

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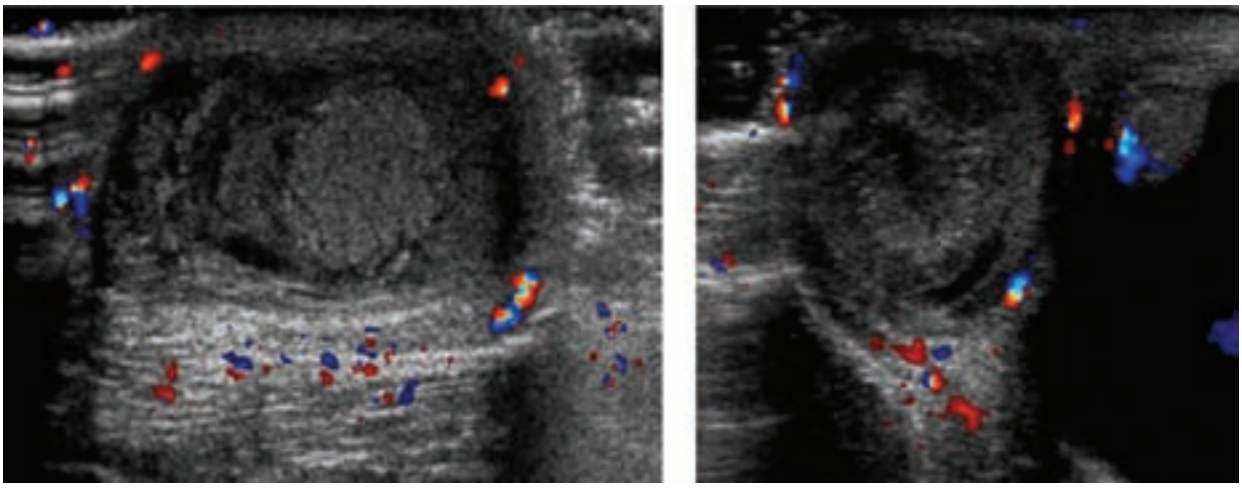

Figure 1. Sagittal (right) and transverse (left) view of the right testes demonstrating absent of arterial and venous flow on a color doppler ultrasound.

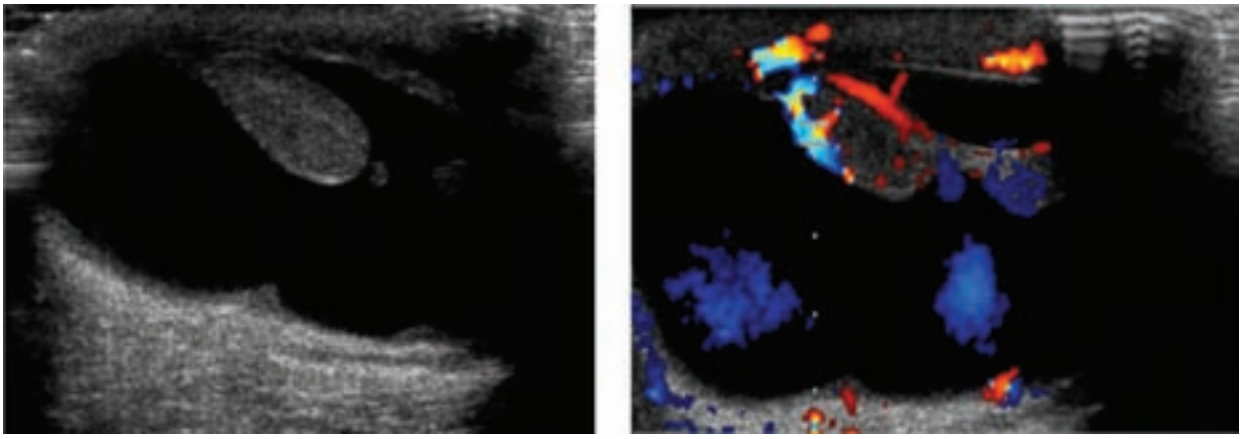

Figure 2. Sagittal view of the left testes demonstrating a bell clapper deformity with hydrocele (right) and a normal color doppler (left).

is strongly suggestive of torsion. A high level of suspicion is a satisfactory indication for surgical intervention and exploration.

Unilateral IUTT is an emergency requiring surgery to preserve the other testes and explore the torsed testes for any viability, especially when torsion is suspected to be recent over a few hours before or after birth. Bilateral IUTT is also considered an emergency if it's a suspected recent event because of risk of anorchia, requiring exploration of the tissue through the scrotal approach.[14,16,17,18] Contralateral hydrocele is also a common finding due to incomplete closure of processus vaginalis.[19] Controversy exists for the management of newborns with prolonged testicular torsion, as the risk of anesthesia outweighs the small benefit of detection of rare occurrence of tumor with torsion.[12,17,20] The testicular mass removed is always sent for histopathological examination to rule out tumor of the testes.

On gross examination, the torsed testes are usually edematous, hemorrhagic and may be surrounded by smooth membrane coverage.[10] Heterogeneous testicular parenchyma is present in most of the patients. Microscopic examination may reveal small areas of non-infarcted testicular tubuli within the hemorrhagic necrotic tissue. Usually the histological appearance is of an atrophic testicle with a necrotic center surrounded by tunica albuginea.[9,14]

Complications of unilateral IUTT include risk of infarction; damage to the contralateral testes because of release of cytokines from the torsed testes, which results in injury to blood testes barrier and germinal epithelium; and risk of retorsion if orchiopexy is not done in timely manner.[14,21,22] Bilateral IUTT may result in anorchia. Testicular tumor is also a remote possibility though not common.[5,12,14] Reduced fertility rate have been shown by some studies but the data are limited. Data from some studies have shown preservation of internal testicular tissue like leydig cells despite external damage.[23,24,25,26] Absent testes can be cosmetically corrected with prostheses, and in case of bilateral orchidectomy, hormone replacement is mandatory. [25]

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