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IN THIS ISSUE

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

Upcoming Meetings

IPA 2010 - 26th International Pediatric Association Congress of Pediatrics
Aug. 4-9, 2010; Johannesburg, South Africa
www.kenes.com/IPA/

Contemporary Management of Neonatal Pulmonary Disorders Conference
Nov. 4-5, 2010; Tempe, AZ USA
www.nalweb.com/cmnpdconference

Hot Topics in Neonatology
Dec. 5-7, 2010; Washington, DC USA
www.hottopics.org

Continuous Quality Improvement Pre-Conference (NEO)
Feb. 23, 2011; Orlando, FL USA
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NEO: The Conference for Neonatology
Feb. 24-27, 2011; Orlando, FL USA
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Recruitment Ads
Pages 2 and 11

A Clinical Dilemma: Formula or Breast Milk for Low Birth Weight Infants of Cocaine Using Mothers

By Richard Scott Taylor, MD and Adele Harrison, MD

Abstract

The American Academy of Pediatrics policy statement "Breast feeding and the use of Human Milk"[1] recognizes the nutritional, immunological, and other benefits of human milk, especially in preterm infants, but states that breast feeding is contra-indicated when the mother uses street drugs. We report a case of a premature infant of a cocaine using mother who died from necrotizing enterocolitis, after formula was substituted for mother's milk. We review the evidence for and against using breast milk, when it may contain cocaine.

Case Report

A 28-week gestation appropriate-for-gestation 1200g girl was delivered vaginally to a 33 year old G10P5 mother at our institution. All five of her previous children had been apprehended by the Ministry for Child and Family Development. The mother admitted to smoking heroin, cocaine and tobacco during the pregnancy and denied alcohol use. She received limited prenatal care and had also been prescribed methadone. She was known to be Hepatitis C positive, but was negative for Hepatitis B surface antigen (with evidence of immunity), syphilis and HIV (including repeat testing). She received intramuscular betamethasone two weeks prior to delivery and was treated with a single dose of rectal indomethacin, intravenous ampicillin, erythromycin, zidovidine and oxytocin intrapartum.

The baby was resuscitated with continuous positive airway pressure (CPAP), drying and oxygen. Cord pH was 7.32. Apgar scores were 3,8,10 at 1,5,10 minutes. She was intubated electively at one hour of age for respiratory acidosis and received a single dose of surfactant. She was ventilated for 24 hours and then extubated to CPAP on

"The American Academy of Pediatrics policy statement "Breast feeding and the use of Human Milk"[1] recognizes the nutritional, immunological, and other benefits of human milk, especially in preterm infants, but states that breast feeding is contra-indicated when the mother uses street drugs."

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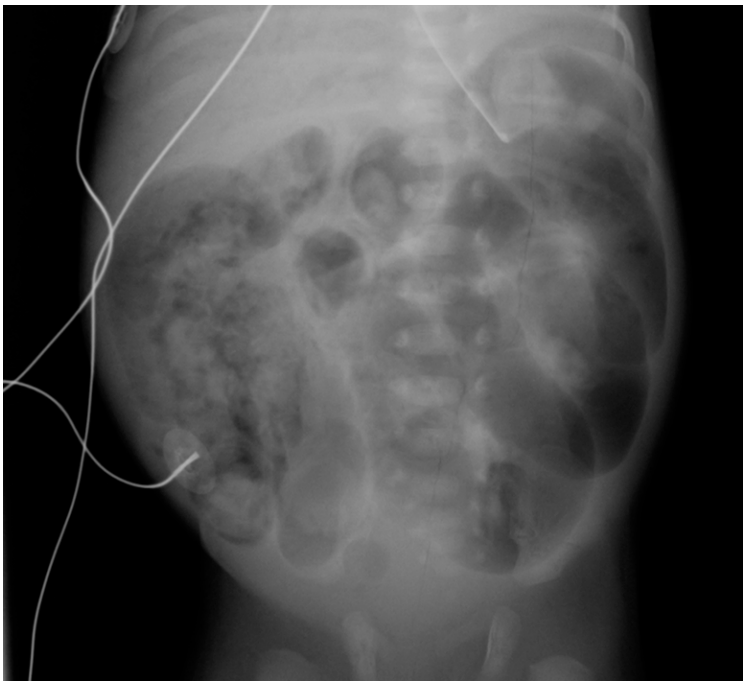
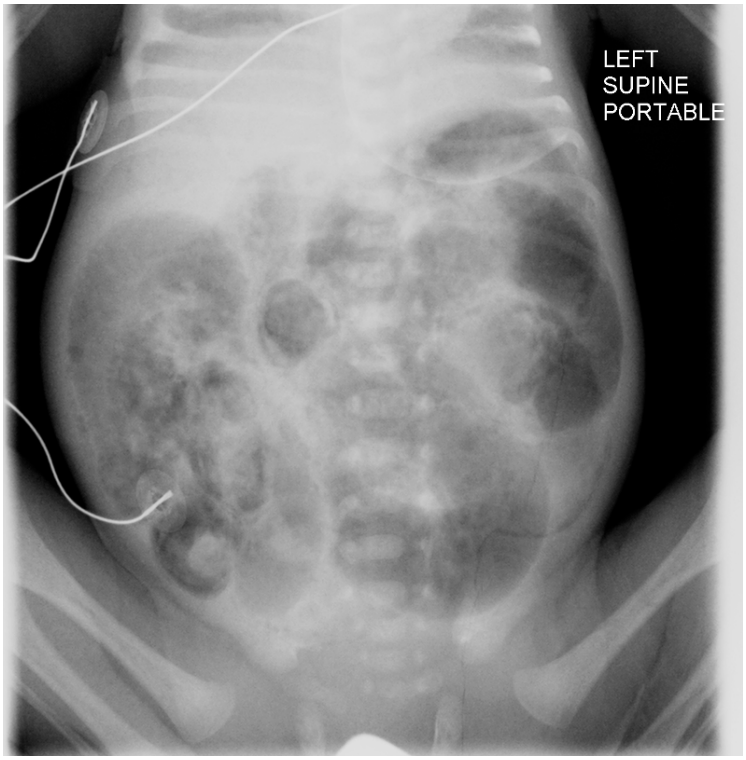


Abdomen AP Neonate at presentation



Abdomen AP Neonate six hours later

Day 1. On Day 2 the umbilical arterial catheter was removed, CPAP was discontinued and she was started on breast milk feeds (mother was still in hospital) at 10ml/kg/day. On Day 3 she was noted to have occasional non-rhythmic jerky movements of her limbs but was otherwise stable in air. She did not receive caffeine, morphine or other sedative. As her blood culture was negative, antibiotics were stopped. The mother was discharged home, and as she could no longer be supervised or observed, feedings were changed to 20 Cal/oz (67 kcal/100 ml) premature formula. A peripherally inserted central catheter was placed on Day 5 and the umbilical venous catheter was removed. Minimal enteral feeds (up to 20ml/kg/day) with formula were continued until Day 6 and then increased by 1ml 6 hourly as tolerated. There was no sign of feeding intolerance so they were advanced to 140ml/kg/day by Day 12. At this point, she was stable, no longer jittery and on no respiratory support. Head sonogram was unremarkable on Day 4. The PICC was removed and she was advanced to 160ml/kg/day premature formula.

On Day 13, soon after changing to 24 Cal/oz (81kcal/100mls) formula, she developed large gastric aspirates which persisted in spite of reverting back to 20 Cal/oz formula. An abdominal radiograph demonstrated widespread pneumatosis and portal venous gas but no free air. She became systemically unwell with bloody stools, irritability and metabolic acidosis. She was electively intubated, started on intravenous antibiotics and placed nil enterally. She continued to deteriorate. In spite of ongoing support with inotropes, broad spectrum antibiotics, blood products, and diuretics, she developed multi-organ failure with coagulopathy and complete anuria. Ventilator support was withdrawn on Day 18. All blood cultures were negative. An autopsy was not performed.

Comprehensive review of the case confirmed that death was clearly due to complications of necrotizing enterocolitis (NEC) which has a number of potentially avoidable risk factors. A literature review was performed which included a search for evidence of risk from breast milk in cocaine using mothers.

Discussion

Necrotizing enterocolitis in premature infants is not uncommon. A cohort study from the UK over 20 years ago found a 6 to 10 times increased risk of NEC associated with formula rather than mother's milk[2] and more recent cohort studies confirm the strong association, with risks -according to a recent study looking at NEC or death in infants under 1000g[3] - ranging from ~2% in exclusively breast milk fed infants up to 14% in exclusively formula fed infants. An older meta-analysis of smaller randomized studies[4] comparing donor human milk (mostly pasteurized) with formula found 2-3 times risk of NEC associated with formula. Evidence for rate of increase, use of trophic feedings, type of formula and milk osmolality (20 cal/oz vs 24 Cal/oz) is equivocal or non-existent.[5] NEC is also associated with cardiovascular instability;[6] however, our infant was very stable with no sign of hypotension or patent ductus arteriosus, prior to becoming unwell.

Cocaine is a potent vasoconstrictor and ingestion has been reported to cause bowel ischemia and gangrene in adults.[7] There

"The documented magnitude of risk from formula (about 10%) versus the theoretical risk from contaminated breast milk (difficult to quantify, but probably far lower) leads us to question the current AAP guidelines."

are also case reports of congenital intestinal atresias linked to prenatal cocaine use[8] and one case of early NEC in a term infant with sepsis who had never been fed.[9] Prenatal exposure to cocaine was strongly associated with NEC in a retrospective cohort study from California,[10] however the authors did not correct for type of feeding, making it plausible that the higher rate of late onset NEC in low birth weight infants was also due to formula feeding instead of human milk feeding.

Theoretically, cocaine in breast milk might also reduce splanchnic blood flow, and so increase the risk for NEC; however, we were unable to find any case reports of an association. There are only two case reports[11, 12] of adverse outcomes associated with ingestion of cocaine in breast fed infants and one of them was associated with direct ingestion due to cocaine application to mothers nipples.[12] Neither exposure led to documented long-term harm. Another review of risk factors for NEC[13] in premature babies found an increased risk of NEC with prenatal exposure to cocaine, but none of the affected infants received human milk, begging the question: Was the association also due to formula feeding?

To summarize the dilemma, there appears to be excellent (level 1 and 2) evidence for the use of mothers (or human) milk for premature infants for the prevention of NEC, and some (level 5 – indirect) evidence against the use of mother's milk when it contains cocaine. The documented magnitude of risk from formula (about 10%) versus the theoretical risk from contaminated breast milk (difficult to quantify, but probably far lower) leads us to question the current AAP guidelines.

We were subsequently able to solve our dilemma with the introduction of human donor milk to our unit.

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Patient has given permission for the case to be published. She remained drug free (so her milk would have been "OK" to use) from discharge until the day her baby died, then started taking cocaine again. She is currently in rehab, and due to be discharged in May.

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Global Neonatology Today: A Monthly Column

By Dharmapuri Vidyasagar, MD, FAAP, FCCM

United Nations Millennium Development Goal (MDG) #3

The goal of MDG #3 is to eliminate gender disparity in primary and secondary education, preferably by 2005, and in all levels of education no later than 2015. The indicators include:

1. Improve girl-to-boy ratio in primary, secondary and tertiary education.
2. Increase percentage of women in wage employment in the non-agricultural sector.
3. Increase the proportion of seats held by women in national parliaments by 2015.

Why MDG #3 Is Important

Gender inequality is a major hurdle in achieving the targets of the Millennium Development Goals. Inequality of women's rights is more obvious in the developing countries than developed countries. But even in developed countries, there is a "glass ceiling" limiting a woman's success.

Ten Staggering Facts About Women's Status in the World

1. Poor Literacy: Seventy percent of the 855 million illiterate adults in the world are female.
2. Poor Wages: Women are paid less for doing the same work as men in every Developed and Developing country of the world.
3. Lack of Ownership of Property: While women produce nearly 80% of the world's food, they receive less than 10% of the agricultural assistance. In many societies women do not inherit land property.
4. Lack of Political Representation: Worldwide, 52% of the population are female, yet women represent only 13% of members of national parliaments.
5. Gender Inequality: Starting from childhood, gender inequality against female children is pervasive in many societies in the world.
6. Violation of Women's Rights: From acid attacks, homicidal and suicidal burning in Asian countries, honor killing in Middle East to the economic inequity in developed countries, women face a vast array of discriminatory practices and human right violations worldwide.
7. Feminization of Poverty: Poverty is disproportionally female, because of women's lack of education, economic independence and political power.
8. Lack of Access to Health: Because of lack of economic independence, many women do not have or seek healthcare. In addition, because of societal constraints, women often are not allowed to seek health care on their own.
9. Narrow View of Women's Health: Most policy makers consider women's health beginning and ending with "reproductive health." On the contrary, women's healthcare extends far beyond reproductive health. In fact, the "cost of health being a women" is over and above the cost of reproductive healthcare.
10. The cumulative effects of the above factors put more than 50% of world's population at risk for poor health; thereby, the health of children and the health of society is negatively impacted as well.

"Gender inequality is a major hurdle in achieving the targets of the Millennium Development Goals. Inequality of women's rights is more obvious in the developing countries than developed countries. But even in developed countries there is a "glass ceiling" limiting a woman's success."

The MDG #3 specifically aims at breaking these barriers, by promoting gender equality and empowering women to attain: greater education, increased earning capacity, equal political status and, more importantly, improvement in their reproductive health.

What Is The Progress Made So Far?

So far, the focus has been mostly on maternal mortality and HIV/AIDS, There is much more to done towards improving women's health. For example, it has been shown that it costs more for "Being a Women" to keep "non-reproductive" healthy life. Women are prone to suffer from numerous healths at different life stages; adolescent, childbearing age, menopausal and post menopausal stages. At each stage women have unique health issues that men do not. Women are unlikely to seek out health services for themselves when they have been conditioned in this way.

Much more work has to be done in the areas of women's rights, wages, and elected offices. Recent passage of a women's rights bill by the Indian parliament is a welcome sign as it represents a sea change in the world's largest and most highly populated democracy. Similar changes must occur in other countries, especially the Middle East, and Africa, to make any discernible positive effect on the world's women.

The Clock is ticking!

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For more information on the United Nations Millennium Development Goals (MDGs), visit - www.un.org/millenniumgoals.

Medical News Products & Information

Child-Specific Doses for Pediatric PET Patients

Studies have shown positron emission tomography's (PET) value as a minimally invasive, painless and safe diagnostic tool for many pediatric conditions. In a study published in the February issue of *The Journal of Nuclear Medicine* (JNM) (http://jnm.snmjournals.org.), researchers at the Children's Hospital of Philadelphia (CHOP) and the University of Pennsylvania (Penn) gathered data that may provide clinicians with new formulas—specific to pediatrics—to calculate the amount of radiotracer that should be injected based on the patient's weight.

"These findings mean that PET—a very common nuclear medicine procedure—can be used in children with methods that are even more patient-specific than those currently employed," said Roberto Accorsi, PhD, former research Assistant Professor of Radiology at CHOP, and lead author of the study.

This study is one more contribution to the medical imaging community's overall efforts to reduce radiation dose to children. Nuclear medicine specialists are continuously refining methodologies in order to preserve image quality and minimize radiation exposure during pediatric PET exams. Since medical research published in recent years highlights the health risks of exposure to ionizing radiation, many have looked to the medical community for ways to curb exposure during medical imaging exams. Although the nuclear medicine exam's benefits to the patient far outweigh any potential risks associated with radiation, the nuclear medicine community seeks to uphold practices that are consistent and mindful of patients' concerns.

In nuclear medicine, there are well-established guidelines for administering radiopharmaceutical doses for adults; however, there is little guidance for administering pediatric doses. Thus, the CHOP-Penn study sets out to examine how nuclear medicine physicians can take into consideration a child's lighter weight and body size and adjust the dose and scan time accordingly, while maintaining high-quality imaging for the best diagnosis possible.

Image quality for PET depends strongly on the patient's weight and body build. In other words, the larger and heavier the patient, the more injection dose or possibly a longer scan time is needed to obtain a quality image. For patients who are lighter and have less body mass—such as in pediatric patients—less injection dose or a reduced scan time may still allow for high-quality images.

"The results of this study show that, due to children's relatively small size and light weight, it is possible to reduce radiological dose (or scan time) while preserving image quality as compared to PET imaging in adults," said Dr. Accorsi, whose research was supported through a Research Fellow Award by the Society for Pediatric Radiology Research and Education Foundation. "Minimizing exposure to radiation is important to all patients, but especially for young children."

CHOP-Penn researchers acquired and analyzed data from 73 patients. The patients' weight ranged from 25 pounds to 200 pounds. Researchers report in their study that when following an injection protocol proportional to weight, the data quality of PET images was found to improve with decreasing weight. The study provides practical injection protocols to trade this advantage for decreased scan time or dose at constant image quality.

Studies such as the one published in JNM are helping physicists and physicians gather new data about improving dose regimens to get the highest-quality diagnostic image while using the lowest amount of radiation practical, adhering to the "As Low As Reasonably Achievable" (ALARA) principle.

Co-authors of "Improved Dose Regimen in Pediatric PET" include Roberto Accorsi, Department of Radiology, Children's Hospital of Philadelphia, and University of Pennsylvania, Philadelphia, Penn.; and Joel S. Karp and Suleman Surti, Department of Radiology, University of Pennsylvania, Philadelphia, Penn.

Community-Acquired MRSA Becoming More Common in Pediatric ICU Patients

Once considered a hospital anomaly, community-acquired infections with drug-resistant strains of the bacterium Staphylococcus aureus now turn up regularly among children hospitalized in the intensive-care unit, according to research from the Johns Hopkins Children's Center.

The Johns Hopkins Children's team's findings, to be published in the April issue of the journal Emerging Infectious Diseases, underscore the benefit of screening all patients upon hospital admission and weekly screening thereafter regardless of symptoms because MRSA can be spread easily to other patients on the unit.

Community-acquired methicillin-resistant Staphylococcus aureus (CA-MRSA) is a virulent subset of the bacterium and impervious to the most commonly used antibiotics. Most CA-MRSA causes skin and soft-tissue infections, but in ill people or in those with weakened immune systems, it can lead to invasive, sometimes fatal, infections.

In 2007, The Johns Hopkins Hospital began screening all patients upon admission and weekly thereafter until discharge. Some states have made patient screening mandatory but the protocols vary widely from hospital to hospital and from state to state.

"MRSA has become so widespread in the community, that it's become nearly impossible to predict which patients harbor MRSA on their body," says lead investigator Aaron Milstone, MD, MHS, a pediatric infectious disease specialist at Hopkins Children's.

"Point-of-admission screening in combination with other preventive steps, like isolating the patient and using contact precaution, can help curb the spread of dangerous bacterial infections to other vulnerable patients."

The new Johns Hopkins study found that 6 percent of the 1,674 children admitted to the pediatric intensive-care unit (PICU) at Hopkins Children's between 2007 and 2008 were colonized with MRSA, meaning they

carried MRSA but did not have an active infection. Of the 72 children who tested positive for MRSA, 60% harbored the community-acquired strain and 75% of all MRSA carriers had no previous history or MRSA. MRSA was more common in younger children, 3 years old on average, and among African-American children. The reasons behind the age and racial disparities in MRSA colonization remain unclear, the investigators say. Patients with MRSA had longer hospital stays (eight days) than MRSA-free patients (five days) and longer PICU stays (three days) than non-colonized patients (two days).

Eight patients who were MRSA-free upon admission became colonized with MRSA while in the PICU. Of the eight, four developed clinical signs of infection, meaning that the other four would have never been identified as MRSA carriers if the hospital was not performing weekly screenings of all patients.

The research was funded in part by the National Institutes of Health, the Thomas Wilson Sanitarium for Children in Baltimore and by the Centers for Disease Control and Prevention.

Other investigators in the study included Karen Carroll, MD; Tracy Ross; Alexander Shangraw; and Trish Perl, MD, MS; all of Hopkins.

Related resources and articles on the web:

- In the Fight Against Life-Threatening Catheter Infections, Length of Use is Key: www.hopkinschildrens.org/In-the-Fight-Against-Life-Threatening-Catheter-Infections-Length-of-Use-of-Key.aspx
- MRSA: www.hopkinsmedicine.org/heic/ID/mrsa/
- Simple Steps Prevent Life-Threatening Bloodstream Infections in Children: www.hopkinschildrens.org/Simple-Steps-Prevent-Life-Threatening-Bloodstream-Infections-in-Children.aspx
  Johns Hopkins Children's Center:
- www.hopkinschildrens.org

Committee Outlines Procedures for Making Newborn Screening Recommendations

The experts who make recommendations for genetic disease screening in newborns face a challenging task: To make conclusions based on the most authoritative available evidence, while considering gaps in the research on such rare conditions, as well as their human impact. An overview of the steps followed by the expert panels tasked with making these recommendations is presented in a special section of a current issue of *Genetics in Medicine* (www.geneticsinmedicine.org), the official peer-reviewed journal of The American College of Medical Genetics (ACMG) published by Lippincott Williams & Wilkins, a part of Wolters Kluwer Health.

The articles seek to communicate a review process that includes "careful assessment of the evidence, elimination of conflicts of interest, and transparency with significant public input throughout," according to an introductory comment by Alan R. Fleischman, MD, and Jennifer L. Howse, PhD, of the March of Dimes Foundation.

Effort Emphasizes 'Unique Role of Unique Evidence'

The Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC) was chartered in 2003 to make recommendations to the Secretary of Health and Human Services regarding which genetic diseases should be included in newborn screening programs. A 2006 ACMG report recommended mandatory newborn screening for a core panel of 29 conditions, most of which are currently included in the newborn screening program of every state.

"The ACMG report was enthusiastically endorsed by the Secretary's Advisory Committee as well as the American Academy of Pediatrics, the March of Dimes and other organizations," Dr. Fleischman and Howse write. However, some commentators have questioned the methods used in making these recommendations, suggesting that the process "does not conform to contemporary standards of evidence-based decision making."

To address these concerns, members of the Secretary's Advisory Committee outline the process followed in making its recommendations. A key issue is the relative scarcity of data concerning most genetic diseases in infants, many of which are very rare. The threshold for evidence is "inherently different" than that for screening of more common conditions, such as cancer or cardiovascular disease.

The multi-step process includes assessment of the availability and quality of research evidence, the accuracy of the available screening tests, and the potential benefits of early detection and treatment. These are similar to the issues involved in screening for more common diseases. However, the process includes "more flexible criteria...to accommodate the data limitations stemming from the rarity of many of these conditions," according to the Secretary's Advisory Committee report.

In addition to considering published scientific evidence, the Committee seeks involvement of parent/advocacy groups, as well as experts who may have specialized knowledge in this rapidly-evolving field. In outlining the process and including the input of advocates and experts, the Committee has sought to develop "consistent and transparent strategies for evidence review."

The special issue also presented updates on the prospects for new tests for specific genetic diseases, some of which may soon be evaluated by the Secretary's Advisory Committee:

- A new and improved diagnostic test for Fragile X Syndrome—the most common inherited cause of mental impairment—which may soon make it practical to perform newborn screening and carrier testing for Fragile X mutations.
- Progress in diagnostic testing for spinal muscular atrophy, a neurodegenerative disease that is the most common genetic cause of death in infants. Last year, the ACMG formally recommended population carrier screening for this condition.
- An update on testing for the 22q11 Deletion Syndrome: A highly variable condition that causes few problems in some children, learning disabilities or autism in others, and heart defects and seizures in others. Although no test is available yet, decisions about this condition are likely to set a precedent for the addition of other chromosomal diseases.
- Connexin-26-associated deafness, a common form of inherited hearing loss that worsens over time in many children.

Mother's Flu During Pregnancy May Increase Baby's Risk of Schizophrenia

Rhesus monkey babies born to mothers who had the flu while pregnant had smaller brains and showed other brain changes similar to those observed in human patients with schizophrenia, a study at the University of Wisconsin-Madison in collaboration with the University of North Carolina at Chapel Hill has found.

The study, published online by the journal Biological Psychiatry, is the first study done with monkeys that examines the effects of flu during pregnancy. Results from this study support findings from rodent studies suggesting this type of infection may increase the risk of schizophrenia in the offspring, said lead author Sarah J. Short, PhD.

Short worked on the study while earning her doctorate at Wisconsin and now is a postdoctoral fellow at UNC working with John H. Gilmore, MD, Professor of Psychiatry in the UNC School of Medicine.

"This was a relatively mild flu infection, but it had a significant effect on the brains of the babies," Short said. "While these results aren't directly applicable to humans, I do think they reinforce the idea, as recommended by the Centers for Disease Control and Prevention, that pregnant women should get flu shots, before they get sick."

In the study, 12 rhesus macaques were infected with a mild influenza A virus 1 month before their baby's due date, early in the third trimester of pregnancy. For comparison, the study also included 7 pregnant monkeys who did not have the flu.

When the babies were 1 year old, magnetic resonance imaging (MRI) scans were taken of their brains. Researchers also assessed the babies' behavioral development at that time.

The babies born to flu-infected mothers showed no evidence of direct viral exposure. Their birth weight, gestation length and neuromotor, behavioral and endocrine responses were all normal.

However, the MRI scans revealed significant reductions in overall brain size in the flu-exposed babies. In addition, the scans found significant reductions of "gray matter" (the portion of brain tissue that is dark in color) especially in areas of the brain called the cingulate and parietal lobe, and significant reductions of "white matter" (brain tissue that is lighter in color) in the parietal lobe.

The cingulate is located in the middle of the brain, but spans a broad distance from front to back and relays information from both halves of the brain. This structure is important for numerous cognitive function related to emotions, learning, memory, and executive control of these processes to aid in decision-making and anticipation of rewards. In addition this structure also plays a role in regulating autonomic processes, such as blood pressure and respiratory control. The parietal lobe comprises a large section on both sides of the brain between the frontal lobes and the occipital lobes, in the back of the brain. This part of the brain integrates information from all the senses and is especially important for combining visual and spatial information.

"The brain changes that we found in the monkey babies are similar to what we typically see in MRI scans of humans with schizophrenia," said Gilmore. "This suggests that human babies whose mothers had the flu while pregnant may have a greater risk of developing schizophrenia later in life than babies whose mothers did not have the flu. Normally that risk affects about 1 of every 100 births. Studies in humans suggest that for flu-exposed babies, the risk is 2 or 3 per 100 births."

Most of the work of the study was done at the Harlow Center for Biological Psychology, which is part of Wisconsin's Department of Psychology. The center's director, Christopher Coe, PhD, is senior author of the study. Gilmore, a schizophrenia researcher who has led several studies that used MRI scans of newborn human brains, led the analysis of MRI data in the pregnancy and influenza study.

Neural Stem Cell Transplantation Offers Hope to Children with Fatal Batten Disease

Newswise — Neuronal Ceroid Liposfuscinosis (NCL), often referred to as Batten disease, is a rare and fatal neurodegenerative disorder that afflicts infants and young children. NCL is caused by a deficiency of a lysosomal enzyme, and is a relatively rare disease, affecting an estimated 2 to 4 of every 100,000 babies born in the US. Although NCLs are classified as rare diseases, they often affect more than one child in families that carry the defective gene, and tragically, are always fatal.

Researchers at Oregon Health & Science University, Doernbecher Children's Hospital in Portland, Ore., investigated the transplantation of neural stem cells in patients with advanced stage infantile and late-infantile NCL. The results of this study, CNS Transplantation of Purified Human Neural Stem Cells in Neuronal Ceroid Lipofuscinoses: Phase I Trial, was presented by Nathan Selden, MD, PhD, May 3, 2010, during the *78th Annual Meeting of the American Association of Neurological Surgeons* in Philadelphia. Co-authors are: Daniel J. Guillaume, MD; Stephen L. Huhn, MD; Thomas K. Koch, MD; Amira Al-Uzri, MD and Robert D. Steiner, MD.

"This is a tragic and devastating disease for children and their families, so research into finding a potential treatment – and eventually a cure – is extremely crucial," remarked Dr. Selden. The onset of the infantile form affects babies at ages 6 mo. - 2 yrs. and progresses rapidly. Patients usually die before age 5, although some have survived a few years longer. The onset of the late infantile form affects young children at ages 2 to 4 years, and progresses fairly rapidly. Children with this form usually die between the ages of 6 and 12. The key lysosomal enzymes that are missing in the infantile and late infantile forms are Palmitoyl Protein Thioesterase 1 (PPT1) and Tripeptidyl Peptidase 1 (TPP1), respectively.

This clinical trial, the first FDA-authorized clinical trial ever undertaken in the US utilizing purified human neural stem cells, was completed in January 2009. The sponsor of this study, StemCells, Inc. of Palo Alto, Calif., isolates and purifies its proprietary neural stem cells (HuCNS-SC® cells) that are naturally resident in donated brain tissue, and then expands these cells into banks from which multiple patient doses can be obtained. These tissue-derived "adult" stem cells are not genetically modified in any way nor grown with any animal feeder cells, and have thus far demonstrated a favorable safety profile both in animal studies and this first human study.

The six children who participated in this trial were comprised of four males and two females with an age range from 2 to 9 years. Two patients had the infantile form and four had the late-infantile form of NCL. The patients, all of whom were in very advanced stages of the disease, underwent bilateral intracerebral and intraventricular transplantation of HuCNS-SC cells in a single-stage surgical procedure. The low dose group received a target dose of approximately 500 million cells and the high dose group received a target dose of approximately 1 billion cells. All patients were placed on immunosuppression for 12 months after transplantation. Patients were assessed both pre- and post-transplant with a comprehensive battery of tests and magnetic resonance imaging of the brain.

The trial data demonstrated that HuCNS-SC cell transplantation in combination with immunosuppression was well tolerated by all six patients. The subjects' neurological and neuropsychological course following transplantation appeared to be consistent with the underlying disease. One patient with the

infantile form died 11 months after transplantation due to the natural progression of the disease. A brain autopsy revealed no abnormalities associated with transplantation of HuCNS-SC cells, and DNA PCR testing of post-mortem brain tissue provided evidence of donor cell engraftment and survival. The remaining five patients completed the Phase I trial assessments and have been enrolled in a separate four-year, long-term follow-up study. At this time, all five patients have lived more than two years post transplant and two of the patients have lived more than three years post transplant. Preliminary interim safety results from the long-term follow-up study will also be presented by Dr. Selden.

"This Phase 1 trial was a very important first step toward finding a viable treatment and extending the life of children with this devastating disease. Initial results regarding safety associated with the transplantation of a significant cell dose are certainly promising. Further investigation of HuCNS-SC cells is warranted for infantile and late-infantile NCL, as well as for exploring this cell therapy approach for other conditions of the central nervous system," concluded Dr. Selden.

The authors report no conflict of interest. This work was funded by StemCells, Inc.

Women & Infants' Researcher Highlighted in Theme Issue of Archives of Pediatrics & Adolescent Medicine - Early Childhood Experiences Have Lasting Emotional and Psychological Effects

Theme issue of *Archives of Pediatrics & Adolescent Medicine* highlights dangers during early development, interventions to improve long-term health

Experiences between birth and age 5 matter significantly to children's long-term emotional and psychological health, and changing these experiences for the better pays dividends, according to an editorial and several new reports in the May issue of *Archives of Pediatrics & Adolescent Medicine*, a JAMA/Archives journal.

In the May journal is a theme issue devoted to the science of early life experience. The articles provide "key, actionable evidence of how we can manipulate the early environment of children and make a tangible difference in their health," write Dimitri A. Christakis, MD, MPH, and Frederick P. Rivara, MD, MPH, both of the University of Washington and Seattle Children's Research Institute as well as associate editor and editor of the Archives, in the editorial.

"This research needs to be translated into action," they continue. "In the new austerity that has been spawned by the national fiscal crisis, states are cutting back broadly on services. In many cases, children are being hit the hardest. Given the importance of early childhood experiences on the entire life course, we can only hope that the people who make decisions about where monies are saved are mindful of the effect those decisions can have."

Articles featured in the May theme issue include: "Prenatal Nicotine, Antidepressant Exposure Associated With Childhood Difficulties."

Children whose mothers smoked during pregnancy appear to have more sleep problems throughout the first 12 years of life, and those whose mothers took a certain type of antidepressant may be more likely to have some behavior problems at age 3, according to two reports in the theme issue.

In one study, Kristen C. Stone, PhD, of the Brown Center for the Study of Children at Risk, Women & Infants Hospital, Providence, R., and colleagues assessed 808 children whose mothers provided information about prenatal care, sociodemographics and their children's sleep and behavior problems, as well as substance exposure during pregnancy.

Of the five substances assessed—cocaine, opiate, marijuana, alcohol and nicotine—only prenatal exposure to nicotine was associated with sleep problems in children. "Higher levels of prenatal nicotine exposure predicted more sleep problems, specifically difficulty falling and staying asleep from one month to 12 years," the authors write.

"Targeting of this group of children for educational and behavioral efforts to prevent and treat sleep problems is merited given that good sleep may serve as a protective factor for other developmental outcomes," they conclude.

In another report, Tim F. Oberlander, MD, FRCPC, and colleagues at University of British Columbia, Vancouver, studied 75 mothers and their 3-year-old children. Of these, 33 mothers took selective serotonin reuptake inhibitors (SSRIs) during pregnancy and 42 did not. Mothers' moods were assessed during the third trimester, three months after birth and at the three-year follow-up.

"Prenatal SSRI exposure and higher current maternal anxiety contributed to increased internalizing behaviors [withdrawal, anxiety and depression] in 3-year-old children," the authors write. "Increased levels of externalizing behaviors were also observed, but they were associated with current levels of three-year postpartum maternal mood." Genetic factors, including an altered version of a gene in the serotonin processing system, moderated the effect of a mothers' mood on her child.

"Even with prenatal maternal SSRI treatment, mothers continue to be symptomatic, and child behavior at 3 years of age continues to be at risk," the authors conclude.

In an editorial accompanying both papers, Gideon Koren, MD, and Irena Nulman, MD, of the Hospital for Sick Children, Toronto, write that "since the thalidomide era, there are concerns regarding potential adverse effects of drug and chemical exposure on the developing fetus in pregnancy, causing physicians and expectant mothers high levels of anxiety toward drugs, even in life-threatening conditions."

"Because pregnant women will never be randomized to exposure to antidepressants or recreational drugs, high-quality observational investigations, such as those by Oberlander and colleagues and Stone and colleagues, will be critical in distinguishing associations from causation in the field of maternal-fetal toxicology," they conclude.

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Standard Heel-Stick Test Ineffective at Screening for CMV in Newborns

A national study involving a UT Southwestern Medical Center neonatologist and pediatric infectious diseases specialist suggests that a screening test routinely performed in newborns is not very good at identifying

cytomegalovirus (CMV) infection, a leading cause of hearing loss in children.

The findings, published in the April 14th issue of the *Journal of the American Medical Association*, suggest that testing blood drawn from a newborn's heel has limited value in detecting CMV infection.

The heel-stick procedure involves pricking a newborn's heel and drawing a small amount of blood that is then absorbed onto a filter paper and dried. The dried blood is analyzed for several diseases including sickle cell disease. Because the procedure already is used to test for several metabolic and genetic disorders, researchers hoped it would be a good candidate for a universal screening program for CMV.

"Our findings tell us that if we rely on the standard heel-stick test to detect CMV, more than half of the babies who are infected will be missed," said Dr. Pablo Sanchez, Professor of Pediatrics at UT Southwestern and a co-author of the study. "The fact that this screening test is virtually ineffective has major public health implications because congenital CMV infection is the most common nongenetic cause of hearing loss in the United States."

Each year, 30,000 to 50,000 US infants are born with CMV, the most common infection passed from a mother to her unborn child. Although only about 10% of infected babies have any clinically detectable abnormalities, half of those with clinical signs and 10-15% of those who appear well are at risk for developing hearing loss.

The study is part of a multicenter investigation seeking to find the most effective screening test for CMV infections in newborns and study the natural history of hearing loss among these babies. Currently, the only way to identify accurately a CMV infection is to culture a urine or saliva sample collected from the patient, a process unlikely to be widely adopted because it is labor-intensive and requires a tissue culture facility.

Prior research has shown that dried blood spots can be used to identify CMV infection. Because no studies have compared it to the gold standard CMV rapid culture test, however, researchers have been unable to say whether the heel-stick method is effective at identifying all infected babies.

For the study, the researchers used a new molecular diagnostic technique, polymerase chain reaction (PCR), to analyze dried blood samples obtained using the heel-stick procedure from more than 20,000 infants born between March 2007 and May 2008 at seven medical institutions nationwide, including Parkland Memorial Hospital in Dallas. Parkland has one of the country's largest and busiest obstetrics services, with about 16,000 births a year. Attending physicians are faculty members of UT Southwestern's obstetrics and gynecology and pediatrics departments.

Of the more than 20,000 babies screened in this study, 92 were confirmed to have congenital CMV infection. The CMV rapid culture method identified all but one of those children.

In contrast, of the 11,422 children screened with a basic version of the diagnostic test of dried blood spots, only 17 out of 60 infected children were identified. Eleven out of 32 infected babies were identified in a group screened with a slightly more sensitive test.

The next step, Dr. Sanchez said, is to determine whether using the molecular technique to analyze saliva samples rather than blood spots is as effective as the CMV rapid culture test.

The project is part of the ongoing CMV and Hearing Multicenter Screening (CHIMES) Study. The other participating centers are the University of Alabama at Birmingham; Saint Peter's University Hospital in New Brunswick, NJ; the University of Mississippi Medical Center in Jackson; the Carolinas Medical Center in Charlotte, NC; the University of Pittsburgh and the Children's Hospital of Pittsburgh; and the University of Cincinnati and Cincinnati Children's Hospital Medical Center.

The study was funded by the National Institute on Deafness and Other Communication Disorders, part of the National Institutes of Health.

Visit www.utsouthwestern.org/pediatrics to learn more.

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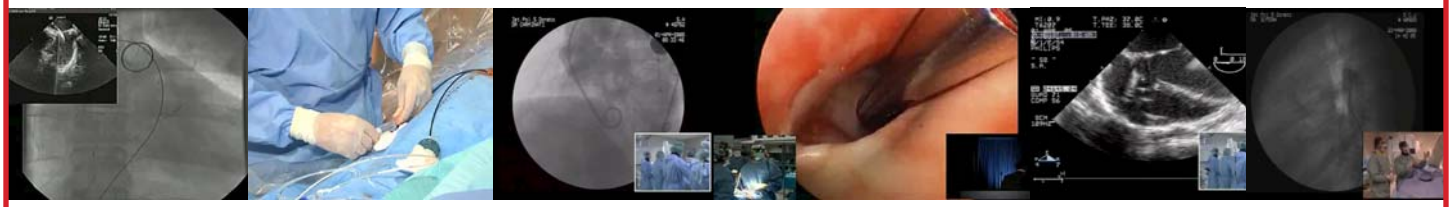

- Percutaneous Pulmonary Valve Implantation
- Pulmonary Artery Rehibilation
- Device Closure is Safe & Should be Continued
- Catheter Management in the Neonate
- Duct Dependent Lesions: Stent vs. Shunt
- Intervention in the Immediate Post-op Period
- The Edwards Valve
- Percutaneous Closure of the VSD
- Transcatheter Implant of a Melody Valve Watch - VSD Closure
- Covered Stent to Eliminate Fontan Baffle Leak & Stenosis
- Native Coarctation of Aorta - Stent Implantation
- Pulmonary Artery Flow Restrictors
- Transcatheter Valve
- Intra-operative PA Stent
- Perventricular Muscular VSD Device Closure
- Closure of Septal Defect Using Real Time 3D Echo Guidance
- Perventricular Membranous VSD
- Hybrid Stage I Palliation for HLHS PA Bands and PSA Stent
- Intraoperative Aortic Stent for CoA
- Intraoperative LPA Stent Using Endoscopic Guidance
- Creation of ASD after PA Bands & PDA Stent for HLHS in a Preemie
- Perventricular Implant of Edwards Valve Stent in the Pulmonary Position
- Closure of Septal Defect Using Real Time 3D Echo Guidance
- High Frequency Ultrasound Creation of ASD
- PmVSD Closure
- Hybrid Stage I Palliation for Complex Single Ventricle in a 1.4 kg Neonate
- Transcatheter Implantation of Implantable Melody Valve
- Perimembranous VSD Closure with Amplatzer Membranous VSD Occluder
- Stent RPA, Pre-Stent Conduit & Melody Valve Implant
- Transeptal LHC Assessment of Residual Coarctation
- Coarctation Stenting Using a Covered CP Stent
- Closure of ASD Under ICE Guidance
- PFO Closure
- Transcatheter Closure of Atrial Septal Defect (ASD)
- Closure of ASD under TEE Guidance
- Transcatheter Closure of Moderate PDA
- Pulmonary Angioplasty
- Hybrid Stage Palliation
- ADOI or MVSD Closure of PDA
- VSD Closure Using a PDA Device
- Balloon Pulmonary Valvuloplasty
- Coil or Vascular Plug II closure of Coronary Fistula
- Device Closure of ASD
- Stent Placement Across Recurrent Coarctation
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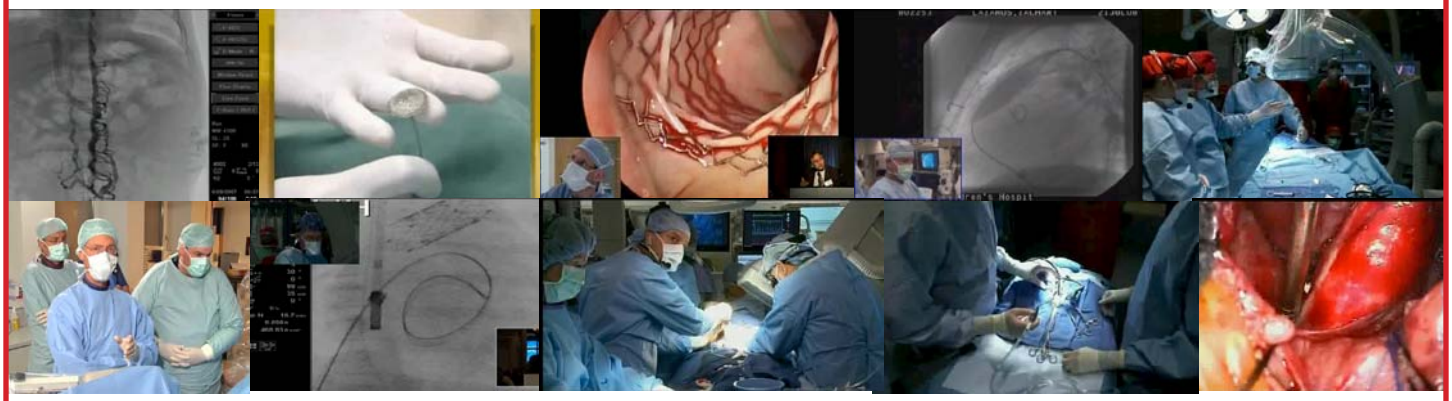

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