

neonatal INTENSIVE CARE

The Journal of Perinatology-Neonatology

Neonatal Intensive Care News

BIOMED CENTRAL NEWS

To further promote Open Data and data sharing, BMC Research Notes has launched a series of articles on data standardization, sharing and publication. BioMed Central is looking for contributions from all fields of biology and medicine. The timely launch of this collection coincides with a themed issue in Science exploring data sharing for biomedical and clinical research that highlights articles from Trials and BMC Bioinformatics. The Scientist magazine also recently emphasized the importance of data standards. Contact biomedcentral.com.

PLACENTA & BRAINS

Researchers at the University of Southampton have found evidence linking brain function variations between the left and right sides of the brain to size at birth and the weight of the placenta. Children who were born small, with large placentas, showed more activity on the right side of their brains than the left. It is this pattern of brain activity that has been linked with mood disorders such as depression. The study adds to a growing body of evidence showing that adverse environments experienced by fetuses during pregnancy (indicated by smaller birth size and larger placental size) can cause long-term changes in the function of the brain. The neurological responses of 140 children from Southampton, aged between eight and nine, were monitored for the study. Tests evaluated blood flow to the brain in response to increased brain activity, exposing differences in the activity of the two sides. Researchers measured tiny fluctuations in the temperature of the tympanic membrane in each ear, which indicate blood flow into different parts of the brain. Disproportionate

growth of the placenta and the fetus is thought to occur in pregnancies where the mother has been experiencing stress or where she hasn't received sufficient nutrients.

WEAK MILK

A study conducted at the University of Granada and at the University Hospital San Cecilio revealed that preemie mothers' milk contains low concentrations of coenzyme Q10, which is an antioxidant and a component of the electron transport train. The study examined the presence of Q10, as well as its concentration in colostrum, transitional, and mature milk. Researchers selected 30 nursing mothers, 15 who had completed their gestation and 15 moms of preemies. Milk samples were taken and moms completed questionnaires about their eating habits. The study revealed colostrum CoQ10 concentrations of about 0.4 $\mu\text{mol/l}$ in preterm mothers and 0.7 $\mu\text{mol/l}$ in term mothers. As such, CoQ10 concentrations in mothers at term are 75% higher than in preterm mothers.

SWIRL AND SPIT

Research funded by Pennsylvania and P&G showed that use of non-alcohol antibacterial mouth-rinse containing cetylpyridinium chloride (CPC) decreases the incidence of preterm birth. Researchers studied 204 pregnant women at 6-20 weeks gestation with periodontal disease. One hundred fifty-five served as untreated controls and 49 received antimicrobial Crest mouthrinse. Dental exams were performed at baseline and prior to delivery. There was no significant difference at baseline in smoking, prior preterm birth or alcohol consumption between groups. Maternal age was

higher in the rinse group than in the control group. No adverse events were observed. The incidence of PTB less than 35 weeks was significantly lower in the subjects using the rinse compared to the controls. Gestational age and birth weight (adjusted for maternal age) were significantly higher in the rinse group.

DEADLY TREATMENT

The FDA said terbutaline administered by injection or through an infusion pump shouldn't be used in pregnant women for prevention or prolonged treatment of preterm labor due to the potential for serious maternal heart problems and death, and that oral terbutaline tablets should not be used for prevention or treatment of preterm labor. Terbutaline is used to treat bronchospasm associated with asthma, bronchitis, and emphysema. The drug is used off-label for obstetric purposes, including treating preterm labor and uterine hyperstimulation. Terbutaline has also been used in an attempt to prevent recurrent preterm labor. There is no evidence, according to the FDA, that use of terbutaline to prevent preterm labor improves infant outcomes. The FDA noted its awareness that administration of terbutaline by injection to pregnant women occurs in hospital settings in certain urgent situations. The FDA warning relates to safety concerns about the prolonged use of terbutaline injection beyond 48-72 hours. Only generic versions of the drug are currently available.

BUDDY SYSTEM

Women who go into labor with a companion are less likely than women going it alone to have a safe uneventful birth experience, according to a study

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by The Cochrane Collaboration. Cochrane studied 15,061 women who participated in 21 randomized controlled trials. Women who received supportive care from a companion throughout labor were less likely than women without such support to have a cesarean section, to use narcotics or any other pain medication, to use epidural analgesia, to give birth with vacuum extraction or forceps, and to rate their childbirth experience poorly. Having continuous support also shortened labor, and also decreased the chance of a baby having a poor Apgar score. Women receiving support were 28% less likely to have a c-section, 31% less likely to use oxytocin to hurry labor, 9% less likely to use pain meds and 34% less likely to rate their childbirth as a negative experience.

HOW IT WORKS

The following note appeared in the latest issue of The Placebo Journal (placebojournal.com). The editor wrote: I have for some years written that society has broken its compact with physicians and in so doing has altered their actual role. The utter consumption of medicine by the third-party payer mentality, and the expectation of perfect care to be enforced by lawyer-threats made physicians largely a commodity; once patients were granted healthcare as a right by their elected officials, that finished the transformation. Through the onerous sanctioning of state, federal, and quasi-governmental institutions, the work of doctors has become largely the property of the state; hence, doctors have become government agents increasingly more akin to the drones at the DMV."

SPINA BIFIDA STUDY

A recent research study, "Management of Myelomeningocele Study," was recently presented at the annual Society for Maternal-Fetal Medicine annual meeting. Catherine Y. Spong, MD, chief, pregnancy and perinatology branch, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, discussed the government study that she co-authored, which also appeared in the New England Journal of Medicine.

The \$22.5 million study looked at the benefits of a surgical procedure used to repair this common defect of the spine while the baby is still in the uterus. The findings reported that the procedure greatly reduced the need to shunt fluid away from the brain. The surgical procedure consists of closing an opening at the back of the fetal spine, which is a departure from the traditional approach of operating on the infant after birth. The fetal procedure increases the chances that a child will be able to walk without crutches or other devices. The study cautioned that there were risks involved and that, because the surgery is highly specialized, it should only be undertaken in facilities with experienced staff. Infants who underwent the prenatal surgery were more likely to be born premature than were the infants who had the surgery performed after birth. Mothers who underwent the procedure were at risk of a thinning or tearing of the uterus at the incision. In spite of these risks though, children who underwent the prenatal surgery did much better than those who had the surgery after birth. The MOMS study, which planned to enroll 200 expectant mothers carrying a child with myelomeningocele, was stopped after the enrollment of 183 women because of the benefits of the surgery.

RADIATED

The New York Times reported on a case over-radiation of a preemie at New York Downstate Medical Center in Brooklyn. A simple chest X-ray had been ordered. Instead, the Times reported, technologists had given the baby 10 whole-body X-rays without so much as gonadal shielding. The hospital's pediatric radiologist found that full-body X-rays of preemies had occurred often, that radiation levels on CT scanners had been set too high for infants, and that babies had been poorly positioned, making it hard for doctors to interpret the images. The Times reported that the hospital performed the so-called "babygrams" though they'd been discredited. The hospital is being investigated by state health officials. The newspaper article went on to say that errors such as at Downstate raised questions about

the techs who operate radiological equipment. The American Society of Radiologic Technologists has lobbied Congress to pass a bill to establish minimum educational and certification requirements for technologists and related imaging and radiation therapy occupations, but nothing happened. Though New York State technologists are licensed through examination, there are no continuing education requirements. Information is from a report in the New York Times by Walt Bogdanich and Kristina Rebebo.

OUNCE OF PREVENTION

Intermountain Healthcare researchers found that women at high risk for preterm birth who participated in a preterm birth prevention clinic delivered more full term babies and had fewer cases of infant morbidity. Researchers conducted a retrospective review of women with a single, non-anomalous fetus and ≥ 1 documented previous spontaneous PTB < 35 wks. Women enrolled in a PTB Prevention Clinic were compared with women identified from a contemporary

large perinatal database. Prevention Clinic patients were offered 17 alpha-hydroxyprogesterone caproate (17OHPHC) and were followed with serial cervical-lengths (CL); recommendations for liberal antenatal corticosteroid and tocolytic use were also made. Regular patients were managed by their primary obstetrician. Two hundred and thirty-two patients (70 PTB Prevention Clinic and 162 regular patients) met inclusion criteria. Groups had similar previous pregnancy characteristics. PTB Prevention Clinic patients had increased utilization of resources (including more cervical length ultrasounds and higher rates of use of prophylactic 17OHPHC) and delivered at later gestational ages. Rates of NICU admission were similar between groups (44.3% vs 40.7%, $p=0.62$). However, rates of major neonatal morbidity (diagnosis of NEC, BPD, IVH, sepsis, or death) were lower among PTB Prevention Clinic neonates (5.3% vs 15.4%, $p=0.025$). The study showed that among this high-risk population, referral to a consultative PTB Prevention Clinic (with

standardized counseling, management recommendations, and close surveillance) resulted in a reduction in the rate of recurrent PTB prior to 37 weeks, led to an average of a one week longer pregnancy, and reduced the rates of major neonatal morbidity.

OFF-LABEL SUCCESS

The Wall Street Journal reported on an inexpensive drug therapy that surpassed conventional laser procedures for fixing ROP in premies, according to a study at the University of Texas. The New England Journal of Medicine said the 15 hospitals in the study have switched to using Avastin, injected into the eyes of newborns, instead of lasers. The drug has been used for treating cancer. An injection of Avastin stopped the blood-vessel growth inherent to ROP. The dosage to treat an infant is about \$40. Genentech, which makes Avastin, said it doesn't promote off-label use. In the study, 150 premies were randomized to receive Avastin or laser treatment. Retinopathy recurred in four infants treated with Avastin compared with

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1. Shankaran, Seetha, et al. "Outcomes of Safety & Effectiveness of a Multicenter Randomized, Controlled Trial of Whole-Body Hypothermia for Neonatal Hypoxic-Ischemic Encephalopathy." *Pediatrics* 122 (2008): 790-799.

2. Zanelli, S.A., et al. "Implementation of a 'Hypothermia for HIE' program: 2-year experience in a single NICU." *Journal of Perinatology* 28 (2008): 171-175.

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19 infants treated with the laser, a 20% reduction in the risk of recurrence. Among infants with zone 1 ROP, the recurrence rate was 6% with Avastin compared with 42% for laser therapy. Reported in the Wall Street Journal, from the article "Drug Shows Promise For Newborn Blindness," by Jennifer Corbett Dooren, Copyright 2011 Dow Jones & Company, Inc.

BABY BLANKET

Neonatologists at Cedars-Sinai in Los Angeles have started using a new neonatal cooling blanket system to minimize brain damage in babies with hypoxic-ischemic encephalopathy. The blanket lowers the baby's body temperature to 92.3 degrees and keeps it there for 72 hours. The cooling procedure is based on research into why people who nearly drown in freezing water suffer less brain damage than other oxygen-deprived victims. The cooling slows down brain metabolism and reduces the secondary phase of damage, and the blanket gradually warms the baby's body temperature back to normal. The therapy is implemented by a specially-trained team of RNs using neuromonitoring with continuous 24-hour EEG.

HAND IT 2 THEM

Researchers funded by the National Institutes of Health have identified a key step in the establishment of a pregnancy. Their discovery shows how the hormone progesterone suppresses the growth of the uterus's lining so that a fertilized egg can implant in the uterus. This key step, the researchers discovered, occurs when a protein called Hand2 suppresses the chemical activity that stimulates growth of the uterine lining, also known as the uterine epithelium. At the start of each menstrual cycle, levels of the hormone estrogen begin to rise. Estrogen stimulates the cells in the uterine lining to increase in

number, causing the epithelium to thicken. However, as the ovary releases an egg, levels of the hormone progesterone begin to rise. The elevated progesterone levels put the brakes on the estrogen-driven growth of the uterine epithelium. In this study, the researchers discovered that Hand2, previously found to increase in uterine cells as progesterone levels rise, is the switch that turns off estrogen's stimulating effect on the epithelium. The researchers found that exposure to progesterone halted growth of the uterine epithelium in mice with functioning genes for Hand2. However, despite exposure to progesterone, epithelial growth continued unchecked in the mice without Hand2 genes. The researchers also determined that estrogen stimulates the production of growth factors, which cause cells in the epithelial layer to multiply and grow. When progesterone is produced, it spurs the release of Hand2, which stops the production of growth factors. The uterine epithelial cells then stop multiplying, mature, and become receptive to the embryo.

STILL AT RISK

Despite fetal pulmonary maturity, babies delivered at between 36 to 38 weeks still have a significantly increased risk of neonatal morbidities. To compare neonatal outcomes, researchers looked at mothers who had positive fetal lung maturity tests at between 36 to 38 completed weeks and compared the neonatal outcomes from these scheduled deliveries prior to 39 weeks with known fetal lung maturity to the outcomes from scheduled deliveries at 39 weeks to 41 completed weeks. Neonatal outcomes of women who were delivered following documented fetal pulmonary maturity at 36, 37, and 38 weeks were compared to women undergoing a scheduled delivery at 39, 40, and 41 weeks. A lamellar body count of $\geq 36,000$, lecithin/sphingomyelin (L/S) ratio >2.0 , or a

PG of 0.3 were considered mature. Neonatal outcomes examined included: NICU admission, length of stay in the NICU, total neonatal respiratory morbidity, cases of RDS, TTN, other respiratory morbidity, neonates requiring mechanical ventilation, proven sepsis, hypoglycemia, and neonatal deaths. Fetuses with major congenital anomalies were excluded. The study concluded that despite fetal pulmonary maturity, deliveries between 36 0/7 to 38 6/7 weeks are associated with significantly increased neonatal morbidity.

AT ODDS

Many women are having different test results for Group B streptococcus GBS between their routine third trimester screening and a rapid test performed at the time of labor, according to researchers at Mass General. Women are routinely tested in their third trimester. Now, a new rapid test that returns results in approximately one hour can be administered at the time of labor. Researchers noted that two-thirds of infants with GBS sepsis are born to mothers with negative third-trimester cultures, so they wanted to see how many women with a negative GBS test in the third trimester have a positive GBS result right before delivery. The study enrolled women who presented to labor and delivery with an antepartum GBS culture. GBS cultures and rapid tests were performed during labor and compared to the third trimester GBS culture results. Among 559 women, GBS prevalence was 19.5% with the third-trimester culture and 23.8% with culture performed on samples collected during labor. Compared with the culture obtained during labor, the third-trimester culture correctly predicted GBS positivity at the time of labor only 69% of the time versus the rapid test which correctly predicted GBS positivity 91% of the time. The incidence of GBS discordance from the



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late third trimester to labor was 10%. African-American and Hispanic women were significantly more likely to have discordant culture results.

PROTEIN SHAKE

Three proteins, XIAP, BID, and Bcl-2 are responsible in part for the success of progesterone treatments in the prevention of preterm labor and may also play an important role in triggering normal labor, according to researchers at Tufts. The proteins prevent preterm birth by hindering apoptosis. The study is titled "Progesterone Inhibits Basal Apoptosis In Fetal Membranes By Altering Expression Of Both Pro- And Anti-Apoptotic Proteins," and was presented at the Society for Maternal-Fetal Medicine's Annual Meeting, "The Pregnancy Meeting."

A NEW SPIN

The UC San Diego Health System has developed the Supporting Premature Infant Nutrition (SPIN) program to help mothers produce sufficient breast milk for their premature infants. The program is now available on line. With a new website and online educational videos, SPIN is ready to broaden its awareness to mothers, fathers and families beyond the UC San Diego Health System. The site has a variety of patient resources, such as pumping log sheets, milk recipes, lactation research and publications. The online tools allow mothers to learn about the program and follow the steps at their own convenience. Since not all hospitals will let mothers and their premature babies have skin-to-skin contact, the videos can also serve as a teaching model for other health institutions and patients. SPIN's goal is to improve the manner in which neonatal intensive care units across the nation support optimal nutrition and growth to premature infants. Contact spinprogram.ucsd.edu.

HORMONES FOR TWINS

Researcher C. Andrew Combs and colleagues conducted a placebo-controlled, double-blind, multicenter, randomized clinical trial where mothers with diamniotic dichorionic twins were randomized to 17-alpha-hydroxyprogesterone caproate (17P) (250 mg IM) or placebo (castor oil

vehicle, 1 mL), starting at 16-23 weeks gestational age (GA), repeated weekly until 34 weeks GA. A sample size of 240 mothers (480 babies) was calculated to give 80% power to detect reduction of composite neonatal morbidity from 45% with placebo to 30% with 17P. One hundred and sixty mothers were randomized to 17P, 80 to placebo at mean GA of 20 weeks. The results showed that baseline characteristics were similar between the groups. There was no significant difference in composite neonatal morbidity (14% with 17P vs 12% with placebo), or in mean GA at delivery (35.3 wks vs 35.9 wks), delivery < 28 wks (2% vs 1%), < 32 wks (9% vs 5%), < 35 wks (33% vs 26%). There were no perinatal deaths in the 17P group and three neonatal deaths in the placebo group, two after withdrawal of life support because of fetal anomalies not discovered prenatally and one attributed to neonatal sepsis. The study concluded that the use of 17P in twin pregnancies did not reduce the rate of preterm delivery or neonatal morbidity.

TOO MUCH CALCIUM

Researchers at Yale School of Medicine found that excessive formation of calcium crystal deposits in the amniotic fluid may be a reason why some pregnant women suffer PPRM. The researchers investigated the idea that calcification of the fetal membranes may lead to PPRM and preterm birth. They noticed that in many women, analysis of the proteins in amniotic fluid did not show signs of inflammation. The researchers could not find any cause for their preterm birth, and wondered if calcifying nanoparticles involved in other degenerative conditions could be responsible for damage to the fetal membranes in pregnant women. The researchers used a stain to look for calcium deposits in placental and fetal membrane tissue from patients with PPRM and preterm birth, as well as full-term deliveries and used a sterile culture technique to determine whether amniotic fluid can form nanoparticles. They then exposed fetal membranes to the cultured nanoparticles to determine their ability to induce cell dysfunction, damage and cell death. The researchers found evidence of calcification of fetal

membranes collected from preterm deliveries. Fetuin, one of the major proteins involved in nanoparticle formation, was found in these deposits. Levels of fetuin in amniotic fluid were lower in women who delivered with PPRM compared to those who delivered early with intact membranes.

X-RAY RISKS?

A US-UK study said clinicians should be careful about using x-rays on pregnant women and infants because of the potential for a slight increase in the risk of children developing cancer. The researchers found small increases in risk of cancer for children who had x-rays at ages less than three months and in children whose mothers had undergone an x-ray while pregnant. These increases were not statistically significant. The researchers reported no increased risk from ultrasound scans. Previous studies of children born between the 1940s and the 1970s, when radiation doses were likely to be higher, found in utero x-ray exposure to be associated with an increased risk of childhood cancer, particularly leukemia. The effect of medical radiation on young children has been less clear. Researchers compiled data on 2,690 children with cancer and 4,858 healthy children from the UK Childhood Cancer Study (UKCCS). All children were born between 1976 and 1996. A total of 305 children received 319 radiographic and related examinations while in utero and 170 children received 247 diagnostic x-ray examinations in early infancy. A total of 13,723 in utero and 138 early infant ultrasound scans were carried out. Researchers measured the risk of childhood cancer overall, and leukemia, lymphoma, and central nervous system tumors. The slightly heightened risk was found to be statistically insignificant, based on only seven cases.

APPROVAL

The FDA granted approval for Makena (hydroxyprogesterone caproate injection). Makena, commonly referred to as "17P," is the first and only FDA-approved treatment indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous

preterm birth. The effectiveness of Makena is based on improvement in the proportion of women who delivered < 37 weeks of gestation. There are no controlled trials demonstrating a direct clinical benefit, such as improvement in neonatal mortality and morbidity. The approval of Makena was based on a study of 463 women who had experienced a previous singleton spontaneous preterm birth. The study, sponsored by the National Institutes of Health, showed that compared to controls, treatment with Makena reduced the proportion of women who delivered preterm at less than 37 weeks. After adjusting for time in the study, 7.5% of Makena-treated subjects delivered prior to 25 weeks compared to 4.7 percent of control subjects. Makena is administered via a weekly intramuscular injection beginning between 16 and 20 weeks of pregnancy and continuing until 37 completed weeks or until delivery, whichever comes first. While there are many risk factors for preterm birth, safety and efficacy of Makena has been demonstrated only in women with a prior spontaneous singleton preterm birth. It is not intended for use in women with multiple gestations or other risk factors for preterm birth. Makena is made by the KV Pharmaceutical Company. Information above was provided by the company.

Regarding the foregoing, Think Progress reported that the cost of the preemie preventing drug Makena is being raised from \$10 per dose to \$1,500 per dose. K-V Pharmaceutical of St Louis recently won FDA approval to exclusively sell Makena last month. A spokesperson for KV said the price was worth it. But, the Think Progress noted, the issue is that the price hike may deter low-income women from getting the drug. According to Massachusetts Medical deputy medical director Dr Roger Snow, "That's a huge increase for something that can't be costing them that much to make... For crying out loud, this is about making money." In addition, KV sent a letter to compounding pharmacies to cease and desist from producing the drug. KV claims that because the FDA designation now makes Makena "commercially available, continuinig

to compound this product after FDA-approval of Makena renders the compounded product subject to FDA enforcement of violating certain provisions of the Federal Food, Drug and Cosmetic Act, as well as FDA guidance." Thus, its privileged status now threatens companies trying to provide a cheaper version. Senator Sherrod Brown of Ohio sent a letter to KV demanding they "immediately reconsider the massive price increase."

TRANSFUSIONS

In 2010, researchers conducted a prospective use study and systematic review of published literature related to blood sample collection in ICU, NICU and PICU settings. The study was designed to assess the impact of lower-volume blood draw and the use of different size collection tubes in these settings. In the findings researchers for the first time have identified a correlation between volume of blood drawn from patients in an ICU and the incidence of transfusions. According to the findings, Each ml of blood drawn from patients in the ICU increases the risk of transfusion in that patient by .2%. This is the first research study to identify a direct correlation between reduced hemoglobin levels and transfusion risk. The rate increases to .3% in PICU and NICU settings. The average ICU patient has an 8% risk of needing a transfusion because of blood draws alone. Nearly 5 million people in the US receive blood transfusions each year. According to a study in the April 2010 edition of Transfusion, annual expenditures on blood and transfusion-related activities for surgical patients range from \$1.62 to \$6.03 million per hospital. According to the analysis, efforts to reduce the amount of blood drawn in a blood sample can reduce the risk of "inappropriate transfusions." In one finding, if hospitals used microtainer tubes for automated process, they could eliminate 75-93% of "inappropriate transfusions" in the ICU settings. The cost savings that the analysis showed was associated with the use of certain technologies for low volume blood sample collection.