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neonatal INTENSIVE CARE

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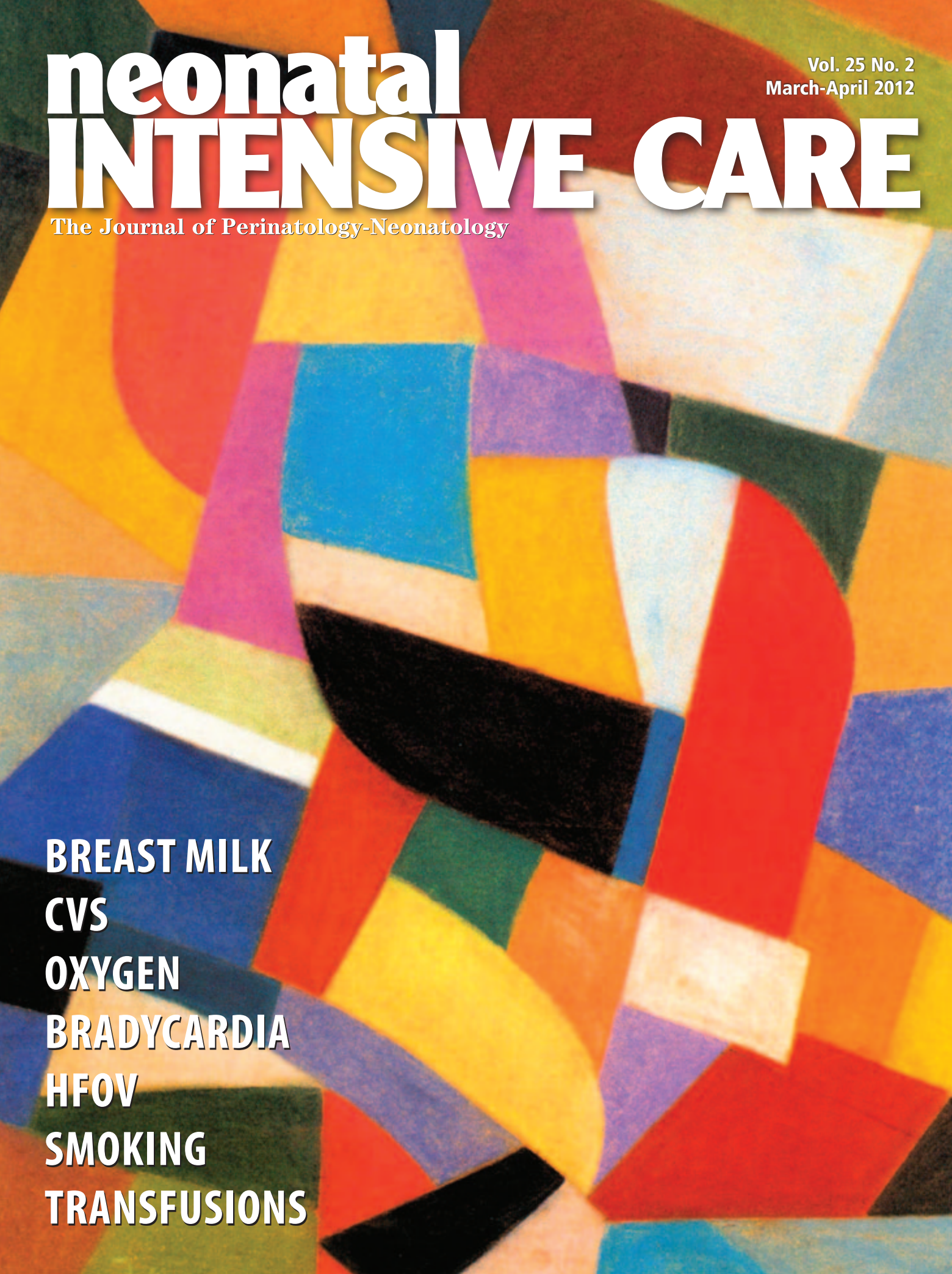

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Table of Contents

Editorial

Complex Decisions

In our previous issue we wrote about a New Yorker article that discussed "forcing" parents to make decisions about their infant in the NICU: "A case can be made for following a neonatologist's recommendations instead of forcing the parents to make the decision whether to provide care. 'A study of French and American NICUs supports the idea that the doctor's recommendation whether to continue intensive care can relieve parents of guilt.... French parents did not express the same level of grief and distress shown by their American counterparts.' The explanation appeared to be that French parents whose children died had not personally made the choice not to pursue treatment." In the US there is a somewhat more tacit assumption that parents should make these decisions, as per this comment by Deborah Davies, PhD on the site preemie-l.org: "When there are options and the best option isn't clear, *parents* should be the primary decision-makers. If medical staff had all the answers or could accurately predict the future, then I'd say let them decide. But they don't and they can't. Parents don't and can't either, but when informed and given time to ponder the realities, they are in the best position to decide which path they and their baby should go down. After all, it is *their* journey. Whether to rely on the guidance of medical opinions, their religion or community standards should be up to them. Whether to be swayed by the grimmest statistics or to grasp for the dimmest rays of hope, should be up to them."

The French approach, however, isn't necessarily presumptuous on its face, but is meant to spare parents of the burden of decision. An article in MCN, The American Journal of Maternal/Child Nursing, notes, "In treatment choices involving ethical decision making, some providers did not give full and accurate information to parents, believing that not all parents were able to understand or cope with the medical complexities of the decisions. When parents were asked about treatment decisions, or to enroll their infants in research protocols, most parents felt they were not given adequate information to make decisions. Other parents, however, reported that they wanted information but did not feel competent to make decisions related to research participation. Both parents and providers agreed that there was rarely enough time to make ethical decisions in the NICU." [Towards Evidence-Based Practice: Parents and Professionals in the NICU, Judy Beal DNSC, PNP, RN; Maureen Heaman, PhD, RN, March/April 2006.]

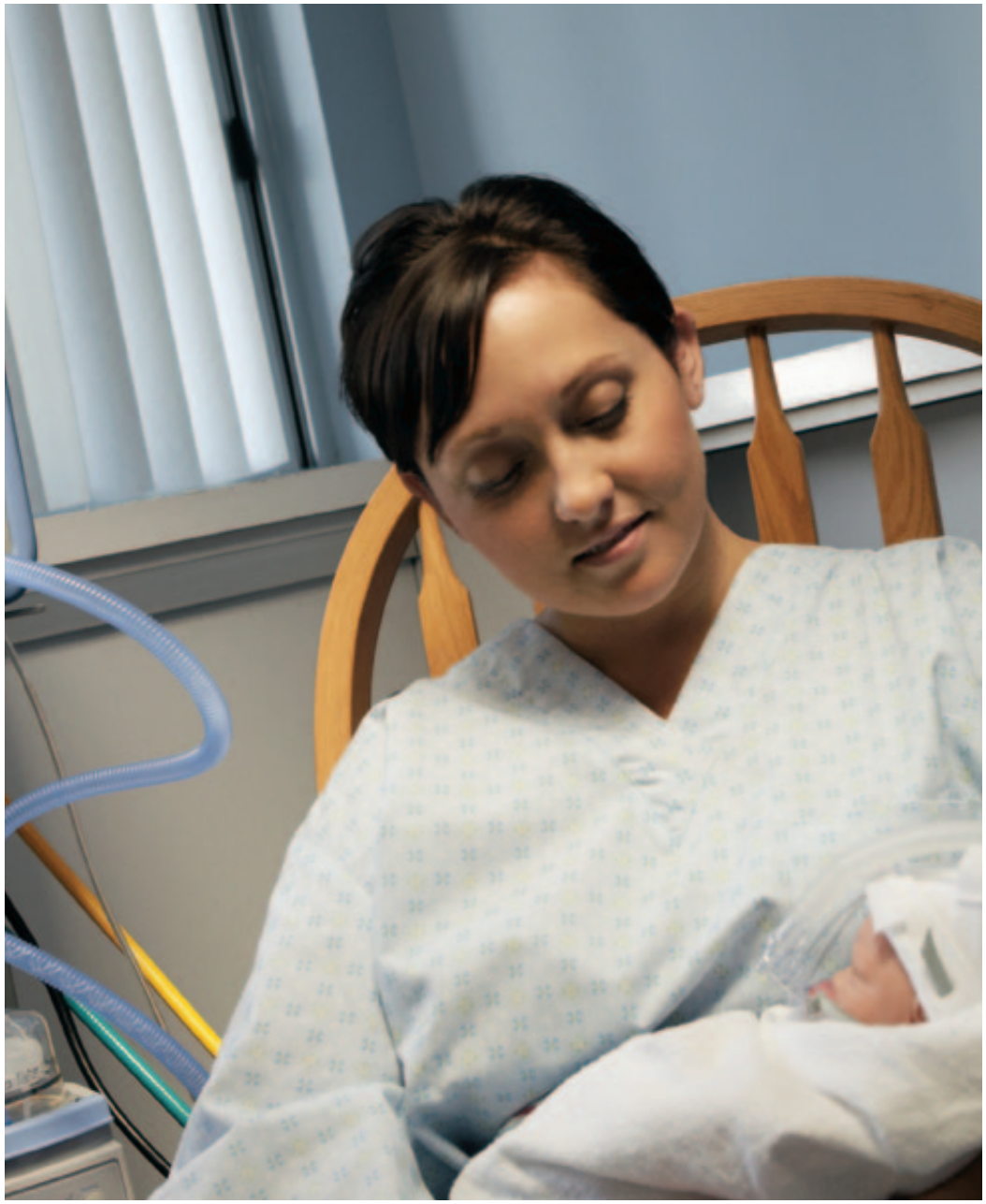
Now the open-source website PLoS One has published the article "Living with a Crucial Decision: A Qualitative Study of Parental Narratives Three Years after the Loss of Their Newborn in the NICU," which discusses NICUs in France and the nature of decision making. Here is an abridged version of the paper:

The importance of involving parents in the end-of-life decision-making-process (EOL DMP) for their child in the neonatal intensive care unit (NICU) is recognized by ethical guidelines in numerous countries. However, studies exploring parents' opinions on the type of involvement report conflicting results. This study sought to explore parents' experience of the EOL DMP for their child in the NICU.

The study analyzed parental experience 3 years after the death of their child in four NICUs in France. 53 face-to-face interviews and 80 telephone interviews were conducted with 164 individuals. Semi-structured interviews were conducted to explore how parents perceived their role in the decision process, what they valued about physicians' attitudes in this situation and whether their long-term emotional well being varied according to their perceived role in the EOL DMP.

Qualitative analysis identified four types of perceived role in the DMP: shared, medical, informed parental decision, and no decision. Shared DM was the most appreciated by parents. Medical DM was experienced as positive only when it was associated with communication. Informed parental DM was associated with feelings of anxiousness and abandonment. The physicians' attitudes that were perceived as

Continued on page 56…



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Publisher
Steve Goldstein

Editor
Les Plesko

Senior Editor
Laszlo Sandor

Associate Editor
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Design, Typography, Prepress and Production Management
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Los Angeles, CA

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News

☐ March-April 2012

OPEN ACCESS

Open access to the latest research became even easier with the launch of BioMed Central's newly redesigned website (www.biomedcentral.com). The company, which pioneered the open access model and now publishes over 220 open access journals, has introduced a streamlined design and new look which makes the high-traffic website site much more straightforward to navigate. The redesigned site also introduces a range of new and enhanced features. Emphasizing the company's commitment to meeting the evolving needs of authors and readers, the new site includes: a greatly improved "My BioMed Central" section offering users convenient access to the latest research in their subject areas together with status updates on manuscripts which they are submitting or reviewing; enhanced navigation for archives, supplements and special article collections; additional RSS feeds and embedded social linking technologies and improved subject gateways, providing a central starting point to find research on particular scientific topics. In addition to the new appearance, the site is built using modern open-source java technologies, which provide a firm foundation for the enhancements and new services still in development.

CAN THEY DO THIS?

The Daily Mail newspaper reported that Beyonce and Jay-Z spent $1.3 million on enhancing New York's Lenox Hill Hospital with a $1.3 million bulletproof security wing, and kept a father and other patients from visiting their babies in the NICU. The singer gave birth to her daughter at the hospital by c-section. According to Alanah Erikson of the Daily Mail, the father complained that he was stopped from visiting his preemie twins. The father was quoted as saying, "I know they spent $1.3 million and I'm just a contractor from Bed-Stuy, but the treatment we received was not okay… This is the NICU. Nobody cares if you're a celebrity. Nobody is star-gazing." The website TMZ reported that moms attending a breastfeeding class were dissed by hospital staff because of the celebrity ruckus and were threatening to sue. According to the Huffington Post, Lenox Hill Hospital countered that nothing of the sort took place, no one complained and that the couple paid standard rates for its executive suite.

BETTER VENTILATION

The journal Pediatrics (Vol 128, No 1) recently published the paper: Impact of Implementing 5 Potentially Better Respiratory Practices on Neonatal Outcomes and Costs. According to the abstract, the objective was to implement 5 potentially better practices to limit mechanical ventilation (MV), supplemental oxygen, and bronchopulmonary dysplasia in newborn infants born before 33 weeks' gestation. The methods used in this study included (1) exclusive use of bubble continuous positive airway pressure (bCPAP), (2) provision of bCPAP in the delivery room, (3) strict intubation criteria, (4) strict extubation criteria, and (5) prolonged CPAP to avoid supplemental oxygen. The authors excluded outborn infants and those with major anomalies and obstetric complications from analysis. Results: Demographics were similar in 61 infants born before and 60 born after implementation. For infants born at 26 to 32 6/7 weeks' gestation, intubation (first 72 hours) decreased from 52% to 11% ($P < .0001$) and surfactant use decreased from 48% to 14% ($P = .0001$). In all infants, the mean ± SD fraction of inspired oxygen requirement (first 24 hours) decreased from 0.27 ± 0.08 to 0.24 ± 0.05 ($P = .0005$), days of oxygen decreased from 23.5 ± 44.5 to 9.3 ± 22.0 ($P = .04$), and days of MV decreased from 8.8 ± 27.8 to 2.2 ± 6.2 ($P = .005$). Hypotension decreased from 33% to 15% ($P = .03$). The percentage of infants with bronchopulmonary dysplasia was 17% before and 8% after ($P = .27$). Nurse staffing ratios remained unchanged. The authors concluded: Implementation of these

potentially better practices reduced the need for MV, surfactant, and supplemental oxygen as well as reduced hypotension among infants born before 33 weeks' gestation without adverse consequences. The costs for equipment and surfactant were lower. [Pediatrics Vol. 128 No. 1 July 1, 2011, Impact of Implementing 5 Potentially Better Respiratory Practices on Neonatal Outcomes and Costs, Bernadette M. Levesque, MD; Leslie A. Kalish, ScD; Justine LaPierre, RRT-NPS; Maureen Welch, NNP; Virginia Porter, RN.] The abstract was provided to us by Respiralogics, which makes the Babi.Plus, Danny Ties, and Venti.Plus products.

SMILE!

A webcam system called NICVIEW streams continuous live video of babies in the NICU to parents when they can't be in the hospital. CNN reported that the unit costs about a thousand dollars, plus an annual service fee. At St. Jude Hospital, for instance, one camera is designated per baby and is turned off only during medical treatments, rounds or at a doctor or nurse's discretion. Parents can share the password with relatives or friends. The only possible downside is that parents may witness an emergency situation before the camera can be turned off. The developers of the system got their idea after visiting Deaconess Hospital, which was using cameras at the bedside, and came up with a way to adapt the camera to be compatible with any web-enabled device and not interfere with the hospital's network. Reported by CNN.

QUAKING

Stress in the second and third months of pregnancy can shorten pregnancies, increase the risk of pre-term births and may affect the ratio of boys to girls being born, leading to a decline in male babies, according to researchers at NYU, who investigated the effects of stress due to a major earthquake in Chile. The researchers analyzed birth certificates of all babies born in a thee-year period, which allowed them to find out how close they were to the earthquake's epicenter. The researchers found that women who experienced a severe quake during their second and third months of pregnancy had shorter pregnancies and were at higher risk of delivering preterm. The pregnancies of women exposed to the earthquake in the second month of pregnancy were on average 0.17 weeks shorter than those in the unaffected areas. The pregnancies of those exposed in the third month were 0.27 weeks shorter. Among women exposed to the earthquake in the third month of pregnancy, more than nine women in 100 delivered their babies early, as opposed to the usual ration of 6 in 100. For female births, the probability of preterm birth increased by 3.8% if exposure to the quake occurred in the third month, and 3.9% if it occurred in the second month. In contrast there was no statistically significant effect seen in male births. There was a decline in the sex ratio among those exposed to the earthquake in the third month of gestation of 5.8%. Previous research has suggested that in times of stress women are more likely to miscarry male fetuses because they grow larger than females and therefore require greater investment of resources by the mother; they may also be less robust than females and may not adapt their development to a stressful environment in the womb.

SALARY STUDIES

Typical pay scales for NICU nurses can be found across the internet, with quite comprehensive info about types of NICU nursing salaries, annual pay, hourly pay, pay rates in various cities, starting pay and years of experience and so on. Some sites we visited include payscale.com, neonatalicu.com, and nursesalaryguide.com. Payscale.com reported a range of $50,812 to $80,225 for NICU RNs, NPs, RTs, and ARNPs, based on 860 respondents to its survey. An NICU nurse can expect to show an increase of $20,000 over a 20-year career, starting at just under $49,000. Neonatalicu.com broke down a salary of $51,00 to $80,000 to $23 to $35 per hour. Nursesalaryguide.com says a neonatal nurse who is a registered nurse makes $50,657; a neonatal nurse practitioner makes $79,735, an RT gets $55,000, a family nurse practitioner makes $75,596. A neonatal nurse working in a hospital makes $59,151; for a medical service, $58,421. As far as which employers pay the best, a sampling shows North Shore LIJ Health System leads with $90,550, and in descending order, Pediatric Medical Group, Clarian Health Partners, Arkansas Childrens Hospital, Tallahassee Memorial Hospital, Coventry Health Care, and the University of Chicago. All figures above are from the respective websites, which are the copyrights of the sites.

FIRST THIS, THEN TWITTER

Researchers at UC San Diego Health System's Department of Reproductive Medicine and the National Latino Research Center (NLRC) at Cal State San Marcos University recently presented data at the American Public Health Association Conference in Washington DC demonstrating the impact of text4baby, a free mobile service that provides pregnant women and new mothers in San Diego with maternal, fetal and newborn health information via text messages and connects them to national health resources. The study, funded by the Alliance Healthcare Foundation, took place with text4baby users in San Diego County and included interviews with 38 women and a phone survey with 122 users. The top study findings are: Women reported high satisfaction with text4baby, with Spanish-speaking women reporting even higher satisfaction scores than English-speaking women. 63.1% reported that text4baby helped them remember an appointment or immunization that they or their child needed. 75.4% reported that text4baby messages informed them of medical warning signs they did not know. 71.3% percent reported talking to their doctor about a topic that they read on a text4baby message. More than 2,200 individuals have enrolled and used text4baby in San Diego. Expectant new parents can enroll in the service by simply texting "baby," or "bebe" for Spanish language messages, to 511411.

THEN AND NOW

A comparison of home-birth trends of the 1970s finds many similarities, and some differences, related to current trends in home births. In the 1970s as well as today, women opting for home births tended to have higher levels of education. Research at the University of Cincinnati also showed that in a survey of 2,000 moms, 36% of the births were attended by a physician in 1978, much higher than now – about 5%. Data from the study released so far counters the stereotypical view of the 1970s home-birth movement as countercultural and peopled by hippies, and notes that the movement included professionals, business people, farmers, laborers and artists.

SHACKLED

An Arizona woman who was shackled to her hospital bed during her C-section and force-walked from the hospital with her hands and feet in cuffs while still bleeding is suing Arizona Sheriff Joe Arpaio, Maricopa County and the hospital. She had been arrested and jailed for using a fake ID to gain employment. Her attorney said a woman guard refused to shackle her during the actual operation, but male police officers did so before and after the

birth. The attorney also noted that the practice is not unique to Arizona, and that one reason for the suit was to bring it to public awareness. The Deputy Police Chief of the county defended the practice of shackling inmates during labor by saying that a woman could be "faking labor" and attempt to escape.

BETTER IMAGING

Fetal brain development can be measured in the womb with fMRT, according to researchers at MedUni in Vienna. As such, pathological changes to brain development will be detectable earlier. Researchers used functional medical resonance tomography on 16 fetuses between the 20th and 36th weeks of pregnancy. Measurements were taken of the brain's resting state networks. The researchers said they demonstrated, for the first time ever, that the resting state networks are formed in utero and that these can be imaged and measured using functional imaging. This means that the developmental progress of brain activity in the fetus can be measured and other findings and prognoses made regarding possible malfunctioning processes. As a result, functional defects, such as of the optic nerves or motor system, can be detected while the fetus is still in the womb.

DON'T DO IT

Screening of pregnant women and new mothers for major depression and conflicts with their partners may help identify women at risk for suicide, according to a University of Michigan Health System study. The study analyzed five years of suicide data from the National Violent Death Reporting System, which links multiple sources of information to provide details that include demographics, pregnancy status, mental health and substance abuse status, and precipitating circumstances. More than half of the women who killed themselves had a known mental health diagnosis, with mood disorder being the most common at 95%. Nearly half were known to have a depressed mood leading up to the suicide. Depressive disorders affect 14-23% of pregnant and postpartum women and anxiety disorders affect 10-12%. Research data revealed that pregnant and postpartum women who killed themselves had a much higher incidence of conflicts with intimate partners than their counterparts. Postpartum women were also more likely to have been identified as having a depressed mood in the two weeks prior to suicide. Fifty-six percent of all victims had a known mental health diagnosis; 32% had previously attempted suicide; and 28% had a known alcohol or substance abuse issue. While education level and marital status were similar across pregnant, postpartum and non-pregnant suicides, Hispanic women were far more likely to take their own lives while pregnant or within a year of pregnancy than when not pregnant.

ON TARGET

Targeting a synthetic molecule to a specific gene could help alleviate the severity of Spinal Muscular Atrophy (SMA), the leading genetic cause of infantile death, according to researchers at the University of Missouri. When the researchers introduced synthetic RNA into mice that carry the genes responsible for SMA, the disease's severity was significantly lowered. The mice that received synthetic RNA gained more weight, lived longer, and had improvements in motor skills. SMA is a rare genetic disease that is inherited by one in 6,000 children, who often die young because there is no cure. Children who inherit SMA are missing a gene that produces a protein which directs nerves in the spine to give commands to muscles. The researchers targeted

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a partially functioning back-up copy of the missing gene, SMN-2, into producing the needed protein.

PRETTY GOOD

The nation's preterm birth rate slipped to just under 12% for the first time in nearly a decade, the fourth consecutive year it declined, according to the National Center for Health Statistics, potentially sparing tens of thousands of babies the serious health consequences of an early birth. Babies born between 34 and 36 weeks accounted for most of the decline in the national preterm birth rate. The decline in the 2010 preterm birth rate, to 11.99%, is a 6% drop from the high of 12.8% in 2006. Preterm birth rates declined significantly in 44 states and the District of Columbia when compared to 2006. Some states or territories did better than others, and the figures are no reason to crow, according to the March of Dimes, which issued its annual "report card" on preterm birth, giving three states and Puerto Rico an F, while 11 states and the District of Columbia earned a D, 19 states got a C, 16 states received a B and only Vermont earned an A. The United States received a C, based on comparing the nation's 2009 preliminary preterm birth rate of 12.2% with the March of Dimes new 2020 goal of 9.6% of all live births.

MOUSE MODEL

Scientists at Cincinnati Children's Hospital developed a novel mouse model mimicking human preterm labor and described a molecular signaling pathway underlying preterm birth, then targeted it to stop the problem. The researchers pointed to molecular signals from the protein complex mTORC1. These signals contributed to early aging in uterine cells, preterm labor and stillbirth in genetically modified mice. When researchers gave the mice a low dose of rapamycin, a known inhibitor of mTORC1 signaling, it stopped the early aging of uterine cells and premature birth. Rapamycin is an immunosuppressant drug widely used to prevent organ rejection in transplant surgery. Previous studies have shown that it can ease respiratory distress caused by enhanced mTORC1 signaling in the premature lungs of preterm mice. The drug also has been tested in humans for treating tumors. In the current research, mice were modified so they lacked the protein p53 in their uteri. The p53 protein, known as the "guardian of the genome," acts as master regulator in multicellular organisms by controlling cell cycles and helping prevent tumor growth. To make a long story short, the researchers found that inhibiting certain proteins prevented premature aging in uterine cells and prevented preterm births.

BETTER STAY SAD

Rats exposed to an antidepressant just before and after birth showed substantial brain abnormalities and behaviors, according to researchers at the University of Mississippi Medical Center. After receiving citalopram, a serotonin-selective reuptake inhibitor (SSRI) before and after birth, long-distance connections between the two hemispheres of the brain showed stunted growth and degeneration. The rats also became excessively fearful when faced with new situations and failed to play normally with peers, behaviors often seen in autism. The abnormalities were more pronounced in male than female rats, just as autism affects many more boys than girls. A recent study reported an association between mothers taking antidepressants and increased autism risk in their children. Children of mothers who took SSRIs during the year prior to giving birth ran twice the normal risk of developing autism, with treatment during the first trimester of pregnancy showing the strongest effect. Another study linked the duration of a pregnant mother's exposure to SSRIs to modest lags in coordination of movement in their newborns. While rats aren't moms or kids, earlier studies had hinted that serotonin plays an important role in shaping the still-forming brain in the days just after a rat is born, which corresponds to the end of the third trimester of fetal development in humans. Experimental manipulations of the chemical messenger during this period interfered with formation of sensory-processing regions of the cortex and triggered aggressive and anxiety-related behaviors in rodents. There is also recent evidence in humans that serotonin from the placenta helps shape development of the fetal brain early in pregnancy. Disrupted serotonin has been linked to mood and anxiety disorders. The researchers at U-Miss gave citalopram to male and female rat pups prenatally and postnatally and examined their brains and behavior as they grew up. Male, but not female, SSRI exposed rat pups froze when they heard an unfamiliar tone and balked at exploring their environment in the presence of unfamiliar objects or scents. These behaviors persisted into adulthood. A key brain serotonin circuit known to shape the developing brain during the critical period when the animals were exposed to the drug showed dramatic reductions in density of neuronal fibers. Evidence of stunted development in the circuit coursed through much of the cortex and hippocampus. Extensions of axons were deformed and myelin was reduced by one-third in the treated rats. The perinatally exposed animals showed evidence of neurons firing out of sync and other electrophysiological abnormalities, suggesting faulty organization of neuronal networks in the cortex.

MORE RODENT NEWS

Newborn mice exposed to Bisphenol A, used in plastics, develop changes in their spontaneous behavior and evince poorer adaptation to new environments, as well hyperactivity as young adults, according to researchers at Uppsala University in Sweden. The cholinergic signal system is also affected by Bisphenol A and the effect persisted into adulthood. Bisphenol A can leak out of plastic products such as baby bottles, tin cans, containers, and mugs. It has been found in human placentas, fetuses, and breast milk. In recent years measurable amounts of Bisphenol have been found in dust from regular homes. Uppsala researchers have shown in previous research studies that various toxic compounds can induce permanent damage to brain function when they are administered to newborn mice during the developmental period that mimics the most important developmental period for fetuses and infants. In this study, researchers examined whether exposure to Bisphenol A during the neonatal period can cause permanent damage to brain function. Different doses of Bisphenol A were given to mice when they were ten days old. The mice underwent a spontaneous behavior test as young adults, in which they were made to change cages from their well-known home cage to another identical one. Normal mice are very active during the first 20 minutes, exploring the new home. A single exposure to Bisphenol A during the short critical period of brain development in the neonatal period leads to changes in spontaneous behavior and poorer adaptation to new environments, as well as hyperactivity among young adult mice. When this is examined again later in their adult life, these functional disturbances persist, which indicates that the damage is permanent. Using the same behavioral method, it was also examined whether the individuals that had received Bisphenol A during their neonatal period reacted differently than normal individuals to nicotine as adults, which would indicate that one of the brain's most important signal systems, the cholinergic signal system, was

KNOWING YOUR REGION'S RSV ACTIVITY CAN HELP

DETERMINE OPTIMAL TIMING FOR DOSING IN HIGH-RISK INFANTS[1]

ENSURE SEASON-LONG PROTECTION FOR YOUR HIGH-RISK INFANTS

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

The start and end of RSV season can vary from year to year, state to state, and can even be different within communities in the same region[2,3]

- Throughout much of the United States, the RSV season begins in the fall and runs into the spring—although year-round RSV activity has been reported in Florida[2–5]
- The CDC defines the end of RSV season as the last 2 consecutive weeks during which the mean percentage of specimens testing positive for RSV antigen is ≥10%

Talk to your MedImmune representative about virology in your area and/or obtaining RSVAlert® reports.

Important Safety Information

Synagis® (palivizumab) is indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients at high risk of RSV disease and is administered by intramuscular injection. Safety and efficacy were established in infants with bronchopulmonary dysplasia (BPD), infants with a history of premature birth (≤35 weeks gestational age), and children with hemodynamically significant congenital heart disease (CHD). Synagis has been used in more than one million children in the U.S. since its introduction in 1998. The first dose of Synagis should be administered prior to commencement of the RSV season. Patients, including those who develop an RSV infection, should continue to receive monthly doses throughout the season.

Synagis should not be used in pediatric patients with a history of severe prior reaction to Synagis or its components. Cases of anaphylaxis and anaphylactic shock, including fatal cases, have been reported following initial exposure or re-exposure to Synagis. Severe acute hypersensitivity reactions have also been reported on initial exposure or re-exposure. The relationship between these reactions and the development of antibodies to Synagis is unknown. If a severe hypersensitivity reaction occurs, therapy with Synagis should be permanently discontinued. If milder hypersensitivity reactions occur, caution should be used on re-administration of Synagis. In post-marketing reports, cases of severe thrombocytopenia (platelet count <50,000/microliter) have been reported.

In clinical trials, the most common adverse events occurring at least 1% more frequently in Synagis-treated patients than controls were upper respiratory infection, otitis media, fever, and rhinitis. Cyanosis and arrhythmia were seen in children with CHD. There have also been post-marketing reports of injection site reactions.

Please see accompanying full Prescribing Information, including patient information.

References: **1.** Panozzo CA, Stockman LJ, Curns AT, Anderson LJ. Use of respiratory syncytial virus surveillance data to optimize the timing of immunoprophylaxis. *Pediatrics*. 2010;126:116–123. **2.** Panozzo CA, Fowlkes AL, Anderson LJ. Variation in timing of respiratory syncytial virus outbreaks: lessons from national surveillance. *Pediatr Infect Dis J*. 2007;*26*(suppl 11):S41–S45. **3.** Centers for Disease Control and Prevention. Respiratory syncytial virus—United States, July 2007–June 2011. *MMWR*. 2011;60:1202–1206. **4.** Centers for Disease Control and Prevention. Brief report: respiratory syncytial virus activity—United States, 2005–2006. *MMWR*. 2006;55:1277–1279. **5.** Centers for Disease Control and Prevention. Brief report: respiratory syncytial virus activity—United States, July 2008–December 2009. *MMWR*. 2010;59:230–233.

MedImmune
Gaithersburg, MD 20878
Customer Support Network: 1-877-633-4411
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SYNAGIS®
PALIVIZUMAB

SYNAGIS® (PALIVIZUMAB)

for Intramuscular Administration **Rx only**

DESCRIPTION: Synagis (palivizumab) is a humanized monoclonal antibody (IgG1κ) produced by recombinant DNA technology, directed to an epitope in the A antigenic site of the F protein of respiratory syncytial virus (RSV). Synagis is a composite of human (95%) and murine (5%) antibody sequences. The human heavy chain sequence was derived from the constant domains of human IgG1 and the variable framework regions of the V_H genes Cor (1) and Cess (2). The human light chain sequence was derived from the constant domain of Cκ and the variable framework regions of the V_L gene K104 with Jκ -4 (3). The murine sequences were derived from a murine monoclonal antibody, Mab 1129 (4), in a process that involved the grafting of the murine complementarity determining regions into the human antibody frameworks. Synagis is composed of two heavy chains and two light chains and has a molecular weight of approximately 148,000 Daltons.

Synagis is supplied as a sterile, preservative-free liquid solution at 100 mg/mL to be administered by intramuscular injection (IM). Thimerosal or other mercury containing salts are not used in the production of Synagis. The solution has a pH of 6.0 and should appear clear or slightly opalescent.

Each 100 mg single-dose vial of Synagis liquid solution contains 100 mg of Synagis, 3.9 mg of histidine, 0.1 mg of glycine, and 0.5 mg of chloride in a volume of 1 mL.

Each 50 mg single-dose vial of Synagis liquid solution contains 50 mg of Synagis, 1.9 mg of histidine, 0.06 mg of glycine, and 0.2 mg of chloride in a volume of 0.5 mL.

CLINICAL PHARMACOLOGY: *Mechanism of Action:* Synagis exhibits neutralizing and fusion-inhibitory activity against RSV. These activities inhibit RSV replication in laboratory experiments. Although resistant RSV strains may be isolated in laboratory studies, a panel of 57 clinical RSV isolates were all neutralized by Synagis (5). Synagis serum concentrations of ≥ 40 mcg/mL have been shown to reduce pulmonary RSV replication in the cotton rat model of RSV infection by 100-fold (5). The *in vivo* neutralizing activity of the active ingredient in Synagis was assessed in a randomized, placebo-controlled study of 35 pediatric patients tracheally intubated because of RSV disease. In these patients, Synagis significantly reduced the quantity of RSV in the lower respiratory tract compared to control patients (6).

Pharmacokinetics: In pediatric patients < 24 months of age without congenital heart disease (CHD), the mean half-life of Synagis was 20 days and monthly intramuscular doses of 15 mg/kg achieved mean ± SD 30 day trough serum drug concentrations of 37 ± 21 mcg/mL after the first injection, 57 ± 41 mcg/mL after the second injection, 68 ± 51 mcg/mL after the third injection and 72 ± 50 mcg/mL after the fourth injection (7). Trough concentrations following the first and fourth Synagis dose were similar in children with CHD and in non-cardiac patients. In pediatric patients given Synagis for a second season, the mean ± SD serum concentrations following the first and fourth injections were 61 ± 17 mcg/mL and 86 ± 31 mcg/mL, respectively.

In 139 pediatric patients ≤ 24 months of age with hemodynamically significant CHD who received Synagis and underwent cardio-pulmonary bypass for open-heart surgery, the mean ± SD serum Synagis concentration was 98 ± 52 mcg/mL before bypass and declined to 41 ± 33 mcg/mL after bypass, a reduction of 58% (see *DOSAGE AND ADMINISTRATION*). The clinical significance of this reduction is unknown.

Specific studies were not conducted to evaluate the effects of demographic parameters on Synagis systemic exposure. However, no effects of gender, age, body weight or race on Synagis serum trough concentrations were observed in a clinical study with 639 pediatric patients with CHD (≤ 24 months of age) receiving five monthly intramuscular injections of 15 mg/kg of Synagis.

The pharmacokinetics and safety of Synagis liquid solution and Synagis lyophilized formulation administered IM at 15 mg/kg were studied in a cross-over trial of 153 pediatric patients ≤ 6 months of age with a history of prematurity. The results of this trial indicated that the trough serum concentrations of palivizumab were comparable between the liquid solution and the lyophilized formulation, which was the formulation used in the clinical studies described below.

CLINICAL STUDIES: The safety and efficacy of Synagis were assessed in two randomized, double-blind, placebo-controlled trials of prophylaxis against RSV infection in pediatric patients at high risk of an RSV-related hospitalization. Trial 1 was conducted during a single RSV season and studied a total of 1,502 patients ≤ 24 months of age with bronchopulmonary dysplasia (BPD) or infants with premature birth (≤ 35 weeks gestation) who were ≤ 6 months of age at study entry (7). Trial 2 was conducted over four consecutive seasons among a total of 1287 patients ≤ 24 months of age with hemodynamically significant congenital heart disease. In both trials participants received 15 mg/kg Synagis or an equivalent volume of placebo IM monthly for five injections and were followed for 150 days from randomization. In Trial 1, 99% of all subjects completed the study and 93% completed all five injections. In Trial 2, 96% of all subjects completed the study and 92% completed all five injections. The incidence of RSV hospitalization is shown in Table 1.

Table 1: Incidence of RSV Hospitalization by Treatment Group

Trial		Placebo	Synagis	Difference Between Groups	Relative Reduction	p-Value
Trial 1 Impact-RSV	N	500	1002			
	Hospitalization	53 (10.6%)	48 (4.8%)	5.8%	55%	< 0.001
Trial 2 CHD	N	648	639			
	Hospitalization	63 (9.7%)	34 (5.3%)	4.4%	45%	0.003

In Trial 1, the reduction of RSV hospitalization was observed both in patients with BPD (34/266 [12.8%] placebo vs. 39/496 [7.9%] Synagis), and in premature infants without BPD (19/234 [8.1%] placebo vs. 9/506 [1.8%] Synagis). In Trial 2, reductions were observed in acyanotic (36/305 [11.8%] placebo versus 15/300 [5.0%] Synagis) and cyanotic children (27/343 [7.9%] placebo versus 19/339 [5.6%] Synagis).

The clinical studies do not suggest that RSV infection was less severe among RSV hospitalized patients who received Synagis compared to those who received placebo.

INDICATIONS AND USAGE: Synagis is indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients at high risk of RSV disease. Safety and efficacy were established in infants with bronchopulmonary dysplasia (BPD), infants with a history of premature birth (≤ 35 weeks gestational age), and children with hemodynamically significant congenital heart disease (CHD) (see *CLINICAL STUDIES*).

CONTRAINDICATIONS: Synagis should not be used in pediatric patients with a history of a severe prior reaction to Synagis or other components of this product.

WARNINGS: Cases of anaphylaxis and anaphylactic shock, including fatal cases, have been reported following initial exposure or re-exposure to Synagis. Severe acute hypersensitivity reactions have also been reported on initial exposure or re-exposure to Synagis. Symptoms may include dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia, hypotension, and unresponsiveness. The relationship between these reactions and the development of antibodies to Synagis is unknown. If a severe hypersensitivity reaction occurs, therapy with Synagis should be permanently discontinued. If milder hypersensitivity reactions occur, caution should be used on readministration of Synagis. **If anaphylaxis or severe allergic reactions occur, administer appropriate medications (e.g., epinephrine) and provide supportive care as required.**

PRECAUTIONS: *General:* Synagis is for intramuscular use only. As with any intramuscular injection, Synagis should be given with caution to patients with thrombocytopenia or any coagulation disorder.

The safety and efficacy of Synagis have not been demonstrated for treatment of established RSV disease.

The single-dose vial of Synagis does not contain a preservative. Administration of Synagis should occur immediately after dose withdrawal from the vial. The vial should not be re-entered. Discard any unused portion.

Drug Interactions: No formal drug-drug interaction studies were conducted. In Trial 1, the proportions of patients in the placebo and Synagis groups who received routine childhood vaccines, influenza vaccine, bronchodilators or corticosteroids were similar and no incremental increase in adverse reactions was observed among patients receiving these agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis, mutagenesis and reproductive toxicity studies have not been performed.

Pregnancy: Pregnancy Category C: Synagis is not indicated for adult usage and animal reproduction studies have not been conducted. It is also not known whether Synagis can cause fetal harm when administered to a pregnant woman or could affect reproductive capacity.

ADVERSE REACTIONS: The most serious adverse reactions occurring with Synagis treatment are anaphylaxis and other acute hypersensitivity reactions (see *WARNINGS*). The adverse reactions most commonly observed in Synagis-treated patients were upper respiratory tract infection, otitis media, fever, rhinitis, rash, diarrhea, cough, vomiting, gastroenteritis, and wheezing. Upper respiratory tract infection, otitis media, fever, and rhinitis occurred at a rate of 1% or greater in the Synagis group compared to placebo (Table 2).

Because clinical trials are conducted under widely varying conditions, adverse event rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information does, however, provide a basis for identifying the adverse events that appear to be related to drug use and a basis for approximating rates.

The data described reflect Synagis exposure for 1641 pediatric patients of age 3 days to 24.1 months in Trials 1 and 2. Among these patients, 496 had bronchopulmonary dysplasia, 506 were premature birth infants less than 6 months of age, and 639 had congenital heart disease. Adverse events observed in the 153 patient crossover study comparing the liquid and lyophilized formulations were similar between the two formulations, and similar to the adverse events observed with Synagis in Trials 1 and 2.

Table 2: Adverse Events Occurring at a Rate of 1% or Greater More Frequently in Patients† Receiving Synagis

Event	Synagis (n=1641) n (%)	Placebo (n=1148) n (%)
Upper respiratory infection	830 (50.6)	544 (47.4)
Otitis media	597 (36.4)	397 (34.6)
Fever	446 (27.1)	289 (25.2)
Rhinitis	439 (26.8)	282 (24.6)
Hernia	68 (4.1)	30 (2.6)
SGOT Increase	49 (3.0)	20 (1.7)

†Cyanosis (Synagis [9.1%]/placebo [6.9%]) and arrhythmia (Synagis [3.1%]/placebo [1.7%]) were reported during Trial 2 in CHD patients.

Immunogenicity
In Trial 1, the incidence of anti-Synagis antibody following the fourth injection was 1.1% in the placebo group and 0.7% in the Synagis group. In pediatric patients receiving Synagis for a second season, one of the fifty-six patients had transient, low titer reactivity. This reactivity was not associated with adverse events or alteration in serum concentrations. Immunogenicity was not assessed in Trial 2.

These data reflect the percentage of patients whose test results were considered positive for antibodies to Synagis in an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Synagis with the incidence of antibodies to other products may be misleading.

With any monoclonal antibody, the possibility exists that a liquid solution may be more immunogenic than a lyophilized formulation. The relative immunogenicity rates between the lyophilized formulation, used in Trials 1 and 2 above, and the liquid solution have not yet been established.

Post-Marketing Experience
The following adverse reactions have been identified and reported during post-approval use of Synagis. Because the reports of these reactions are voluntary and the population is of uncertain size, it is not always possible to reliably estimate the frequency of the reaction or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: severe thrombocytopenia (platelet count < 50,000/microliter)

General Disorders and Administration Site Conditions: injection site reactions

Immune System Disorders: severe acute hypersensitivity reactions and anaphylaxis have been reported (see *WARNINGS*).

Limited information from post-marketing reports suggests that, within a single RSV season, adverse events after a sixth or greater dose of Synagis are similar in character and frequency to those after the initial five doses.

OVERDOSAGE: No data from clinical studies are available on overdosage. No toxicity was observed in rabbits administered a single intramuscular or subcutaneous injection of Synagis at a dose of 50 mg/kg.

DOSAGE AND ADMINISTRATION: The recommended dose of Synagis is 15 mg/kg of body weight. Patients, including those who develop an RSV infection, should continue to receive monthly doses throughout the RSV season. The first dose should be administered prior to commencement of the RSV season. In the northern hemisphere, the RSV season typically commences in November and lasts through April, but it may begin earlier or persist later in certain communities.

Synagis serum levels are decreased after cardio-pulmonary bypass (see *CLINICAL PHARMACOLOGY*). Patients undergoing cardio-pulmonary bypass should receive a dose of Synagis as soon as possible after the cardio-pulmonary bypass procedure (even if sooner than a month from the previous dose). Thereafter, doses should be administered monthly.

Synagis should be administered in a dose of 15 mg/kg intramuscularly using aseptic technique, preferably in the anterolateral aspect of the thigh. The gluteal muscle should not be used routinely as an injection site because of the risk of damage to the sciatic nerve. The dose per month = patient weight (kg) x 15 mg/kg ÷ 100 mg/mL of Synagis. Injection volumes over 1 mL should be given as a divided dose.

Administration of Synagis

- **DO NOT DILUTE THE PRODUCT**
- **DO NOT SHAKE OR VIGOROUSLY AGITATE THE VIAL**
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use any vials exhibiting particulate matter or discoloration.
- Using aseptic techniques, attach a sterile needle to a sterile syringe. Remove the flip top from the Synagis vial, and wipe the rubber stopper with a disinfectant (e.g., 70% isopropyl alcohol). Insert the needle into the vial, and withdraw into the syringe an appropriate volume of solution. Administer immediately after drawing the dose into the syringe.
- Synagis is supplied as a single-dose vial and does not contain preservatives. Do not re-enter the vial after withdrawal of drug; discard unused portion. Only administer one dose per vial.
- To prevent the transmission of hepatitis viruses or other infectious agents from one person to another, sterile disposable syringes and needles should be used. DO NOT reuse syringes and needles.

HOW SUPPLIED: Synagis is supplied in single-dose vials as a preservative-free, sterile liquid solution at 100 mg/mL for IM injection.

50 mg vial NDC 60574-4114-1
The 50 mg vial contains 50 mg Synagis in 0.5 mL.

100 mg vial NDC 60574-4113-1
The 100 mg vial contains 100 mg Synagis in 1 mL.

There is no latex in the rubber stopper used for sealing vials of Synagis. Upon receipt and until use, Synagis should be stored between 2°C and 8°C (35.6°F and 46.4°F) in its original container. DO NOT freeze. DO NOT use beyond the expiration date.

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Gaithersburg, MD 20878
U.S. Gov't. License No. 1799
(1-877-633-4411)

Revision Date: April 2011 RAL-SYNV14
Component No.: 8308

Information for Patients and Their Caregivers

SYNAGIS® (SĬ-nă-jĭs)

(palivizumab)

Read this Patient Information before your child starts receiving SYNAGIS and before each injection. The information may have changed. This leaflet does not take the place of talking with your child's healthcare provider about your child's condition or treatment.

What is SYNAGIS?

SYNAGIS is a prescription medication that is used to help prevent a serious lung disease caused by Respiratory Syncytial Virus (RSV). Your child is prescribed SYNAGIS because he or she is at high risk for severe lung disease from RSV.

SYNAGIS contains man-made, disease-fighting proteins called antibodies. These antibodies help prevent RSV disease. Children at high risk for severe RSV disease often do not have enough of their own antibodies. SYNAGIS is used in certain groups of children to help prevent severe RSV disease by increasing protective RSV antibodies.

SYNAGIS is not used to treat the symptoms of RSV disease, once a child already has it. It is only used to prevent RSV disease.

SYNAGIS is not for adults.

Who should not receive SYNAGIS?

Your child should not receive SYNAGIS if they have ever had a severe allergic reaction to it or any of its ingredients. Signs and symptoms of a severe allergic reaction could include:

- a drop in blood pressure
- severe rash, hives or itching skin
- difficult, rapid or irregular breathing
- closing of the throat, difficulty swallowing
- swelling of the lips, tongue, or face
- bluish color of skin, lips or under fingernails
- muscle weakness or floppiness
- unresponsiveness

See the end of this leaflet for a list of ingredients in SYNAGIS.

What should I tell my child's healthcare provider before my child receives SYNAGIS?

Tell your child's healthcare provider about:

- **Any reactions** you believe your child has ever had to SYNAGIS.
- All your child's medical problems, including **any bleeding or bruising problems.** SYNAGIS is given by injection. If your child has a problem with bleeding or bruises easily, an injection could cause a problem.
- **All the medicines your child takes, including prescription and non-prescription medicines, vitamins, and herbal supplements.** Especially tell your child's healthcare provider if your child takes a blood thinner medicine.

How is SYNAGIS given?

- SYNAGIS is given as a monthly injection, usually in the thigh (leg) muscle, by your child's healthcare provider. Your child's healthcare provider will prescribe the amount of SYNAGIS that is right for your child (based on their weight).
- Your child's healthcare provider will give you detailed instructions on when SYNAGIS will be given.
    - "RSV season" is a term used to describe the time of year when RSV infections most commonly occur (usually fall through spring). During this time, when RSV is most active, your child will need to receive SYNAGIS shots. Your child's healthcare provider can tell you when the RSV season starts in your area.
    - Your child should receive their **first SYNAGIS shot before the RSV season starts** to help protect them before RSV becomes active. If the season has already started, your child should receive their first SYNAGIS shot as soon as possible to help protect them when exposure to the virus is more likely.
    - **SYNAGIS is needed every 28-30 days during the RSV season.** Each dose of SYNAGIS helps protect your child from severe RSV disease for about a month. **Keep all appointments with your child's healthcare provider.**
- **If your child misses an injection, talk to your healthcare provider and schedule another injection as soon as possible.**
- Your child may still get severe RSV disease after receiving SYNAGIS. Talk to your child's healthcare provider about what symptoms to look for.
- If your child already has an RSV infection and is sick, they still need to get their scheduled SYNAGIS injections to help prevent severe disease from new RSV infections.
- If your child has certain types of heart disease and has corrective surgery, your healthcare provider may need to give your child an additional SYNAGIS injection soon after surgery.

What are the possible side effects of SYNAGIS?

Over one million babies have been given SYNAGIS. Like all medicines, SYNAGIS has been associated with side effects in some patients. Most of the time, the side effects are not serious. If side effects do occur, your child may need medical attention.

Possible, serious side effects include:

- Severe allergic reactions (may occur after any dose of SYNAGIS). Such reactions may be life-threatening or cause death.
    - See "Who should not take SYNAGIS?" for a list of signs and symptoms.
- Unusual bruising and/or groups of tiny red spots on the skin.

Call your child's healthcare provider or get medical help right away if your child has any of the serious side effects listed above after any dose of SYNAGIS.

Common side effects of SYNAGIS include:

- fever
- cold-like symptoms (upper respiratory infection), including runny nose and ear infection
- rash

Other possible side effects include skin reactions around the area where the shot was given (like redness, swelling, warmth, or discomfort).

In children born with certain types of heart disease, other possible side effects include bluish color of the skin, lips or under fingernails and abnormal heart rhythms.

These are not all the possible side effects of SYNAGIS. Tell your child's healthcare provider about any side effect that bothers your child or that does not go away.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088 or call MedImmune at 1-877-633-4411.

General Information about SYNAGIS

Medicines are sometimes prescribed for purposes other than those listed in Patient Information leaflets.

This leaflet summarizes important information about SYNAGIS. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about SYNAGIS that is written for health professionals.

For more information, go to www.synagis.com or call 1-877-633-4411.

What are the ingredients in SYNAGIS?

Active Ingredient: palivizumab

Inactive Ingredients: histidine, glycine, and chloride

What is RSV?

Respiratory Syncytial Virus (RSV) is a common virus that is easily spread from person to person. RSV infects nearly all children by their second birthday. In most children, RSV infection is usually no worse than a bad cold. For some children, RSV infection can cause serious lung disease (like pneumonia and bronchiolitis) or breathing problems, and affected children may need to be admitted to the hospital or need emergency care.

Children who are more likely to get severe RSV disease (high risk children) include babies born prematurely (35 weeks or less), or babies born with certain heart or lung problems.

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affected. Normal animals exposed as adults to the given dose of nicotine experience dramatically increased activity compared with animals that were not. Animals that had been exposed to Bisphenol A during their neonatal period and then received nicotine as adults did not evince the same hyperactivity as normal animals at all. Once again, this effect was induced during the neonatal period but persisted into adulthood.

FORGET THE FHR

Fetal heart rate patterns may not be a good indicator of a baby's health as delivery-time nears, and may lead to unnecessary interventions, according to researchers at Intermountain Medical Center. The researchers studied fetal heart rate patterns from more than 48,000 labor and delivery cases at 10 Intermountain Healthcare hospitals over a 28-month period. The fetal heart rates were classified using a system comprised of three categories: Category I heart rate patterns are considered normal, and, as a rule, do not indicate fetal stress. Category III patterns are abnormal and rare, and usually indicate a problem. Category II patterns are considered indeterminate, and their significance uncertain. Researchers examined the time babies spent in each of these categories and neonatal outcomes. The fetal heart rate patterns were classified as category I nearly 78% of the time, as category II patterns 22% of the time, and as category III rates only very rarely, 0.004% of the time when data from all stages of labor were analyzed. However, when looking at the data for just the final two hours of delivery, the data showed that category I rates decreased to 61%, while category II rates increased to 39%, and category III rates increased to 0.006%. Babies who spent the entire time in category I scored well. Five minutes after birth, only 0.6% had Apgar scores of less than seven. Only 0.2% required admission to the NICU. Category III fetal heart rates were very uncommon, occurring in only 0.1% of the patients studied, and resulted in admission to the NICU about half the time. Category II fetal heart rate patterns showed up in 84% of all labors and the amount of time spent in category II increased in the two hours before delivery. This also coincided with lower Apgar scores and increased admissions to the NICU. Regardless, the vast majority of category II babies had no short-term problems after delivery. This means that using category II heart rate patterns as an indicator of fetal health is an unreliable method, researchers say. So, researchers say, it would be good to sort out which Category II patterns mean the baby is sick.

OCCUPY INFANT MORTALITY

The nation's leading healthcare organizations in obstetrics-gynecology, family medicine, and pediatrics recently issued a call to action today for the nation's health care providers and administrators. The collaboration, which includes the American Academy of Family Physicians; the American Academy of Pediatrics; the American College of Nurse-Midwives; the American College of Obstetricians and Gynecologists; the American College of Osteopathic Obstetricians & Gynecologists; the Association of Women's Health, Obstetric and Neonatal Nurses; and the Society for Maternal-Fetal Medicine, was brought about by the need to develop an interdisciplinary collaborative approach to patient care to optimize maternal and fetal health outcomes. While infant mortality rates in the United States declined in 2010, the rate remains higher than most European nations. In addition, US health care providers have seen an increase in pregnancy complications. These trends, along with the recognition that collaboration among physicians, midwives, and nurses is essential to positive health outcomes, prompted the organizations to develop joint recommendations. Here are the Call to Action recommendations: Ensure that patient-centered care and patient safety are organizational priorities that guide decisions for policies and practices. Foster a culture of openness by promoting the active communication of good outcomes and opportunities for improvement. Develop forums to facilitate communication and track issues of concern. Provide resources for clinicians to be trained in the principles of teamwork, safety, and shared decision-making. Develop methods to systematically track and evaluate care processes and outcomes. Facilitate cross-departmental sharing of resources and expertise. Ensure that quality obstetric care is a priority that guides individual and team decisions. Identify and communicate safety concerns, and work together to mitigate potential safety risks. Disseminate and use the best available evidence, including individual and hospital-level data, to guide practice patterns.

TOO MANY NEURONS

A study by researchers at the University of California, San Diego shows that brain overgrowth in boys with autism involves an abnormal, excess number of neurons in areas of the brain associated with social, communication and cognitive development. The scientists discovered a 67% excess of cortical cells, which are made before birth, in children with autism. The findings suggest that the disorder may arise from prenatal processes gone awry. Researchers compared postmortem tissue from the prefrontal cortex of seven boys, ages 2 to 16 years, who had autism, to that of six typically developing boys. Using an advanced computerized analysis system developed at the University of South Florida, along with blinded anatomical and cell count measurements, the study found that children with autism had 67% more neurons in the prefrontal cortex than control subjects. The brains of the autistic children also weighed more than those of typically developing children of the same age.

COMPULSION

The majority of research regarding a woman's mental health after she gives birth has addressed postpartum depression, and very little has focused on postpartum anxiety disorders, such as obsessive-compulsive disorder (OCD). Postpartum OCD, a serious disorder, typically involves obsessive thoughts and behaviors related to an infant being harmed. An article in the November/December issue of the Journal of Obstetric, Gynecologic and Neonatal Nursing (JOGNN), published by the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN) discusses the current available information for nurses about postpartum OCD. The article, "Postpartum Obsessive-Compulsive Disorder," by Brittany B. Speisman, Eric A. Storch, and Jonathan S. Abramowitz examines the prevalence, cause, symptoms, and treatment of postpartum OCD and the role women's health nurses can play in its early identification and treatment. The article highlights four major aspects of postpartum OCD: Prevalence – 25-70% of women reported that childbirth was the life stressor in the development or significant worsening of OCD symptoms. Etiology or cause – Several theories have been proposed for the cause of postpartum OCD. The first theory indicates that the sudden increase in responsibility following a birth in combination with the misinterpretation of intrusive thoughts regarding the infant's safety lead to OCD. Another theory involves the dramatic decrease in estrogen and progesterone during a woman's pregnancy and the postpartum period. The final theory suggests that susceptibility to stress and anxiety may also be a factor. Symptoms – The presentation of symptoms varies widely depending on the woman. However, the majority of women

with postpartum OCD experience aggressive obsessions about possibly harming their newborns and develop compulsions that involve their infants' safety. Treatment – The treatment for postpartum OCD is no different from other OCD occurrences. The primary treatments are typically medication and discussing dysfunctional emotions, behaviors and conditions with appropriate mental health practitioners. However, it is important to note that treatment must be sensitive to the unique characteristics of postpartum OCD including sudden onset, symptoms and patient preferences. "Information about the frequency, cause, symptoms and treatment of postpartum OCD are not only important to new parents, but also for the nurses who spend considerable time caring for new mothers," said AWHONN's Chief Executive Officer Karen Peddicord, PhD, RN. "Education and information for nurses about postpartum OCD is essential." Ultimately, nurses can help women identify postpartum OCD, and if obsessions and compulsions are problematic, they can facilitate timely and necessary referrals for treatment. For more info contact jognn.awhonn.org.

CANCER VARIABLES

The cancer-causing potential of fetal exposure to carcinogens can vary substantially, according to researchers at Oregon State University, depending on when the fetus is exposed. The damage manifests due to epigenetic changes in the cells. (See our guest commentary on page 56 of the Jan/Feb issue.) Researchers gave mice four separate doses of a carcinogen commonly found in air pollutants or other combustion products. The mice had triple the level of ovarian cancer at the rodent equivalent of middle age. About 80% also got lung cancer, and many of the male mice had abnormally small testes. In previous research the same amount of this carcinogen given in a single dose caused a much higher rate of T-cell lymphoma, while in this study, lymphoma disappeared when the carcinogen exposure was spread out over time, as was liver cancer. The mice in these experiments were exposed to polycyclic aromatic hydrocarbons, commonly produced by many processes, from coal combustion to automobile exhaust. PAHs can also get into soils, be taken up by plants and get into the human food chain.

JUST BEAR IT

Pregnant women are being warned about taking common cold medicines by the California Teratogen Information Service. According to the CTIS, expectant moms should only take medications needed for their specific symptoms, and not those medications with multiple combinations of ingredients. Instead of taking oral decongestants in the first trimester, moms should use saline drops or short-term nasal sprays. Pregnant moms should beware of unresearched herbal ingredients. Don't take too many vitamins or throat lozenges. The ideal amount of daily vitamin C for pregnant women is 80 to 100 mg, and 11 mg of zinc. Moms are also urged to get alcohol-free cough syrup. Information is from Medical News Today, written by Grace Rattue, copyright Medical News Today.

INHALE

Inhaled glucocorticoids for the treatment of asthma during pregnancy are not associated with an increased risk of most diseases in childhood, except for endocrine and metabolic disorders, as compared to the risk in asthmatic mothers without glucocorticoid inhalation during pregnancy. Of the study

population, 61,002 had no asthma during pregnancy (93.7%) and 4,083 (6.3%) had it. At the median age of about 6 years, use (versus no use) of inhaled glucocorticoids was associated with a significantly increased risk for the first diagnosis of endocrine and metabolic disorders. Results were similar when analyses were restricted to mother-child pairs exposed only to budesonide, the inhaled glucocorticoid used by the majority of women (79.9%) in the study.

ALCOHOL MARKER

A study by the Instituto Superiore di Sanita in Rome provided further evidence of using fatty acid ethyl esters in meconium as a marker of gestational alcohol exposure during the second and third trimester. Researchers examined prenatal exposure to alcohol in seven Italian cities through analysis of FAEEs and of a new biomarker, ethylglucuronide (EtG), in neonatal meconium samples, finding that fetal alcohol exposure is underestimated or misreported in Italy. Alcohol ingested by moms, as well as EtGs, are accumulated by the fetus in meconium, which can be examined to find the level of accumulation. The researchers said this is valuable info because moms often under-report their drinking. The researchers obtained 607 meconium samples from neonatal wards in seven public hospitals. The FAEEs and EtG were measured in meconium and categorized to differentiate between heavy maternal alcohol use during pregnancy and occasional or no use at all. Researchers found a prevalence of 7.9% newborns prenatally exposed to maternal alcohol, with a range of 0% in Verona to 29.4% in Rome. Low maternal education and younger maternal age were associated with the high biomarker scores.

GLOBAL WARMING FALLOUT

A link has been found between increases in temperature and the incidence of stillbirth and shorter pregnancies. Researchers at Queensland University of Technology looked at the incidence of still and premature births in Brisbane, Australia over a four-year period from 2005. A total of 101,870 births were recorded throughout the period and of these 653 or 0.6% were stillbirths. Increases in temperature increased the risk of stillbirth, and this was particularly true in the earlier stages of pregnancy before 28 weeks. The researchers estimated that at 15°C there would be 353 stillbirths per 100,000 pregnancies, as compared with 610 stillbirths per 100,000 pregnancies at 23°C. Increased temperatures also shortened gestation times. The researchers noted that the rise in global temperatures had serious public health implications.

SURVIVAL IMPROVES

Fetal tracheal occlusion improves infant survival rate in severe cases of congenital diaphragmatic hernia, according to researchers at the University of Sao Paulo. Twenty patients were assigned randomly to undergo FETO and 21 patients were assigned to no prenatal intervention. FETO was performed between 26 and 30 weeks' gestation following a well-established protocol under maternal epidural anesthesia. Delivery occurred at 35.6+2.4 weeks in the FETO group and at 37.4+1.9 weeks in the control group. Results found that 10 of the 20 infants in the FETO group and one infant out of 21 (4.8%) in the control group survived. The findings demonstrate that FETO improves the chance of surviving after birth from less than 5% without this treatment to about 50% after this treatment. The FETO procedure appears to improve survival by enhancing pulmonary growth as a consequence of fetal tracheal occlusion.

SHORT CERVIX TREATMENT

Medical News Today reported on a landmark global study spearheaded by the NIH which showed that women with a short cervix should be treated with vaginal progesterone to prevent preterm birth. The study demonstrated that vaginal progesterone lowered the risk of preterm birth by 42% and substantially reduced the rate of respiratory distress syndrome, the need for mechanical ventilation, as well as a multitude of several complications in premature newborns, such as infection, necrotizing enterocolitis, and intracranial hemorrhage. Follow-up studies of babies exposed to progesterone in utero to the age of 18 or 24 months showed no evidence of any behavioral or physical problems. The authors recommended that transvaginal sonographic measurement of the cervix be performed in all pregnant women between 19 to 24 weeks of gestation to assess the risk of preterm delivery. Other studies have covered this subject, but this was the first that pooled a huge set of data for a meta-analysis, and it allows for subgroup evaluation. The study included 775 women and 927 infants with the primary endpoints determined as preterm birth of 33 weeks or less, as well as a multiple index of perinatal morbidity and mortality. The researchers also examined other secondary endpoints on progesterone action, such as investigating the effect of cervical length, a history of previous preterm birth, race/ethnicity, body mass index, and maternal age. Progesterone was found to be beneficial not only to women with a short cervix but also for moms with short cervixes who have given birth preterm previously. Information is from Medical News Today, Petra Rattue, copyright Medical News Today.

ONE IN FIFTY

More than one baby in every 50 in England and Wales is born with a congenital anomaly, according to the latest annual report by the British Isles Network of Congenital Anomaly Registers (BINOCAR). These anomalies are significantly more common than previously reported estimates of around one in 80. The study by researchers at the University of London brought together four years of data from the region. The researchers expressed concern that substantial parts of the country were not monitored for babies with birth defects, and that regional increases in defects go unnoticed and uninvestigated. The current report collated data from five regional registers, which cover 28% of the population of England and Wales. The researchers estimate that there were at least 14,500 babies born with birth defects in England and Wales in 2009. The most common defect was congenital heart disease. Neural tube defects were found to affect one in a thousand babies, as was gastroschisis. More than half of all major birth defects were detected during pregnancy.

CLINICAL FEATURE

INFRARED MONITORING

A recent study in the journal BioMedical Engineering OnLine featured a new way to monitor respiration in neonates through real-time infrared thermography. Here are some highlights from the study, Neonatal Non-contact Respiratory Monitoring based on Real-time Infrared Thermography, which is available on BioMed Central.

Monitoring of vital parameters is an important topic in neonatal daily care. Progress in computational intelligence and medical sensors has facilitated the development of smart bedside

monitors that can integrate multiple parameters into a single monitoring system. This paper describes non-contact monitoring of neonatal vital signals based on infrared thermography as a new biomedical engineering application. One signal of clinical interest is the spontaneous respiration rate of the neonate. It will be shown that the respiration rate of neonates can be monitored based on analysis of the anterior naris (nostrils) temperature profile associated with the inspiration and expiration phases successively. The aim of this study is to develop and investigate a new non-contact respiration monitoring modality for neonatal intensive care unit (NICU) using infrared thermography imaging. This development includes subsequent image processing and optimization. Moreover, it includes further optimization of this non-contact respiration monitoring to be considered as physiological measurement inside NICU wards. Continuous wavelet transformation was applied to detect the breathing signal within an image stream. Respiration was successfully monitored based on a 0.3 °C to 0.5 °C temperature difference between the inspiration and expiration phases. Although this method has been applied to adults before, this is the first time it was used in a newborn infant population inside the neonatal intensive care unit (NICU). The promising results suggest to include this technology into advanced NICU monitors.

Essentially, respiration measurement can be performed by using nasal thermocouples, respiratory-effort belt transducer, piezoelectric transducer, optical sensor (pulse oximetry) and electrocardiography ECG. However, all these techniques are inconvenient to take in at home and they may bring discomfort and soreness to the patient. Apnea and bradycardia are common and serious problems in premature infants. One of the methods to quantify respiratory rate in these infants is to use a thermistor that is fixed above the upper lip directly in front of the nares. This by itself can induce apneas because of upper respiratory airway obstruction. Therefore, one of important field in such monitoring system is the NICU, where neonates need continuous monitoring without creating a discomfort or irritation.

IR THERMOGRAPHY

The acquisition protocol for the IRTR measurement consists of three distinct phases with 2 minute duration for each phase, and between these phases intervals, there is a recalibration time to correct any non-uniformity with IR themrography. All measurements were conducted at the Department of Neonatology (RWTH Aachen University Hospital). We examined seven premature infants with a median gestational age of 29 weeks. They were all consecutively admitted directly after birth to our Department of Neonatology. None of the infants was mechanically ventilated. They all had respiratory support via CPAP directly after birth. One of them still had a CPAP during the study. While five infants were handled in an incubator, two infants were positioned in an IR radiant warmer bed. Cardiorespiratory stability was a precondition to be included into the study to get a reliable signal over the whole time period of the IRT. During IRT, vital parameters including oxygen saturation were continuously monitored to make sure that there were no negative side effects. To the authors' knowledge, this is the first time that IRTR signal analysis has been applied to monitor neonates. [Our] results indicate that the IRTR thermal signature detection may be included into the future neonatal monitoring modalities. At present, the results acquired during IRTR measurement are not fully categorized and need more reliable measurement protocols. Additionally, the neonatal IRTR measurement are not correlated with a classical reference respiration sensing method, ie a thermistor that is fixed above the upper lip directly in front of the nares with the danger of inducing apneas because of upper airway obstruction. To overcome this problem, the neonate's respiration rate was manually registered from the bedside monitor. The disadvantage is that there is no information about the quality of breathing. The results from this experiment have shown clear changes in temperature over the nasal region and also a difference during inspiration and expiration.

In conclusion, whereas respiration jet and nostril temperature monitoring has been applied to adult volunteers, in this work IR thermography was shown to allow non-contact respiratory monitoring in neonates inside the NICU. Physically, the work is based on changes of convective heat transfer at the infra-nasal region, induced by breathing. Until now the method seems more effective in adults than in newborns, due to the larger lung volumes in adults. Both the IR imaging device and the method itself still face drift problems due to variation in background temperatures. This requires improvements in image processing and boundary detection of the nasal region separated from the rest of the imaging scenario (eg incubator internal wall, mattress, and other facial regions). Moreover, the presented results are preliminary and need further studies in a larger number of neonates and under different care setups. In comparison to the ECG derived respiration rate, the IRTR signal is correlated to this acquired signal from bedside monitor, while there is a slight difference in respiration rate estimated from each method. The main impediments to high resolution IRTR signature detection are the IR camera physical coverage and the thermal detector's resolution.

However, these preliminary results provide a good basis for further investigation of the neonatal thermal respiration signature. More studies performed under standardized clinical conditions are needed, so that the method can be applied to examine the symmetrical pattern of the IRTR signature. Moreover, clinical investigations should explore a range of upper respiratory tract diseases. Furthermore, this method may be an effective quantitative technique to measure the nasal symmetrical air-flow pattern in preterm infants. This possibly can give information about the depth and the frequency of each breath cycle to get an early sign of changes in the infant's behavior. Also, the temperature difference up to 0.66 °C can be interpreted as a part of the infant's thermoregulation and gives an interference of heat loss through expiration. Despite the remaining problems, the authors feel that the presented technique is a promising and effective step toward establishing cable-free monitoring of infants under intensive care conditions.

The above is reprinted, highly abridged, from BioMed Central, BioMedical Engineering OnLine, by Abbas K. Abbas, Konrad Heimann, Katrin Jergus, Thorste Orlikowsky and Steffen Leonhardt. The authors wish to thank Prof V. Blazek and Prof V. J. Kumar for their valuable recommendation and reviewing of this paper. All experimental device (IR camera and temperature sensors were provided by MedIT, RWTH Aachen University. The authors also thank the medical staff in the Department of Neonatology at University Hospital, Aachen University. © 2011 Abbas et al; licensee BioMed Central Ltd. This is an open access article distributed under the terms of the Creative Commons Attribution License.

Initiating and Maintaining Human Milk in the NICU: A Literature Review of Best Practices

Irene Murphy Zoppi, RN, MSN, IBCLC

Introduction

Human milk is recognized as the gold standard for infant nutrition. Expert opinion acclaims the many health benefits of human milk for healthy newborns and especially for infants born prematurely.[1] In the last decade, a plethora of research studies have substantiated the health benefits of human milk for premature infants. These studies have shown that mother's milk provides protection from a host of prematurity-specific morbidities and their long term consequences. Mother's milk has been designated a "medicine" that both nourishes and protects fragile premature infants.[2]

Unfortunately, prematurity does not always allow infants to feed at the breast. As a result, mothers find it necessary to employ breast expression techniques that allow them to provide sufficient volumes of breastmilk for their infants. This provision of human milk requires a coordinated effort between mothers wishing to express their milk and the clinicians who provide care to them. Clinicians find it necessary to search for evidence-based technology and practices that will ensure mothers provide an adequate supply of human milk for their infants.

This paper is written for all clinicians who work with pump-dependent mothers. It is meant to provide a literature review of best pumping practices that help to ensure pump-dependent mothers initiate and maintain adequate volumes of human milk for their premature infants. A review of the normal lactation process will first be presented.

Irene Zoppi currently serves as a Clinical Education Specialist for Medela, Inc. In this role, she acts as a vital resource for groups assisting breastfeeding mothers and infants. She has been frequently interviewed on radio and online regarding breastfeeding issues for mothers and clinicians. Zoppi spent many years caring for new families in antenatal, labor and delivery, postpartum and NICU settings and was involved in direct patient care and family-based education. She has extensive experience teaching in a variety of nursing education programs where she consistently received the Outstanding Lecturer title awarded by her students. She produced a video presentation on nursing students' involvement in Community Health Nursing for the National League for Nursing. Ms. Zoppi, an IBCLC since 2000 and former 1st Lieutenant in the Army Nurse Corps, has authored numerous continuing educational programs for health professionals on topics ranging from breastfeeding support to evidence-based practices on the use of human milk. She has been instrumental in developing hands-on education for clinical staff regarding breastpump technology. Irene graduated from Boston University with a master's degree in Parent Child Health Nursing and is a member of Sigma Theta Tau. This article was provided by Medela.

Initiation of Milk Volumes: the normal process of lactation

All females have the capacity to lactate, to provide a species specific nutrition for their infants after delivery. This process originates during pregnancy, under the influence of a variety of hormones. A woman's breast undergoes changes to ductal and glandular tissue in preparation for the provision of nutrition after delivery.[3] This hormonally controlled process, referred to as Secretory Differentiation or Lactogenesis I, occurs irrespective of the mother's decision to provide human milk for her infant after birth.

After the delivery of the placenta and the sudden decline in circulating progesterone, serum prolactin levels rise resulting in an increase in maternal milk volume. Termed Secretory Activation or Lactogenesis II, this onset of copious milk production occurs normally between 36 and 96 hours after birth and occurs, again, irrespective of the mother's decision to provide human milk for her infant. This initial increase in volume happens in the absence of a sucking infant or milk expression. [4]

After the onset of copious milk production, milk synthesis continues if milk is removed either by a healthy suckling infant or by mechanical expression. Involution of the milk secreting cells results, however, if milk is not removed. Milk stasis within the breasts occurs resulting in over-distention or engorgement. Thus, if the mother chooses not to provide human milk to her infant, she simply does nothing; her milk supply will gradually decrease or "dry-up." When an infant is born prematurely and unable to feed from the breast, the mother will need to rely on mechanical measures to repeatedly empty her breasts. Repeated and effective milk expression after Lactogenesis II will continue to drive milk synthesis.

What happens if infants are born prematurely?

However, pump-dependent mothers with premature infants appear to experience multiple lactation difficulties. This assumption is supported by numerous studies that indicate mothers of premature infants are at greater risk for delayed Lactogenesis II and or low milk volume than mothers with healthy term infants.[2,5,6,7,8,9]

Cregan's work (2002) with preterm mothers concluded that many preterm mothers experience a compromised initiation of lactation resulting in low milk production in the early days post birth. Hill's study (2005) demonstrated that pump-dependent mothers of premature infants were more likely to produce

Table 1

Checklist of Best Practices for Pump Dependent Mothers

- ✓ Assist mother to initiate pumping as soon as possible after delivery.
- ✓ Have a hospital-grade, double electric pump available for mother.
- ✓ Instruct mother to pump a minimum of 8 times daily until target volumes are reached.
- ✓ Instruct mother to initially pump for 15 minutes until milk volumes increase.
- ✓ Once milk volume increases, instruct mother to pump for 2 minutes after last droplets are noted.
- ✓ Assess for risk factors associated with delayed lactogenesis.
- ✓ Guide mother to begin a daily pumping journal.
- ✓ Provide pumping target volumes for mother.
- ✓ Assess breast shield fitting daily during 1st two weeks after birth.
  - o Outfit each hospital pump with breast shield sizing information.
- ✓ Support bedside pumping.
- ✓ Assist with frequent skin-to-skin care.
- ✓ Help with transition to infant tasting breast milk.

less milk in the early days post birth along with reduced milk volumes as they continued to express milk. Schanler and colleagues (2005) also witnessed pump dependent mothers struggle to maintain milk volumes for their premature infants.

Several risk factors have been identified that pose a risk for delayed Lactogenesis II.[8,10,11,12] Risk factors such as diabetes mellitus, preterm labor, pregnancy induced hypertension, excessive maternal blood loss, prolonged bed rest, maternal stress during labor and delivery, an unscheduled Cesarean delivery, obesity, and the use of selective serotonin re-uptake inhibitors (SSRIs) pose risks for any breastfeeding mother, but so commonly occur in mothers who give birth prematurely. Assessment for these lactation risk factors should be included when providing lactation support for mothers of premature infants.

Although insufficient volume of milk is commonplace among preterm mothers, Meier (2007, 2010) and Spatz (2004) contend that many occurrences may be avoided if mothers receive instruction and individualized care regarding best clinical practices during both the initiation phase (Lactogenesis II) and maintenance phase of lactation. The following paragraphs describe these best practices. A quick reference list (Table 1) identifies these practices.

Initiation and Maintaining Milk Volumes: Best Practices

The first two weeks post-birth represents a critical period in lactation for all breastfeeding mothers. Due to the complex endocrine, anatomic and biochemical changes occurring during this first two week period, breastfeeding needs to get off to a good start. For the healthy term breastfeeding baby, this requires frequent feeding at the breast in the range of 8 to 12 times per day. In the absence of a healthy term breastfeeding baby, the mother of a preterm infant is at risk for diminishing milk volume; her milk supply may decrease and be insufficient to meet the nutritional needs of her infant. Hill (2005) cites decreasing maternal milk volume as the reason many NICU mothers are unable to meet their lactation goals.

Table 2

Criteria for Correct Breast Shield Fit

C	Centered nipple which moves freely in the tunnel
O	Only little or no aerola tissue pulled into the tunnel
M	Motion of the breast is gentle and rhythmic with each cycle of the pump
F	Feels comfortable pumping
Y	You find a well-drained breast. If an area of the breast still feels full or a bit firmer, the milk duct in that area of the breast may not be empty.

Getting Started: When and How

Studies indicate[15,16,17] mothers of premature infants should initiate milk expression as soon as possible after delivery. Hill (2001) demonstrated correlation of early breast expression and milk volumes during 2-5 days postpartum. Furman (2002) demonstrated that mothers who initiated milk expression within 6 hours of delivery were more likely to continue lactation beyond 40 weeks. Spatz (2004) recommends mothers begin milk expression within the first 6-12 hours after birth. A pilot study[17] of 20 mothers who delivered VLBW premature infants and began milk expression within 1 hour of delivery produced significantly more milk during the first 7 days after birth than mothers who initiated milk expression between 1 and 6 hours after delivery.

The use of a hospital-grade, double electric breast pump has been recommended for pump dependent NICU mothers to help them achieve adequate volumes of breast milk.[14,18,19,20] Meier (2010) states, "A breast pump is fundamental to a mother's ability to produce milk, and it is critical that NICU mothers receive the most effective, efficient, comfortable, and convenient breast pump available" (p 34). Mothers should be instructed to pump at the same frequency that duplicates the breastfeeding frequency of a healthy term infant. This frequency is required to drive continued milk production. The more milk is removed from the breast either by a healthy baby or by a breast pump, the more milk will be made. This is known as the supply and demand principle of continued lactation. Spatz (2004) and Rodriquez et al (2005) recommend mothers pump every 2 to 3 hours each day. Walker (2010) suggests pumping eight or more times in twenty-four hours. Participants in Parker's study (2011) were instructed to pump at least eight times in twenty-four hours.

Simultaneously pumping both breasts reduces the time mothers spend while pumping. One study (Hill, 1996) suggested that milk volumes may be increased with simultaneous pumping.

No research evidence exists to recommend how long an individual pumping session should last. It is frequently recommended that during the Initiation Phase of lactation, mothers should pump for approximately fifteen minutes. After the onset of Lactogenesis II, mothers should be instructed to pump for two minutes after the last droplets are noted (Meier 2010). This ensures all available milk has been expressed and the high fat milk has been removed. A well-drained breast will more rapidly synthesize breast milk than a breast that is partially drained.[24] Kent (2008) recommends mothers pump using Maximum Comfort Vacuum (MCV), the highest yet comfortable vacuum setting of the pump while expressing milk. Research has demonstrated this allows a mother to pump more efficiently; she will pump more milk in less time.

Hand expression has been mentioned to aid in the retrieval of the small quantities of colostrum produced during the initial stages of lactation. Morton (2009) demonstrated greater volumes of colostrum in mothers who performed hand expression 5 times a day combined with use of a double, electric breast pump more than five times a day in the first few days after birth. Ohyama (2010) found gentle manual expression

during the first 48 hours was the best way to obtain small quantities of produced colostrum.

A recent study by Meier (2011) demonstrated increased volumes of expressed milk when mothers utilized a breast pump suction pattern that mimicked the unique sucking action of the healthy term infant.

Meier (2010) recommends mothers be given volume targets they should achieve during the first two weeks of pumping. During this initial phase of lactation, identification and treatment for insufficient milk volumes is critical. Meier (2010) refers to this transition period from Lactogenesis II to a milk volume sufficient for exclusive breastfeeding as "coming to volume." Providing target volumes helps identify pumping issues that need modification. Achieving ideal pumped volumes of 750-1000ml per twenty four hours within the first two weeks after birth is correlated with adequacy of breast milk for the infant over the entire NICU stay.

Spatz (2004) and Meier (2007, 2010) also recommend mothers document daily pumping sessions and collected milk volumes in a journal or diary. Keeping a milk volume record enables mothers and clinicians to identify milk volume issues early so that interventions can by instituted to rectify any problems. Bedside clinicians are able to guide and support mothers' pumping efforts when they review the daily pumping logs with them.

Breast shields, the portion of the breast pump collection kit that comes in direct contact with the mother's breast, nipple and areola areas, require careful fitting to the mother's anatomy. A breast shield that is either too large or too small may cause injury to the mother or impede breast milk drainage leading to the eventual down regulation of a mother's milk supply. Meier (2010) recommends daily assessment of breast shield sizing during the two week "coming to volume" period. Zoppi [this author] (2011) refers clinicians to the use of an acronym; COMFY as a simple tool to emphasize criteria to correctly fit breast shields (Table 2). Zoppi recommends outfitting all breast pumps within the hospital setting with laminated cards detailing these fitting guidelines. Kent et al (2011) described an increase in efficiency of removing milk when breast shields were warmed before use.

Pumping directly at the infant's bedside instead of a designated pumping room provides the mother the opportunity to visit with her infant as she pumps (Meier 2007). The mother may find it more pleasurable to watch and even speak to her infant as she pumps. It also provides an opportunity for the bedside clinician to detect and correct any improper pumping technique used by the mother.

Another non-pharmacologic technique cited in the literature that enhances physiologic stability and breastfeeding behaviors of preterm infants in the NICU is skin-to-skin holding or kangaroo care. Numerous studies[2,13,14,16,31,32] have demonstrated that mothers were able to express significantly more milk after a skin-to-skin episode with their infant.

The next step in the lactation process for NICU mothers and their infants is nonnutritive sucking at the breast or tasting breast milk (Spatz (2004), Meier (2007). This is accomplished by having the mother position her infant skin-to-skin on her breast after she pumped her breasts. Tasting drops of breast milk during a scheduled gavage feeding allows the infant to associate breast milk with his feeding. Nonnutritive sucking can be initiated after the infant has been extubated. It has been shown to improve the transition to direct breastfeeding, shortens the period of pump dependency for mothers and is associated with longer breastfeeding rates.[33]

Summary

Breast milk is undeniably the best nutrition for premature infants. The process of initiating and maintaining adequate volumes of breast milk to meet the nutritional needs of the premature infant requires dedication from mothers and a commitment on the part of bedside clinicians to teach, support and provide up to date evidence on best practices. Many mothers find the challenges of pumping milk for their premature infants overwhelming. They struggle with many issues and have to overcome many obstacles to be successful. Yet many mothers find the process of milk expression for their preterm infants rewarding and empowering.[34]

Bedside clinicians can make a tremendous difference in the pumping experiences of pump dependent mothers challenged to provide expressed milk for their premature infants. Clinicians need to be knowledgeable about current best pumping practices and integrate them into the care they provide to pump dependent mothers.

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during the first 48 hours was the best way to obtain small quantities of produced colostrum.

A recent study by Meier (2011) demonstrated increased volumes of expressed milk when mothers utilized a breast pump suction pattern that mimicked the unique sucking action of the healthy term infant.

Meier (2010) recommends mothers be given volume targets they should achieve during the first two weeks of pumping. During this initial phase of lactation, identification and treatment for insufficient milk volumes is critical. Meier (2010) refers to this transition period from Lactogenesis II to a milk volume sufficient for exclusive breastfeeding as "coming to volume." Providing target volumes helps identify pumping issues that need modification. Achieving *Ideal* pumped volumes of 750-1000ml per twenty four hours within the first two weeks after birth is correlated with adequacy of breast milk for the infant over the entire NICU stay.

Spatz (2004) and Meier (2007, 2010) also recommend mothers document daily pumping sessions and collected milk volumes in a journal or diary. Keeping a milk volume record enables mothers and clinicians to identify milk volume issues early so that interventions can by instituted to rectify any problems. Bedside clinicians are able to guide and support mothers' pumping efforts when they review the daily pumping logs with them.

Breast shields, the portion of the breast pump collection kit that comes in direct contact with the mother's breast, nipple and areola areas, require careful fitting to the mother's anatomy. A breast shield that is either too large or too small may cause injury to the mother or impede breast milk drainage leading to the eventual down regulation of a mother's milk supply. Meier (2010) recommends daily assessment of breast shield sizing during the two week "coming to volume" period. Zoppi [this author] (2011) refers clinicians to the use of an acronym; COMFY as a simple tool to emphasize criteria to correctly fit breast shields (Table 2). Zoppi recommends outfitting all breast pumps within the hospital setting with laminated cards detailing these fitting guidelines. Kent et al (2011) described an increase in efficiency of removing milk when breast shields were warmed before use.

Pumping directly at the infant's bedside instead of a designated pumping room provides the mother the opportunity to visit with her infant as she pumps (Meier 2007). The mother may find it more pleasurable to watch and even speak to her infant as she pumps. It also provides an opportunity for the bedside clinician to detect and correct any improper pumping technique used by the mother.

Another non-pharmacologic technique cited in the literature that enhances physiologic stability and breastfeeding behaviors of preterm infants in the NICU is skin-to-skin holding or kangaroo care. Numerous studies[2,13,14,16,31,32] have demonstrated that mothers were able to express significantly more milk after a skin-to-skin episode with their infant.

The next step in the lactation process for NICU mothers and their infants is nonnutritive sucking at the breast or tasting breast milk (Spatz (2004), Meier (2007). This is accomplished by having the mother position her infant skin-to-skin on her breast after she pumped her breasts. Tasting drops of breast milk during a scheduled gavage feeding allows the infant to associate breast milk with his feeding. Nonnutritive sucking can be initiated after the infant has been extubated. It has been shown to improve the transition to direct breastfeeding, shortens the period of pump dependency for mothers and is associated with longer breastfeeding rates.[33]

Summary

Breast milk is undeniably the best nutrition for premature infants. The process of initiating and maintaining adequate volumes of breast milk to meet the nutritional needs of the premature infant requires dedication from mothers and a commitment on the part of bedside clinicians to teach, support and provide up to date evidence on best practices. Many mothers find the challenges of pumping milk for their premature infants overwhelming. They struggle with many issues and have to overcome many obstacles to be successful. Yet many mothers find the process of milk expression for their preterm infants rewarding and empowering.[34]

Bedside clinicians can make a tremendous difference in the pumping experiences of pump dependent mothers challenged to provide expressed milk for their premature infants. Clinicians need to be knowledgeable about current best pumping practices and integrate them into the care they provide to pump dependent mothers.

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Does Chorionic Villus Sampling Increase the Risk of Echogenic Bowel?

Boris Petrikovsky, MD; Shilpa Monga, MD; Allan Klapper, MD; Christian Borberg, MD; William Huang, MD; Roseann Covatto, MD

Introduction

The reported incidence of echogenic bowel detected by antepartum ultrasound screening varies from 0.2% (30 out of 12776 fetuses)[1] to a little over 1%.[2] The causes are numerous and include certain pathological conditions such as ancephloiodes, cystic fibrosis[3] and fetal infections. In cases of cystic fibrosis, echogenic bowel is detected in 50-78% of the fetuses. Furthermore, echogenic bowel has been reported to be associated with cytomegalovirus and toxoplasmosis.[4] In addition, echogenic bowel has been seen in many fetuses with fetal growth restriction. Nyberg et al[5] reported a threefold increase in incidence of fetal growth restriction in fetuses with echogenic bowel.

Objective

To determine if there was an association between chorionic villus sampling (CVS) and the appearance of echogenic bowel.

Selection and Elimination Criteria

All patients who underwent CVS or amniocentesis due to either advanced maternal age (AMA) or prior genetic history were selected for participation in the study. Patients with an abnormal first trimester screen (nuchal translucency and/or serum screening), evidence of infection during the pregnancy, carriers of cystic fibrosis or other anomalies detected on antepartum screening were eliminated from the study. The study group consisted of patients who met the above inclusion and elimination criteria and were managed with CVS while the control group consisted of similar patient managed with amniocentesis.

Material and Methods

A total of 420 patients underwent CVS between 2006 and 2009 and were entered into the study. Of these patients, a total of 311 satisfied the inclusion and elimination criteria and comprised the study group. The control group consisted of 418 patients who underwent an amniocentesis at 16-18 weeks for AMA or prior genetic history during the same study period. All patients were evaluated for the presence of echogenic bowel between 18-21 weeks during their anatomy ultrasound.

A transcervical approach to CVS was performed on 133 patients while a transabdominal approach was performed on 178 patients. Vaginal bleeding was seen in 10% of patients who underwent a transcervical approach and none of the patients who underwent a transabdominal approach or those in the amniocentesis group. Echogenic bowel was defined as the presence of echogenic material in the bowel that was of similar or greater echogenicity to that of bone. All anatomy ultrasounds were performed using the same technicians and equipment (GE Voluson 730 or Phillips H7). All CVS and amniocentesis procedures were performed by the same maternal fetal medicine specialists (BP and WH). A Chi square test was used for statistical analysis.

Authors Petrikovsky, Monga and Huang are with the Department of Obstetrics and Gynecology, New York Downtown Hospital; Klapper, Borberg and Covatto are with the Department of Obstetrics and Gynecology, West Penn Allegheny Health System, Pittsburgh.

Complication

Vaginal bleeding was seen in 10% of patients with a transcervical CVS and none with a transabdominal approach or amniocentesis.

Results

The incidence of echogenic bowel in the control group of patients who underwent amniocentesis was 0.5%. The overall incidence of echogenic bowel in the study population was 1.6%. Although not statistically significant, the incidence of echogenic bowel in those patients who underwent a transabdominal CVS was 1.1%, while the incidence of echogenic bowel in the patients who underwent a transcervical CVS was 3%. There was no difference between transabdominal, transcervical or control group with regards to demographic criteria such as maternal age, gestational age and parity as well as antepartum complications such as preterm labor, miscarriage and preterm premature rupture of membranes.

Discussion

Although echogenic bowel has been associated with a number of antepartum anomalies including growth restriction, infections and genetic conditions, its association with chorionic villus sampling remains unclear. It is possible that invasive antepartum procedures such as CVS may lead to iatrogenic intraamniotic bleeding that is in turn swallowed by the fetus. This intracolonic blood may then be responsible for the echogenic appearance of the bowel on the subsequent anatomy ultrasound survey.

A number of studies support the hypothesis that CVS can lead to intramniotic bleeding. Quintero et al[6] report on 43 pts undergoing elective terminations who had transcervical endoscopy before and after CVS. They found that 20 out of 43 pts had placental and embryonic hemorrhagic lesions after the procedure.

Several studies support the hypothesis that intramniotic bleeding can lead to the echogenic appearance of fetal bowel. Sepulveda

et al[7] in 1996 demonstrated an association between fetal bowel echogenicity and amniotic fluid spectrophotometry at 410 nm (OD 410). In 104 pregnancies undergoing second trimester amniocentesis, an optical density suggesting the presence of heme was significantly more frequent in fetuses with echogenic bowel. In another study[8] by the same author involving 726 patients who underwent a second trimester amniocentesis for advanced maternal age, fetuses with blood stained intraamniotic fluid had a significantly higher incidence of fetal echogenic bowel compared to those with clear fluid. Furthermore, Petrikovsly[9] [this author] evaluated 28 fetuses with visible intraamniotic bleeding after intrauterine blood transfusions. Increased bowel echogenicity was detected within 12 hrs in 25% of these fetuses.

The exact mechanism for fetal bowel echogenicity after invasive procedures such as CVS remains unknown. A proposed mechanisms involves intraamniotic bleeding with resulting fetal swallowing, confirming the benign nature of this finding after invasive diagnostic procedures. Although not statistically significant, the higher incidence of echogenic bowel with transcervical CVS should be considered in counseling patients with echogenic bowel post CVS.

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The Use of a 100% Human Milk Diet in the Neonatal Intensive Care Unit

David Rechtman, MD

For the past two decades evidence has been accumulating that breast milk is protective for premature babies in the neonatal intensive care unit (NICU).[1,5] The data seem to show that infants who are fed breast milk have fewer infections and fewer complications than infants being fed formula. Over much of the same period, however, it has become less and less likely that an infant will exclusively be fed breast milk while on the unit. This is because cow milk-based formula is used when the mother runs short of milk. However, even when the mother has plenty of milk, cow milk-based fortifiers may be used to increase the nutritional density of milk to a level required by premature infants.

Human milk fortifiers (HMFs) must be used for extremely premature infants because although breast milk is the ideal form of nutrition for all infants – including the premature – it was never intended to support infants who may have missed all or part of their last trimester in the womb. Until the advent of the modern NICUs, these infants simply did not survive. The third trimester is a period of tremendous transfer of minerals, proteins and other nutrients from mother to fetus. If an infant is born prematurely it misses out on this transfer. In addition, the baby is now developing outside of the womb, where it requires more energy merely to survive, let alone grow, than it would have required in the womb. As a result, HMFs are used to increase the mineral, caloric and protein content of mother's milk to meet these additional nutritional needs.

Until very recently, all fortifiers were cow milk-based. Although representing a major advance in infant nutrition, these products were sub-optimal in the extremely premature infant for a number of reasons. One reason was that one could not provide enough protein to meet the theoretical needs of these infants. As a result, extremely premature infants tended to leave the hospital at the lowest 10% in terms of weight and length, even if they were born average for gestational age. In addition, use of the fortifiers was often associated with intolerance to feeds and other gastrointestinal complications including necrotizing enterocolitis (NEC).

In 2007, Prolacta Bioscience undertook a clinical trial of a new human milk-based HMF. This fortifier, which is produced from the donated milk of carefully screened mothers, allows premature infants to receive up to 4 1/2 g of protein per kilogram of body weight per day in addition to at least 120 and up to 150 or more calories per kilogram per day within the standard daily fluid allotments. The study was undertaken to determine whether the 100% human milk diet would have any clinical benefits when compared to the standard feeding regimen in premature infants; that is to say, a regimen consisting of mother's milk to start, premature infant formula to make up any shortfall in volume, and cow milk-based fortifier at the appropriate time. This remains the standard feeding regimen in many NICUs around the country.

It was hypothesized that the use of a 100% human milk diet would result in a seven-day reduction in the need for total parenteral nutrition, as well as a 30% decrease in the incidence of NEC. The study was conducted at 12 academic centers in the United States, and one center in Innsbruck, Austria. A total of 207 babies weighing between 500 g and 1250 g were enrolled.

The study employed three groups, two receiving an exclusive human milk diet and one control group receiving the standard regimen described above. The two human milk groups differed only at the point where fortification began: the first at the generally accepted time-point where fluid intake reached 100 mL per kilogram per day, and the other group where fluid intake reached 40 mL per kilogram daily. Fortification for the control group began at 100 mL per kilogram per day. The study followed babies until they left the NICU or they were taking 50% of their feedings from the bottle. A description of the study and the results was published in the Journal of Pediatrics in April 2010.[4]

Surprisingly, the results of this study did not show the expected seven-day decrease in TPN. In fact, no difference was seen between groups. However, a close inspection of the data revealed that roughly 82% of the nutrition by volume received by the babies in the control group was breast milk. This was a level much higher than had been seen in previous clinical trials, and was probably sufficient to wash out any difference in TPN usage that might otherwise have been observed. (Further analyses undertaken that seem to confirm this hypothesis are beyond the scope of this article.)

More surprising was the magnitude of the effect seen in the incidence of NEC, and even more so in the requirement for surgical intervention for NEC. The control group had an incidence of developing NEC of 15.9% (11/138,) while the combined human milk group had an incidence of 5.8% (8/69), a decrease of approximately 65%. Of the babies who developed

David Rechtman is Chief Medical Officer, Prolacta Bioscience. Prolacta Bioscience provided this article.

NEC in the control group, 7 out of 69 required surgery, while only 2/138 of those in the combined human milk group required surgery. This means that an infant who was fed the 100% human milk diet and developed NEC had an eightfold lower risk of requiring surgery than a baby who had been on the standard diet. There was also a meaningful decrease in the incidence of the combined endpoint of NEC or death. All of these findings were statistically significant.

Also of interest was the fact that for every 10 infants on the 100% human milk diet, one case of surgery for NEC was eliminated. And, for every eight babies fed the 100% human milk diet, either one case of NEC or one death would be avoided.

Following the publication of this data, more and more NICUs across the country have adopted the 100% human milk diet for their very premature infants. As the experience with a human milk diet has increased, various institutions have reported publicly on the results they are seeing with its use.

At the NEO conference held in Orlando, FL in February 2011, the group from Baylor Children's Hospital showed a slide illustrating similar results. The Baylor researchers revealed that their NEC incidence rate had decreased from about 11% in 2007 to 0% for infants participating in the clinical trial in 2008, and stabilized at about 1 1/2% in the years subsequent to the completion of the trial.

At the November 2011 conference of the Academy of Breastfeeding Medicine, the Mednax group in Fort Worth, TX reported that in the nine months since they switched their premature infants to a 100% human milk diet, they treated 84 extremely premature infants and saw their NEC incidence rate drop from 16% to 4.8%, while their surgical intervention rate dropped from 10% to 2.4%. Other reports in nonpublic settings have also demonstrated similar changes following institution of the 100% human milk diet.

A separate study by the pharmaco-economics group at the University of Southern California, published in Breastfeeding Medicine[6] showed that by decreasing the incidence of NEC and the necessity for surgical intervention, this feeding regimen is also saving healthcare dollars. The investigators found that based on hospital costs obtained from the state of California, if all infants born between 500 g and 1250 g were fed the 100% human milk diet, there would be a savings of approximately $8000 per each extremely premature infant, compared to the standard feeding regimen based on the results of the clinical trial described above.

Adoption of the 100% human milk diet for extremely premature infants has been clinically proven to improve outcomes in these babies, thereby saving the health care system badly needed dollars. Not a bad outcome from simply choosing to feed infants with what the American Academy of Pediatrics has called the ideal source of nutrition for infants.[7]

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Best Practice Checklist – Oxygen Management for Preterm Infants

Mitchell Goldstein, MD; Augusto Sola, MD

This document refers mainly to infants with birth weight < 1,750 grams; < 32-34 weeks gestation and < 4-8 weeks of postnatal age, with the need for supplemental oxygen and with one or more of the following conditions:

Indications for supplemental oxygen

- ☐ Need for delivery room resuscitation
- ☐ Respiratory distress syndrome
- ☐ Air leak
- ☐ Pulmonary edema
- ☐ Pneumonia
- ☐ Atelectasis
- ☐ Chronic lung disease
- ☐ Other non respiratory conditions: _____

Equipment

- ☐ Pulse Oximeter
  - ☐ Utilize a pulse oximeter that will monitor through infant motion and low perfusion to minimize SpO_2 false alarms and detect true SpO_2 values
- ☐ Suggested Alarm and operational settings
  - ☐ Low SpO_2 limit = 86%, high S SpO_2 limit = 93-94% (or up to 95% in larger VLBW infants)
- ☐ Sensor
  - ☐ Use appropriate adhesive sensor for patient size
  - ☐ Clean sensor site
  - ☐ Turn monitor on to ensure operational and confirm alarm and sensitivity settings
  - ☐ Connect sensor to patient cable, then to the patient, and begin monitoring
  - ☐ Whenever the sensor is to be moved it should be disconnected from the cable, moved and then reconnected to the cable
  - ☐ Sensor should only have power when it is connected to a patient
- ☐ Oxygen blender
  - ☐ Confirm readily available, operational and connected to a reliable oxygen and air source

Therapy, Titration and Monitoring

- ☐ In all circumstances, aim to avoid hyperoxia, hypoxia and periodic cycles of hyperoxia/hypoxia
- ☐ Based on current literature and evidence, targeted SpO_2 for preterm infants receiving supplemental oxygen should be 87-89% as a minimum and 93-95% as maximum after about 10 minutes of life:
  - ☐ Aim to avoid SpO_2 levels > 95% and < 87%
  - ☐ Infants > 32 weeks gestation SpO_2 = target 87% - 95%
  - ☐ Infants ≤ 32 weeks gestation SpO_2 = target 87% - 93%
- ☐ Based on current available evidence, hyperoxia must also be avoided during the first 10 minutes of life in the delivery room
  - ☐ Use the SpO_2 monitor and have available "guiding" parameters (see table)
  - ☐ If the SpO_2 is low, initiate oxygen at FiO_2 of 30% and then titrate FiO_2 according to SpO_2 levels
- ☐ If the SpO_2 is below the 10th percentile for postnatal age, the FiO_2 should be increased until the SpO_2 reaches at least the 10th percentile
- ☐ If there is no improvement in SpO_2 or the heart rate falls, recheck ventilation strategy and then increase FiO_2 until SpO_2 stabilizes betweenthe10th and 90th percentile
- ☐ If when providing oxygen in the delivery room SpO_2 is > 90th percentile for postnatal age or > 92%, reduce the FiO_2 until the SpO_2 is < 90 th percentile or < 92%

Guide for normal SpO_2 during transition (10 first minutes of life)	
Posta natal age (minutes)	SpO_2 (%)
1	55-65
2	65-70
3	70-75
4	75-80
5	80-85
10	85-95

Alarms and Assessments

- ☐ Do not disable alarms
- ☐ Evaluate infant and pulse oximeter signal quality and perfusion index before changing FiO_2
- ☐ If SpO_2 < 85-86%
  - ☐ Is the heart rate > 100bpm?
  - ☐ What are respiratory parameters (on respirator)?
  - ☐ Is the respiratory effort good?
  - ☐ Is the pulse rate in the targeted range?
  - ☐ How low is the SpO_2 and for what period of time has it been below acceptable values?
- ☐ If SpO_2 > 93-94%
  - ☐ Was FiO_2 increased recently?
  - ☐ Is the baby clinically improving?
  - ☐ Was surfactant administered recently?

Weaning FiO_2 to Target SpO_2 Levels

Delivery, Transport, and NICU

- ☐ In delivery room and during transport to NICU after 10 minutes of life, if SpO_2 high, wean FiO_2 as rapidly as possible, observing the changes in SpO_2 (using a target range 87% - 95%)
- ☐ In NICU, if SpO_2 is high, gradually wean FiO_2 incrementally by 2%-5% at a time

During Procedures (ie Airway Suctioning)

- ☐ Do not increase FiO_2 to "pre-oxygenate"
- ☐ Adjust FiO_2 in conjunction with:
  - ☐ Transient increase in positive end-expiratory pressure (PEEP)
  - ☐ Consider transient increase in ventilator rate
  - ☐ Do not increase FiO_2 as only action to avoid hypoxia in these situations
  - ☐ If FiO2 was increased, do not leave FiO_2 above baseline value

During Apneic Spells And Spontaneous Desaturations

- ☐ Treat according to severity
- ☐ In general, use gentle tactile stimulation
- ☐ In general, the same FiO_2 setting that the infant was receiving before the episode should be used during and after the episode to avoid significant hyperoxemia as soon as breathing resumes
- ☐ If infant not on ventilator, consider non-invasive ventilation or intubation if non-invasive ventilator is ineffectual
- ☐ If infant is on respirator: Increase respiratory rate, or if no response increase respiratory parameters

Charting

- ☐ When infant and SpO_2 are reliable at constant FiO 2: record that FiO_2 as the baseline
- ☐ If infant is weaned, wait until SpO_2 has stabilized in targeted range before leaving bedside and record new SpO_2 reading and FiO_2 setting
- ☐ When a change is made, the change and reason for the change should be charted

Duration of oxygen management: Continue until 4 to 8 weeks or longer after birth, depending on duration of oxygen therapy, gestational age at birth and retinal vascular maturity

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Mitchell Goldstein is Associate Professor, Pediatrics, Loma Linda University Children's Hospital, Loma Linda, CA; Immediate Past President of the National Perinatal Association, Chair Oxygen Administration Guidelines Committee. Augusto Sola, MD is President Elect, Ibero-American Society of Neonatology (SIBEN); National Perinatal Association Board Member, Oxygen Administration Guidelines Committee. The authors would like to acknowledge contributions and suggestions for this final document from: Ronald Goldberg, Max Vento, Ola Saugstad, Eduardo Bancalari and Hernando Baquero. This information was published in a slightly different form by the National Perinatal Association. This Best Practice Checklist is based on current literature and available evidence. It is educational in nature and is not intended to replace practice guidelines or individual clinician preference. Always consult the currently available guidelines and evidence prior to implementing any protocol or checklist into clinical practice.

Bradycardia and Apnea of Prematurity: Nature or Nurture?

Yamile Jackson, PhD, PE, PMP

At any given time in the history of medicine, there are many medical conditions that are considered unavoidable and are the result of the baby's premature birth. Others are preventable by providing the best possible developmentally supportive habitat to the baby in the NICU.

Through research we create new understandings of phenomena, with the goal of finding ways to minimize the negative consequences of the "nature" of being born prematurely. Often the results of research find that there are conditions that can be reversed, and that , by practicing evidence-based developmentally supporting care, can lessen, or even prevent – without the need for expensive equipment, invasive procedures, or medication. I call it "nurture."

Here are some examples:

- Preemies have undeveloped organs and systems (nature), so we work to provide the appropriate habitat to provide the best possible physical, psychological, physiological, and neurological development, including the effective inclusion into the family (nurture.)
- Preemies are born with underdeveloped skeletal structure (nature), so we now know how to successfully prevent plagiocephaly/flat head caused by poor positioning (nurture.)
- Preemies no longer feel the sense of protection provided by the womb (nature), so we simulate it (to the best of our ability) by providing proper lighting, sound protection, minimal disruptions, proper positioning, boundaries, containment, closeness to the mother, and we introduce the father as an effective source of sense of security and comfort (nurture.)

I don't have a medical background. I have a PhD in ergonomics engineering and for a decade have been the leader in applying ergonomic principles and best practices to improving the morbidity and habitat of convalescent infants, especially those in the NICU. By definition, "Ergonomics (or human factors) is the scientific discipline concerned with the understanding of interactions among humans and other elements of a system, and the profession that applies theory, principles, data and methods to design in order to optimize human well-being and overall system performance. Practitioners of ergonomics, ergonomists, contribute to the planning, design and evaluation of tasks, jobs, products, organizations, environments and systems in order to make them compatible with the needs, abilities and limitations of people."[1]

As an ergonomist, as an engineer, and as the mother of a former preemie, I work with NICU staff and families and acquire evidence-based knowledge to continuously enhance the standard of care during the stay NICU so that we can give the babies and families a chance for the best possible quality of life, not only in the hospital but for a lifetime.

My son was born prematurely in 2001 in Houston, Texas where I have resided since 1988. Everything about having a preemie felt unnatural and foreign to me, except Kangaroo Care (KC). I was born and raised in Bogota, Colombia, and I had heard about Kangaroo Mother Care because the method was first born in my city in 1978. According to the US Institute for Kangaroo Care (USIKC), "Kangaroo Care, Skin-To-Skin Contact, and Kangaroo Mother Care are terms that relate to the holding of a diaper clad infant bare-chest to bare-chest, ventral-surface to ventral-surface by the mother, father, or others." [2]

I appreciate very much the existence of the NICU for saving Zachary's life; however, it was not a place I dreamt about when I was pregnant. In fact, I don't wish anyone to go through what we went through. My reality was that I was in the NICU for 155 days watching my son struggling to survive, holding on to his every breath. His cry broke my soul and I heard it loud and clear even when he couldn't make any sound.

After a "mourning" period for not having a healthy pregnancy, and the guilt of getting better while he was getting worse (I had preeclampsia), I had to be strong for him. One of my biggest challenges was to learn how to combine my maternal instinct with ergonomics in understanding my son's limitations and his interaction not only with me, but also with the NICU staff, the equipment, and with his own environment (on the bed/incubator/Kangaroo Care).

My son, like the majority of extremely low birth weight preemies, had bradycardia and apnea of prematurity. Uncountable times I heard the alarms go off and saw (and learned) how he had to be "reminded" to breathe by touching him. Every nurse and doctor told me, "it is normal for preemies to have apnea and bradycardia and they will resolve as Zachary grows."

Many clinical factors including recurrent apnea and bradycardia, as well as stressful environmental conditions, including infant-

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provider interaction, constant noise, and bright light, may act in combination to impact on the developing brain, even in the absence of overt hemorrhage and/or ischemia.[3]

One of the consequences of brain development is that apnea and bradycardia contribute to the infant's sleep deprivation. Nurses spend a significant amount of time monitoring, assessing, and managing apneic and bradycardic episodes, given that nearly all ELBW infants experience them.[4]

Here is how I see it:

1. Preemies need to sleep. Only while in REM sleep do babies develop sensory systems: somasthetic (touch), kinesthetic (motion), proprioception (position), chemosensory (smell and taste), auditory (hearing), vision, limbic (emotion), social learning, and hippocampus (memory).[5] A presentation by Drs Stan and Michael Gravens in Vienna in 2008 explained that "sleep is necessary for: neurosensory development, preservation of brain plasticity, and learning and long-term memory." They explained that REM Sleep Deprivation leads to: 1. Disordered sensory system- infants, 2. Disordered or disrupted learning and memory creation, 3. Loss of cortical plasticity into adult life, and 4. Smaller adult brain size. Non REM Sleep Deprivation Leads to: 1. Decreased learning and memory consolidation from sensory experiences (vision, hearing and touch). 2. Less ability to learn in childhood and adult life. 3. Loss of brain plasticity into adult life, and 4. Smaller adult brain size."

2. If preemies have apnea/bradycardia, we wake them up. Clinical interventions for apnea include tactile stimulation, provision of thermoneutral environment, methylxanthine therapy, continuous positive airway pressure or ventilatory support.[6,7]

Stimulants such as caffeine that are considered drugs, since they cause difficulty sleeping, increase of heart rate, etc. Methylxanthines (theophylline and caffeine) have been used for almost four decades to treat apnea of prematurity.[8] These medications are successful in decreasing the episodes of apnea/bradycardia but they may be causing sleep deprivation.

3. If babies don't sleep, they don't develop their brains. Apnea/bradycardia usually resolve as the baby grows;[9] however, these events don't allow babies to fall or stay asleep and any negative consequences from lack of sleep may never be outgrown.

4. There is evidence that episodes of apnea and bradycardia can be reduced. Evidence shows that during Kangaroo Mother Care Method (KMC) preemies sleep significantly better than in the incubator/bed.[10] Several studies have been done about apnea and bradycardia during KMC and some results show a decrease or even an absence of these life-threatening events while using Kangaroo Care.[11] Also, control studies of intubated infants who have been given 1 to 2 hours of KC have shown among other benefits, fewer apnea and bradycardia spells[12] and fewer or no desaturation events.[13]

Kangaroo Care is still in its infancy in the US. Unfortunately, parents in the US do not kangaroo 24/7 as they do in Sweden. Often and for many reasons, parents are not available, they don't know about KMC, and/or the baby is not "stable" enough to be held. Those babies still need an ergonomic habitat and my job is to use my personal and professional experience and my education to provide it.

Yamile C. Jackson (Ph.D. in ergonomics and human factors engineering, a licensed Professional Engineer, and a certified Kangaroo Care Professional) founded Nurtured by Design, Inc, the global leader in neonatal ergonomics, developmental care, and Kangaroo Care. Yamile designs ergonomic devices that effectively facilitate evidence-based developmental care around the clock while engaging the parents' natural instincts to nurture and heal: The Zaky and the Kangaroo Zak. She is also one of the facilitators of the Kangaroo Care Certification Course offered by the United States Institute for Kangaroo Care (USIKC) since 2010. For her work and inventions, Yamile has won over 16 awards including "Groundbreaking Latina Entrepreneur of the Year" by Catalina Magazine, "Outstanding Woman-Owned Small Business of the Year" by the SCORE Foundation, "Ultimate Latina Award - Health Category" by the US Hispanic Chamber of Commerce, and was a finalist for the Institute of Industrial Engineers' "Creativeness in Ergonomics Practitioner of the Year Award." Zachary's story of survival and/or the products have been featured in national and international media and served as inspiration for the made-for-TV movie called "14:Hours" aired on TNT in 2005. Visit www.nurturedbydesign.com for more information. Yamile's email is yamile@nurturedbydesign.com.

A recent independent randomized control trial about the effectiveness of simulating maternal intervention was presented at the American Public Health Association's (APHA) Annual Meeting. The results: Infants receiving the maternal simulated intervention device had fewer episodes of apnea/bradycardia ($p < 0.05$).[14] The group using the maternal simulation intervention device that was maternally scented experienced zero apnea and zero bradycardia events.[15]

That leads me to my question:
If all the current literature and experts explain that apnea/bradycardia is caused by *nature* (the immaturity of the brain, heart, and respiratory systems), why is it that we can see an improvement when the baby is in Kangaroo Care or when we simulate the mother's intervention (*nurture*)? After all, the baby's circulatory, respiratory, and nervous systems are just as developed when the baby is in the incubator as they are when the infant is transferred to Kangaroo Care.

I, like you, cannot ignore the evidence that preemies respond differently during diverse environmental conditions (Kangaroo Care/Maternal Simulation vs incubator/bed). With more research we can prevent and/or lessen apnea and bradycardia of prematurity, move preemies from the category "nature" to "nurture," and elevate the standard of care in NICUs.

My "call to arms" for neonatal professionals is to work together to give preemies an ergonomic, nurturing and most effective and developmentally supportive care: an individualized environment with high interaction of the parents, which promotes and understands the importance of sleep.

Let's increase parental involvement and Kangaroo Care and allow parents to work with you to reduce the episodes of apnea and bradycardia. Having a positive impact in each baby's neurological development has the potential to decrease the cost of healthcare/therapy/etc, reduce the time spent dealing with episodes of apnea/bradycardia, reduce the alarms and sound

levels of the NICU, and improve the quality of life not only of the infant, but also of the family and society at large.

Imagine how you will feel when together we significantly decrease or even eradicate apnea and bradycardia of prematurity. May I count you in?

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High-Frequency Oscillatory Ventilation and Short-Term Outcome in Neonates and Infants Undergoing Cardiac Surgery

Mirela Bojan, Simone Gioanni, Philippe Mauriat, Philippe Pouard

Abstract

Introduction: Experience with high-frequency oscillatory ventilation (HFOV) after congenital cardiac surgery is limited despite evidence about reduction in pulmonary vascular resistance after the Fontan procedure. HFOV is recommended in adults and children with acute respiratory distress syndrome. The aim of the present study was to assess associations between commencement of HFOV on the day of surgery and length of mechanical ventilation, length of intensive care unit (ICU) stay and mortality in neonates and infants with respiratory distress following cardiac surgery.

Methods: A logistic regression model was used to construct a propensity score, which accounted for the probability of being switched from conventional ventilation to HFOV, and included baseline characteristics, type of procedure and postoperative variables. It was used to match each patient in the HFOV group with a control. Length of mechanical ventilation, ICU stay and mortality rates were compared in the matched set.

Results: Overall 3549 neonates and infants underwent cardiac surgery from January, 2001 through June, 2010, and 120 were switched to HFOV. After matching and adjustment for delayed sternal closure, duration of renal replacement therapy, pulmonary hypertension and year of surgery, the probability of successful weaning over time was significantly higher in the HFOV group, adjusted hazard ratios and 95% confidence intervals (CI): 1.63, 1.17 to 2.26 (P = 0.004). The probability of ICU delivery over time was significantly higher in the HFOV group, adjusted hazard ratios and 95% confidence intervals: 1.65, 95% CI 1.20 to 2.28 (P = 0.002). No association was found with mortality.

Conclusions: When commenced on the day of surgery, HFOV was associated with shorter lengths of mechanical ventilation and ICU stay in neonates and infants with respiratory distress following cardiac procedures.

Introduction

High-frequency oscillatory ventilation (HFOV) is an established treatment for acute respiratory distress in preterm neonates. However, there is no evidence that it improves outcome in term or near-term neonates with pulmonary disease.[1] HFOV is considered as a rescue therapy in children with severe acute respiratory distress syndrome (ARDS), but to date there is lack of evidence to support it.[2,3] HFOV is also used to achieve lung recruitment and improve oxygenation when recruitment maneuvers have failed, as part of the "open lung" and lung protective ventilation strategies in adults with severe ARDS, and early initiation of HFOV has been associated with improved outcome.[4-6] Mild acute lung injury occurs in 12% of adults following CPB, and more severe lung injury, indistinguishable from ARDS, in 0.4%,[7,8] as a result of accumulation of excessive extrapulmonary lung water, decreased lung compliance, atelectasis and increased shunting.

Experience with HFOV following cardiac surgery is limited, due to concerns about hemodynamic impairment in animal and human studies.[6,9-13] However, HFOV has been associated with a significant reduction in pulmonary vascular resistance (PVR) after the Fontan procedure in children.[14] Thought to be beneficial upon gas exchange and PVR, the present authors have used HFOV in neonates and infants with respiratory distress following cardiac surgery since January, 2007. The aim of the present study was to assess associations between commencement of HFOV on the day of surgery (day 0) and the length of mechanical ventilation and intensive care unit (ICU) stay, and mortality in this population.

Materials and methods

This retrospective cohort study was conducted at the Necker University Hospital in Paris, France. It was reviewed and approved by the Ethics Committee of the French Society of Thoracic and Cardiovascular Surgery, which waived the requirement for consent to use anonymized records. All parents had provided informed consent to surgery.

Records of all neonates and infants who underwent cardiac surgery between January 1, 2001 and June 30, 2010 were reviewed, patients switched to HFOV on the day of surgery (day 0) were identified as the HFOV group. Those switched to HFOV after day 0, as a rescue therapy, were not analyzed. The remaining patients were included in the control group. Data for each patient were extracted retrospectively from a prospective database, which is updated daily by clinical staff. These concerned: demographics, surgical and cardiopulmonary bypass (CPB) techniques, short-term outcome variables

Authors Bojan, Gioanni and Pouard are with the Anesthesiolgy and Critical Care Department, Necker-Enfants Malades Hospital, Assistance Publique-Hôpitaux de Paris; Mauriat is with the Anesthesiolgy and Critical Care Department, Haut-Lévêque Hospital, 1 avenue de Magellan, Pessac, France.
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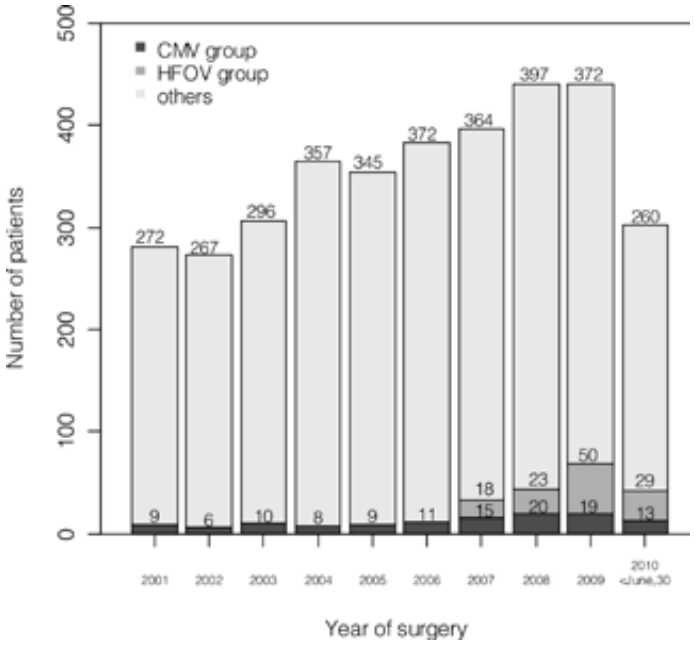

Figure 1. Number of neonates and infants who underwent surgery during the study period. The number of patients included in each group after matching is shown on the bottom of each column. High frequency oscillation was used since 2007. CMV, conventional mechanical ventilation; HFOV, high-frequency oscillatory ventilation.

accounting for the severity of the postoperative illness, such as re-operation, delayed sternal closure, extracorporeal membrane oxygenation (ECMO), acute kidney injury requiring renal replacement therapy (RRT), and hospital-acquired pneumonia, length of mechanical ventilation, length of ICU stay, and inhospital mortality.[15] Normothermic CPB with intermittent warm blood cardioplegia was performed in every patient during the study period, except in cases where deep hypothermic circulatory arrest (DHCA) was indicated.[16] Pulmonary arterial pressure was measured in every patient, either continuously by a catheter inserted into the pulmonary artery by the end of surgery, or by serial echocardiography. Persistent pulmonary hypertension was noted whenever it occurred during the postoperative course, and inhaled nitric oxide was administered.[17]

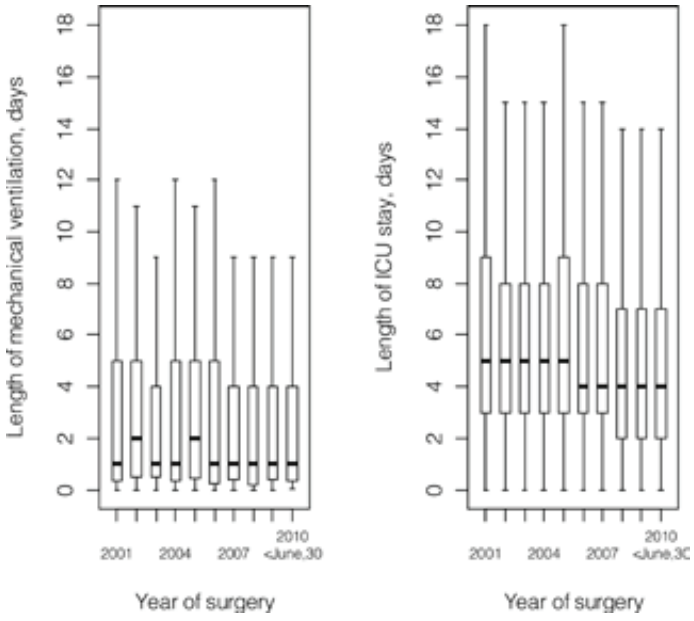

Figure 2. Length of mechanical ventilation and Intensive Care Unit stay across the study period. The median values and the inter-quartile ranges were used to construct the boxes. 10th and 90th percentiles are given as whiskers. Outliers are not shown. ICU, Intensive Care Unit.

All patients were initially commenced on pressure controlled conventional mechanical ventilation (CMV) using a SERVO-300 (Siemens – Elema AB, Sweden) before 2002, then a SERVO-i ventilator (Maquet GmbH&Co. KG, Rastatt, Germany). This was set to provide a positive end expiratory pressure of 2cmH_2O, a tidal volume of 6-8ml Kg-1, and a fraction of inspired oxygen which was dependent upon the underlying cardiac disease. In the event of severe respiratory failure, recruitment maneuvers by stepwise increase in the mean airway pressure were applied. The patients were switched to HFOV when hypoxemia and acidosis occurred despite increasing alveolar ventilation on CMV, when the tidal volume exceeded 10ml kg-1, or when there was evidence of pulmonary hypertension and right ventricular failure. The decision to switch was made by the attending intensivist. A SLE 2000 or a SLE 5000 HFO ventilator (SLE Ltd, South Croydon, UK) was used. This was set to a mean airway pressure (Paw) of 12cmH_2O, an inspiratory to expiratory ratio of 33%, and an oscillation frequency of 8Hz. Amplitude was adapted to achieve adequate chest wall vibrations. All parameters were adjusted to achieve optimal inflation, a $PaCO_2$ of 35-45mmHg and a pH >7.35. The adequacy of the PaO_2 level was judged according to the underlying cardiac disease. Patients were switched back to CMV when these conditions had been achieved with an oscillation frequency ≥ 10Hz and a mean Paw ≤ 10cmH_2O. Sedation was achieved through a continuous infusion of midazolam and morphine. Whenever possible, muscular relaxants were avoided and spontaneous breathing was maintained. Catecholamine support (milrinone and epinephrine), fluid support and diuretics were administered as appropriate to achieve hemodynamic stability and a negative fluid balance. All patients were weaned from mechanical ventilation when the underlying indication had resolved and following a successful 1-hours trial of spontaneous breathing with a continuous positive pressure of 2cmH_2O and a pressure support of 10cmH_2O.

Statistical analysis

After testing for normality, baseline characteristics of the two groups were compared using Student's t or Mann-Whitney tests for continuous variables and $\chi 2$ or Fisher's exact tests for categorical variables.

The hypothesis tested was that patients switched to HFOV had shorter length of mechanical ventilation and ICU stay and lower mortality rates. To control for the bias due to selection of patients switched to HFOV, 1:1 propensity score matching was carried out.[18] Logistic regression was used to develop a propensity score quantifying the probability for each patient undergoing surgery since January 2007 to be switched to HFOV. This included all baseline and post-operative variables accounting for severity of illness found to be different between groups in univariate analysis ($P < 0.10$), and the HFOV index. Given the large number of surgical procedures and the absence of guidelines for HFOV in this context, an empirical HFOV index was attributed to each procedure. This accounted for the influence of each specific procedure on the probability to be switched to HFO, and was calculated as the prevalence of HFOV per procedure between January 2007 and June 2010.

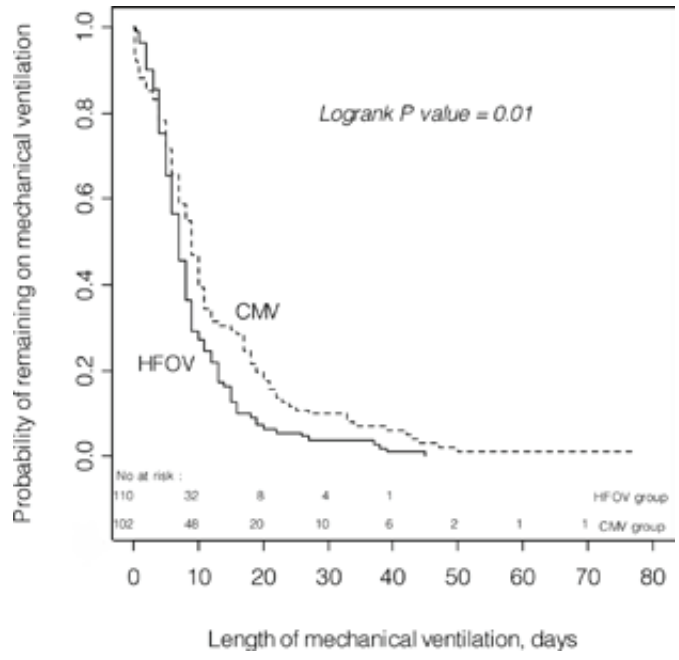

Figure 3. Kaplan-Meier plots of the probability of successful weaning over time for each ventilation group. The median length of mechanical ventilation was 7 days in the high-frequency oscillatory group, inter-quartile range 5 to 11, and 9 days in the conventional mechanical ventilation group, inter-quartile range 5 to 17, logrank test = 6.18, P = 0.01. CMV, conventional mechanical ventilation; HFOV, highfrequency oscillatory ventilation.

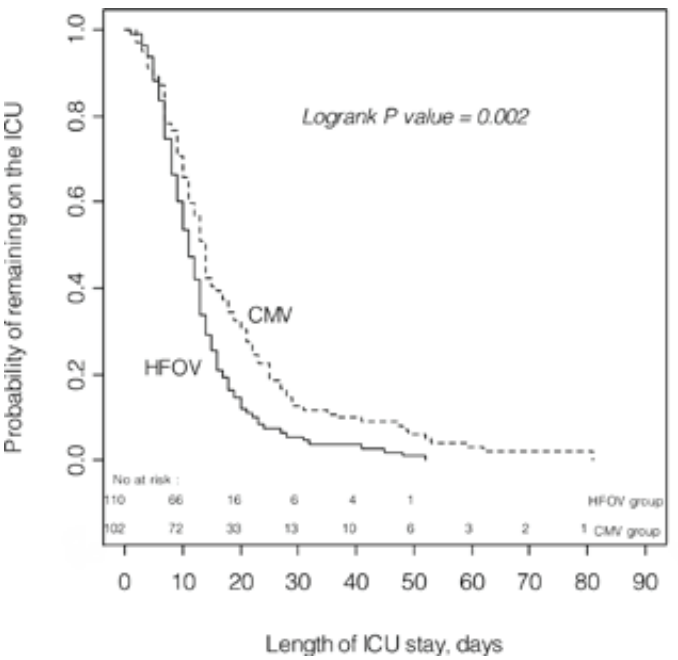

Figure 4. Kaplan-Meier plots of the probability of ICU delivery over time for each ventilation group. The median length of ICU stay was 11 days in the high-frequency oscillatory ventilation group, inter-quartile range 7.2 to 15.7 compared with 14 days in the conventional mechanical ventilation group, inter-quartile range 9 to 22, logrank test, 9.39, P = 0.002. CMV, conventional mechanical ventilation; HFOV, highfrequency oscillatory ventilation.

In accordance with previous authors, length of mechanical ventilation and length of ICU stay were modeled as censored variables in survivors, with weaning from mechanical ventilation and ICU delivery as censoring events.[19] The probability over time of successful weaning from mechanical ventilation and of ICU delivery for each group was calculated using the Kaplan-Meier method, and compared using the log-rank test. Results were confirmed using a multivariable Cox proportional-hazards model, controlling for variables related to length of ICU stay following pediatric cardiac surgery in a previous study,[20] variables unbalanced after matching (P < 0.10), for the propensity score and the year of surgery. Adjusted Hazard ratios (HR) were estimated.

The R statistical package, "Design" and "optmatch" libraries[21] were used for the analyses.

Results

Overall 3549 neonates and infants with cardiac surgery were retrospectively enrolled. Life support was withdrawn from four patients with obstructed total anomalous pulmonary venous connection and one patient with severe pulmonary hypoplasia, with hopeless prognosis secondary to pulmonary lymphangienctasia. Another two patients died periprocedural, leaving 3542 cases to be analyzed. The number of patients, their length of mechanical ventilation and ICU stay across the study period are shown in Figures 1 and 2.

Patient characteristics are shown in Table 1. The 120 neonates and infants switched to HFOV on day 0 were younger and smaller, had undergone more complex surgery and had experienced more severe postoperative illness. Patients switched to HFOV had longer durations of both mechanical ventilation, median 7 days, inter-quartile ranges (IQR) 5-11 vs. 1 day, IQR 0.3-4 in controls (P < 0.001), and ICU stay, median 11 days, IQR 7-15.7 vs 4 days, IQR 3-7 (P < 0.001). The median duration of HFOV was 4 days, IQR 2-7. The inhospital mortality rates for the two groups were similar, 8.3% in patients switched to HFOV vs 4.8% in controls (P = 0.08).

Table 2 shows the most prevalent procedures and their HFOV indexes, range 0 - 0.82, median 0.04, IQR 0.03 - 0.08. Table 3 shows the variables included in the propensity score. When data was missing, the median of the respective variable was used (< 5% of all information concerning CPB technique was missing). The propensity score model was well calibrated (Hosmer Lemeshow test, P = 0.14) and discriminated well between patients on HFOV and the others (c index = 0.82). Patients were more likely to be switched to HFOV on day 0 if they were small, had undergone a procedure with high HFOV index, required CPB and DHCA, had hemodynamic impairment precluding closure of the sternum or required RRT on day 0. Patients commenced on postoperative ECMO were not matched due to their high mortality rate (39.1%).

Matching resulted in two well-balanced groups of 120 patients respectively: the HFOV and the CMV groups (Table 1). The HFOV group had shorter durations of mechanical ventilation, 7 days, IQR 5 - 11 vs 9 days, IQR 5 - 17 in the CMV group (P = 0.03), shorter durations of ICU stay, 11 days, IQR 5 - 17 vs 14 days, IQR 9 - 22 (P = 0.009), a higher prevalence of pulmonary hypertension, 36.7%, compared to 23.3% (P = 0.03) and a similar prevalence of hospital-acquired pneumonia, 49.2% in the HFOV group compared to 47.5% in the CMV group (P = 0.80). Ten patients in the HFOV group (8.3%) died during ICU stay, compared to 18 in the CMV group (15.8%) (P = 0.08). Median follow-up was 411 days, IQR 32-3060, 18 patients (15.8%) died during follow-up in the HFOV group, compared to 22 in the CMV group (18.3%) (P = 0.66).

Table 1 Perioperative patient characteristics before and after matching

	Before matching			After matching	
	HFOV group (*n* = 120)	Overall controls (*n* = 3,422)	*P*-value[a]	CMV group (*n* = 120)	*P*-value[b]
Age (days)	27, 7.7 to 100.2	58, 10 to 149	0.001	33.0, 7.0 to 89.5	0.83
Weight (kg)	3.4, 2.9 to 4.3	3.9, 3.2 to 5.4	< 0.001	3.3, 2.8 to 4.2	0.93
Surgery with cardiopulmonary bypass, n (%)	109 (90.8)	2560 (74.8)	< 0.001	110 (91.7)	0.80
Duration of cardiopulmonary bypass (min)	128.0, 99.5 to 177.0	109.0, 77.0 to 134.0	< 0.001	128.0, 90.0 to 165.0	0.64
Conventional ultrafiltration rate (mL kg^{-1} h^{-1})	93.3, 69.9 to 120.6	96.6, 66.9, 132.3	0.27	98.3, 87.2 to 127.3	0.40
Aristotle score[c]	9.0, 7.5 to 10.8	8, 6 to 10	< 0.001	9.0, 7.3 to 10.8	0.99
Surgery with deep hypothermic circulatory arrest, n (%)	19 (15.8)	251 (7.3)	< 001	21 (17.5)	0.72
Re-sternotomy, n (%)	19 (15.8)	406 (11.9)	0.19	16 (13.3)	0.59
Requiring re-operation, n (%)	13 (10.8)	177 (5.2)	0.007	16 (13.3)	0.56
Re-operated within 48 hours, n (%)	3 (2.5)	18 (0.5)	0.03	2 (1.7)	0.66
Extracorporeal membrane oxygenation, n (%)	0	23 (0.7)		0	
Requirement for delayed sternal closure, n (%)	56 (46.7)	331 (9.7)	< 0.001	57 (47.5)	0.85
Delay to sternal closure (days)	3, 2 to 4.2	4, 2 to 6	0.21	4, 3 to 7	0.08
Acute kidney injury requiring renal replacement therapy, n (%)	42 (35.0)	127 (3.7)	< 0.001	39 (32.5)	0.58
Requirement for renal replacement therapy on the day of surgery, n (%)	37 (30.8)	89 (2.6)	< 0.001	32 (26.7)	0.36
Duration of renal replacement therapy (days)	2, 1 to 4	3, 2 to 6	0.02	3, 2 to 7	0.09
The propensity score	0.07, 0.02 to 0.31	0.02, 0.01 to 0.03		0.07, 0.02 to 031	

The "HFOV group" included all patients switched to high frequency oscillation on the day of surgery, "Overall controls" included all patients ventilated exclusively conventionally during the study period, and the "CMV group" included the patients ventilated exclusively conventionally in the matched set.

CMV, conventional mechanical ventilation; HFOV, high-frequency oscillatory ventilation.

[a]calculated before matching, using unpaired tests which compared the HFOV group with overall controls

[b]calculated after matching, using paired tests which compared the HFOV group with the CMV group

[c]accounting for the surgical complexity

Data are shown as medians and inter-quartile ranges, or as numbers and percentages.

Kaplan-Meier plots of the probability of successful weaning over time are shown in Figure 3. The median length of mechanical ventilation was 7 days in the HFOV group, IQR 5- 11, and 9 days in the CMV group, IQR 5 - 17 (P = 0.01). Four patients in the HFOV group underwent mechanical ventilation for ≥ 30 days. Of these, one developed tracheal stenosis and underwent slide tracheoplasty, another required tracheostomy. Ten patients in the CMV group underwent mechanical ventilation for ≥ 30 days. Of these, two developed tracheal stenosis, one of whom died, one developed oeso-tracheal fistula and died, and seven developed chronic lung disease, of whom four required tracheostomy and two died. Kaplan-Meier plots of the probability of ICU delivery over time are shown in Figure 4. The median length of ICU stay was 11 days in the HFOV group, IQR 7.2 - 15.7 and 14 days in the CMV group, IQR 9-22 (P = 0.002). Differences between length of ventilation and ICU stay were found significant with a statistical power of 0.77 and 0.89 respectively.

Cox proportional-hazards regression analysis, adjusted for the delay to sternal closure, duration of RRT, occurrence of pulmonary hypertension and year of surgery, showed that patients in the HFOV group had a higher probability of successful weaning over time, adjusted HR 1.63; 95% confidence interval (CI) 1.17 - 2.23 (P =0.004) (Table 4). The probability of ICU delivery over time was also higher in the HFOV group, adjusted HR 1.65, 95% CI 1.20 - 2.28 (P = 0.002) (Table 4). Longer delay to sternal closure was independently associated with longer length of mechanical ventilation and ICU stay.

Discussion

The present study reports experience with HFOV in a mixed pediatric cardiac surgery population of neonates and infants with respiratory distress. Previous findings reported from randomized trials of HFOV in term or near-term neonates with pulmonary disease showed no benefit in terms of 28-day mortality,[1] and our findings were similar. But, unlike previous research on elective use of HFOV, length of mechanical ventilation and hospital stay were reduced among patients with a similar severity of illness when they were switched to HFOV on the day of surgery.

HFOV and PVR: The most common reasons for late weaning from mechanical ventilation following congenital cardiac surgery are a low cardiac output state or a respiratory complication. Even when ventricular function is well preserved and no residual anatomical lesion is present, a low cardiac output may result from inadequate pulmonary blood flow, secondary to elevated PVR. Maintenance of cardiac output by fluid challenge, to ensure adequate preload, leads to extravascular fluid accumulation, pleural and pericardial effusions, pulmonary interstitial edema and decreased compliance. The loss of intravascular volume must be replaced to maintain cardiac output, which may initiate a vicious cycle, and should therefore be avoided.

PVR is multifactorial after CPB[22,23] and highly sensitive to changes in intrathoracic pressure[24] and acidosis.[25] Changes in intra-thoracic pressure have been extensively investigated in the Fontan procedure, where high-frequency ventilation has been found to be associated with an increase of up to 25% in cardiac output and lead to halve PVR and mean Paw.[14] Although HFOV is known to be effective in settings leading to hypoxemia, the use has been described in reports of asthma and severe bronchiolitis to treat respiratory acidosis.[26,27] According to Babik et al,[23] CPB

Table 2 Most prevalent procedures in the matched set, along with their "HFOV indexes"

Most prevalent procedures	HFOV group (*n* = 120)	CMV group (*n* = 120)	"HFOV index"[a]
Obstructed TAPVC repair	14	12	0.82
Unrestrictive VSD repair	10	10	0.06
Complete common atrioventricular canal	9	7	0.11
Aortic arch repair	8	7	0.19
Arterial switch operation, VSD repair	6	9	0.08
Truncus arteriosus repair	6	7	0.30
Arterial switch operation	5	8	0.03
Norwood operation	6	6	0.41
Modified Blalock Taussig shunt	5	5	0.09
Tetralogy of Fallot repair	6	4	0.04
Coarctation repair	7	2	0.04
Pulmonary atresia, VSD repair	5	3	0.18
Arterial switch operation, VSD, coarctation repair	3	4	0.18
Bidirectional Glenn	2	4	0.05
Konno Ross procedure	2	4	0.50
Aortic valvuloplasty	3	3	0.10
Other	22	25	

CMV, conventional mechanical ventilation; HFOV, high-frequency oscillatory ventilation; TAPVC, total anomalous pulmonary venous connection; VSD, ventricular septal defect.

[a]accounting for the prevalence of HFOV from 1 January 2007 through 30 June 2010

is responsible of an obstructive process in the bronchi, leading to bronchospasm and acidosis. Bronchospasm is also a frequent postoperative finding in patients with a large preoperative left to right shunt.[28] Thus, the use of HFOV to treat respiratory acidosis in an attempt to decrease PVR after CPB appears justified. In the present study, when switching to HFOV, ventilation frequency was initially set to 8 Hz to promote decarboxylation and, thus, rapidly increase pH. But the retrospective design of the present study rendered collection of reliable data concerning PVR, Paw and gas exchanges impossible. Nevertheless, documented pulmonary hypertension was more prevalent in the HFOV group (before or after transition to HFOV) even after propensity score matching, showing that the HFOV group was still more severely ill. Therefore, the shorter durations of mechanical ventilation in the HFOV group suggested beneficial effect of HFOV upon PVR.

Hemodynamic status: Usually, HFOV involves slightly higher mean Paw values than CMV, and low cardiac output may occur due to increased pleural pressure and reduced venous return. Studies of HFOV in animal models of ARDS have reported hemodynamic impairment when high airway pressures were applied.[9-11] Studies of adults[6,12,13] and infants[29,30] switched from CMV to HFOV have found effects such as increased pulmonary artery occlusion pressure, increased central venous pressure, and small decreases in cardiac output and stroke volume index, although it was unclear whether these changes were clinically relevant.

By contrast, sedation may lead to excessive venous vasodilatation and impaired venous return following cardiac surgery, whereas spontaneous breathing maintains a negative pleural pressure, facilitates venous return and improves cardiac output. Spontaneous ventilation can be maintained easily in neonates and small children on HFOV without increasing the work of breathing,[31,32] thus allowing reduced sedation.

Table 3 Estimates and standard errors for variables included in the propensity score model

Variable	Coefficient estimate	Standard error	*P*-value
Intercept	-2.87	0.58	< 0.001
The "HFOV index"[a]	3.94	0.48	< 0.001
Age (days)	0.002	0.002	0.19
Weight (kg)	-0.37	0.12	0.002
Aristotle score[b]	-0.09	0.06	0.10
Surgery with cardiopulmonary bypass	0.87	0.37	0.02
Surgery with deep hypothermic circulatory arrest	-0.97	0.33	0.004
Re-operation	0.59	0.34	0.09
Requirement for a delayed sternal closure	0.81	0.29	0.005
Acute kidney injury requiring renal replacement therapy	0.36	0.62	0.56
Requirement for renal replacement therapy on the day of surgery	1.82	0.63	0.004

The propensity score model included only patients operated from 1 January 2007 through 30 June 2010.

HFOV, high-frequency oscillatory ventilation

[a]calculated as the prevalence of HFOV from 1 January 2007 through 30 June 2010

[b]accounting for the surgical complexity

Table 4 Independent predictors of successful weaning from mechanical ventilation and ICU delivery over time

	Successful weaning from mechanical ventilation			ICU delivery		
Variable	**Adjusted Hazard Ratio**	**95% CI**	***P*-value**	**Adjusted Hazard Ratio**	**95% CI**	***P*-value**
HFOV	1.62	1.17 to 2.25	0.004	1.65	1.19 to 2.28	0.002
Delay to sternal closure (days)	0.87	0.82 to 0.93	< 0.001	0.88	0.82 to 0.94	< 0.001
Pulmonary hypertension	0.74	0.54 to 1.02	0.07	0.73	0.53 to 1.01	0.05
Duration of renal replacement therapy (days)	0.95	0.89 to 1.02	0.19	0.94	0.87 to 1.01	0.08
Year of surgery	0.93	0.87 to 0.99	0.03	0.95	0.88 to 1.02	0.16
The propensity score	2.59	1.10 to 6.08	0.03	2.38	0.99 to 5.75	0.05

Adjusted Hazard ratios and 95% CI were estimated using Cox proportional-hazards regression analysis

CI, confidence interval, HFOV, high-frequency oscillatory ventilation

Reliable evaluation of hemodynamic consequences when changing ventilatory settings is impossible in a retrospective study. The low mean Paw strategy employed in the present study may have allowed preserve the hemodynamic stability on HFOV in our patients. Furthermore, if a long delay to sternal closure and a long duration of RRT were considered markers of hemodynamic impairment, then switching to HFOV may have resulted in hemodynamic improvement in the present cohort, since both the delay to sternal closure and the duration of RRT were slightly reduced in the HFOV group (Table 1).

Limitations: The present study was retrospective, and thus the validity of the results must be viewed with caution. Attempts were made to minimize bias related to selection of patients switched to HFOV through propensity score matching. Even though, and despite adjustment for the year of surgery, the choice of historical controls cannot rule out bias related to improvements in surgical and medical management of congenital heart diseases throughout the study period. Besides, the choice of transition to HFOV was made by the attending intensivist, and, despite the propensity score methodology employed, we cannot rule out residual bias related to pre-held beliefs about HFOV's performance. Furthermore, analysis of ventilation parameters and hemodynamic consequences were lacking. Because of the various intra-cardiac shunting patterns in the study population, oxygenation indexes were not analyzed. Future studies should address these limitations.

Conclusions

When commenced on the day of surgery, HFOV was associated with a shorter duration of mechanical ventilation and ICU stay in this population of neonates and infants with respiratory distress following congenital heart surgery. No association was observed between HFOV and mortality.

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Maternal Bodies and Medicines: A Commentary on Risk and Decision-making of Pregnant and Breastfeeding Women and Health Professionals

Karalyn McDonald, Lisa H. Amir, Mary-Ann Davey

Abstract

Background: The perceived risk/benefit balance of prescribed and over-the-counter (OTC) medicine, as well as complementary therapies, will significantly impact on an individual's decision-making to use medicine. For women who are pregnant or breastfeeding, this weighing of risks and benefits becomes immensely more complex because they are considering the effect on two bodies rather than one. Indeed the balance may lie in opposite directions for the mother and baby/fetus. The aim of this paper is to generate a discussion that focuses on the complexity around risk, responsibility and decision-making of medicine use by pregnant and breastfeeding women. We will also consider the competing discourses that pregnant and breastfeeding women encounter when making decisions about medicine.

Discussion: Women rely not only on biomedical information and the expert knowledge of their health care professionals but on their own experiences and cultural understandings as well. When making decisions about medicines, pregnant and breastfeeding women are influenced by their families, partners and their cultural societal norms and expectations. Pregnant and breastfeeding women are influenced by a number of competing discourses. "Good" mothers should manage and avoid any risks, thereby protecting their babies from harm and put their children's needs before their own – they should not allow toxins to enter the body. On the other hand, "responsible" women take and act on medical advice – they should take the medicine as directed by their health professional. This is the inherent conflict in medicine use for maternal bodies.

Summary: The increased complexity involved when one body's actions impact the body of another – as in the pregnant and lactating body – has received little acknowledgment. We consider possibilities for future research and methodologies. We argue that considering the complexity of issues for maternal bodies can improve our understanding of risk and public health education.

The authors are with Mother & Child Health Research, La Trobe University, Melbourne, Australia. Mc Donald is also with the Australian Research Centre in Sex, Health and Society. The authors wish to thank the reviewers, for their insightful and helpful comments and Kay Stewart, Faculty of Pharmacy and Pharmaceutical Sciences, Centre for Medicine Use and Safety, Monash University, for comments on an earlier version of the paper. Reprinted from BioMed Central, BMC Public Health, © 2011 McDonald et al; licensee BioMed Central Ltd. This is an open access article distributed under the terms of the Creative Commons Attribution License. This article has been slightly edited for our readers. For references please visit BioMed Central and type the full title. This article has been published as part of BMC Public Health Volume 11 Supplement 5, 2011: Navigating complexity in public health. The full contents of the supplement are available online at http://www.biomedcentral.com/1471-2458/11/S5.

Background

The aim of this paper is to generate a discussion that focuses on the complexity around risk, responsibility and decision-making of medicine use by pregnant and breastfeeding women. By medicines, we mean prescribed, over-the-counter (OTC) and complementary medicines.

The purpose of this commentary is to draw on both the biomedical and sociocultural perspectives in recognition that these are usually discussed separately. We hope our multidisciplinary approach can deepen the discussion of this issue. To set the scene, we consider risk in the context of medicine use and decision-making for pregnant and breastfeeding women and the role of the 'good mother' discourse. We then examine the evidence surrounding the use of medicines during pregnancy and breastfeeding from three perspectives: the first from biomedicine, the second from the health care professional and the third from women. We suggest that the perspectives of the biomedical and the expert health care provider are generally privileged by public health campaigns. The paper concludes with suggestions for future research and the most appropriate methodologies to explore this relatively uncharted area of health research.

Risk for pregnant and breastfeeding women

Our modern society has become increasingly concerned with understanding, calculating, managing, reducing or eliminating the risks associated with everyday life and it is within this context that pregnant and breastfeeding women have a social and moral responsibility to manage risk. The perceived risk/benefit balance of prescribed and OTC medicine, as well as complementary therapies will significantly impact on an individual's decision to use medicine. For the maternal body – women who are pregnant or breastfeeding – this weighing of risks and benefits becomes immensely more complex because they are considering the effect on two bodies rather than one. Indeed the balance may lie in opposite directions for the mother and baby/fetus.

Pregnancy and breastfeeding, while inherently very private events, attract vast public attention and scrutiny. Deborah

Lupton wrote that "the pregnant woman is surrounded by a complex network of discourses and practices directed at the surveillance and regulation of her body" and that "risk is a central discourse." Helman pointed out that all cultures share beliefs about the vulnerability of the mother and fetus during pregnancy and that this usually continues throughout the early postpartum or lactation period." Medical technology has embraced this vulnerability and the use of technologies, such as ultrasound, has meant that the fetus has increasingly acquired an individual identity that is separate from the mother and that the intensification of the health and well-being of the fetus has sometimes resulted in the mother being viewed primarily as the "maternal environment."

Yet, despite the separation of the mother and fetus, the mother is responsible for her fetus' health and wellbeing. "Her body therefore, is constructed as doubly at risk and she is portrayed as doubly responsible, for two bodies." In addition, Lupton points out that pregnant women are expected to be extremely attentive in monitoring their bodies to ensure the health of their babies is not threatened in any way. This self-regulation is extended to include the expectation that pregnant women, and one could argue, "good mothers," are vigilant in their attendance at antenatal appointments and undergo all medical tests and examinations suggested by their health care professionals.

None of this is surprising when one considers the thalidomide disaster of the late 1950s and early 1960s.

Pregnant women were prescribed thalidomide for morning sickness until it was recognized that it was a potent teratogen resulting in deformities in thousands of babies. Since that time, women have been given strong messages about the importance of maintaining their health and avoiding toxins that can transfer from mother to baby. Pregnant women are even cautioned against simple analgesics such as paracetamol. Deborah Lupton details how: "women are told that as well as avoiding any consumption of alcohol and tobacco (and illicit drugs such as marijuana and cocaine), they have been advised to give up tea, coffee and cola drinks, avoid certain sugar substitutes, avoid spa baths, be wary of microwave ovens, not use electric blankets, avoid having diagnostic x-rays, be careful in using household cleaning products and insecticides and not take prescription or over-the-counter therapeutic drugs (even headache pills) if possible."

The phenomenon of "intensive mothering" was identified by Sharon Hays whereby women must mother their children intensively to ensure they are seen to be "good mothers." More recent work has positioned this phenomenon as contemporary motherhood and suggests it still holds considerable power in societies such as Australia, the US and the UK. Intensive mothers are also risk averse in their parenting approach whilst recognising that "professional support" is essential to risk management.

The "good mother"

Most pregnant and breastfeeding women are significantly influenced by the discourse of the "good mother" (and, in turn, intensive mothering) which is widely discussed in the research literature. In essence, good mothers protect their babies from harm and put their children's needs before their own – which includes pregnant women. On the other hand, "responsible" women take and act on medical advice – they should take the medicine as directed by their health professional. This is the inherent conflict in medicine use for maternal bodies. Women in our society feel that they are ultimately responsible for producing a "perfect baby" and presumably feel responsible for maintaining optimum infant health by providing breast milk free of possible contaminants such as medicines. Others have taken this further, arguing the rights of the baby or fetus are always prioritized above the mother. This has been linked to the shift in western cultures during the middle of the 20th century where the optimum way to raise children requires a "good mother" who anticipates and adapts to their children's needs.

Once pregnancy is confirmed, women are faced with a multitude of decisions and risk assessments. They must decide what to eat (and not eat), what to drink (and not drink), what tests they will undergo (and what actions will be taken if test results indicate abnormality), what type of birth they want, how they will feed their infant, and so it goes on. However, in making these decisions, women become solely responsible for the welfare of their fetus. As Lupton writes, "there is no such thing as 'no risk' in pregnancy, but it is ultimately the woman's responsibility to ensure she has done all that she can to minimize risk."

As a result of the risk discourse that is prolific around pregnancy, it is now regarded as a hazardous journey that requires a high level of expert surveillance as well as vigilance on behalf of the woman. However, one of the "implications of this discourse is that the woman who fails to heed expert advice is portrayed as posing a risk to her fetus." The 20th century saw the rise of the "monster mother" discourse where women are accused of causing harm to their children and fetuses. Tsing argues that this discourse has extended to women who choose to give birth without medical assistance, regardless of the reasons why women make such decisions. Others have identified that this discourse reduces women to an "environment" and that while society may consider it irresponsible for individuals to neglect their own health, it may be considered criminal for pregnant and breastfeeding women to place the health of their fetus or baby at risk. Western societies' condemnation of women who are perceived to fail by not putting their unborn babies' or children's needs ahead of their own is indicative of women's social positioning and exemplifies the privileging of biomedical knowledge over the women's own knowledge.

Discussion

Biomedical perspective: Need for medicines during pregnancy and lactation: Of course, the use of medicines in pregnant and breastfeeding women may sometimes be essential to maintain the health of the woman (and baby). Poorly managed epilepsy in pregnancy can result not only in harm to the mother, but an increased risk of miscarriage. Untreated depression during pregnancy has been associated with increased cesarean sections and higher admissions to neonatal intensive care units, poor decision-making such as increased alcohol use and missed medical appointments, as well as difficulties in bonding with the baby. Despite the low risk of birth defects associated with commonly used antidepressants, many women are reported to discontinue their treatment upon confirmation of pregnancy.

HIV infection is another example where treatments contribute to the health of the mother. Furthermore, treatment of HIV during pregnancy has, potentially, another beneficiary: the baby. Use of antiretroviral (ARV) medicine during pregnancy and as

prophylaxis to the baby, in addition to other interventions, can significantly reduce mother-to-child transmission (MTCT) of HIV to less than two percent. However, there are considerable side-effects associated with ARV medicine and there is a history of toxicity, morbidity and mortality associated with its use early in the HIV epidemic. This has led to considerable skepticism and concern resulting in reduced uptake; pregnant women have been particularly cautious about ARV use.

It is not surprising that both clinicians and women find decision-making difficult, given the lack of safety data about medicine use in pregnant and breastfeeding women. In the past, women were often completely excluded from drug trials – the United States (US) Food and Drug Administration (FDA) started advocating for women to be included in 1993. Although women have been included in drug trials more recently, pregnant and breastfeeding women are usually still excluded. The reason given for this exclusion was to protect the child. The result is that existing safety data are limited: whilst there are small case series of women who have taken a particular medicine in pregnancy or lactation, systematic longterm follow-up remains lacking.

Actual risks for medicine use during pregnancy and breastfeeding are small. The real number of medicines proven to be teratogenic – that is an agent that irreversibly alters growth, structure or function of the developing embryo or fetus – remains fewer than 30. Looking at breastfeeding women, Anderson and colleagues reviewed all published case studies of adverse events in infants caused by medicines, prior to June 2002. They evaluated 94 papers describing adverse reactions in 100 infants, of which none were "definite," 47% were "probable," and 53% were "possible." A case report of neonatal death from maternal codeine use has since been reported. Obviously caution is needed but, considering the numbers of breastfeeding women who take medicines, the risk is small.

It is important to note that drug transfer (from mother to child) is not the same in pregnancy and breastfeeding. Most drugs taken by women during pregnancy cross the placenta from the mother's circulation to the fetus by simple diffusion – resulting in drug transfer to the fetal circulation up to 100%. In contrast, the breastfed infant receives far less maternal medicine than the fetus does. Medicines in the mother's circulation may transfer into milk, but usually only in small amounts: infant exposure to the drug is five- to ten-fold less than during pregnancy.

Health professionals' perspective: Health professionals' perception of risk: Health professionals must also assess risk for their pregnant and breastfeeding patients. Lyerly and colleagues found that risk perception affects medical decision-making in pregnancy, pointing out that the tendency for health care professionals has been to "pursue zero risk to the fetus, independent of the absolute size of the risk, of competing considerations, or of recognition that fetal risk exists in other acceptable contexts." They cite the example of vaginal birth after cesarean (VBAC), where cesarean section may be promoted in order to reduce the risk of perinatal death, without considering that even for a primary vaginal birth or cesarean section there are risks to the infant. They also identified that the risks of intervening are given precedence over the risks of failing to intervene. For example, radiological investigations may be delayed in pregnant women because of perceived potential harm from x-rays, while the real risk of septicemia from an undiagnosed ruptured appendix is ignored; fetal loss may be more than 30% after a perforated appendix. The use of medicines is similar. Halting medicines in pregnancy, or avoiding them in lactation, can lead to worsening maternal and therefore child health. Lyerly and colleagues suggest that, "It is the physician's obligation not to eliminate risk, but to help patients weigh risk, benefit, and potential harm, informed by best scientific evidence and guided by a patient-centered ethic."

Health professionals are expected to be knowledgeable about medicines, yet are unlikely to have received specific education about prescribing for pregnant and breastfeeding women. Many pharmacology textbooks do not support the use of medicines for breastfeeding women, eg: "It is prudent only to expose the infant to such risks if it is absolutely essential." A recent survey of general practitioners (GPs), conducted by one of the authors found that some GPs advised women to avoid breastfeeding while taking medicines like metronidazole and ibuprofen, which are considered compatible with breastfeeding. Furthermore, our research has shown that health professionals often rely on the safety ratings given to medicines in pregnancy when making decisions about prescribing for breastfeeding women. If health provider knowledge is poor, it is not surprising that the general public has little understanding of medicine use for breastfeeding women.

Decision making by health professionals: Our research suggests that decision-making for health professionals appears to be a spectrum from a straightforward decision, such as treatment of mastitis, to a complicated one requiring multiple inputs and consideration. We need to be aware that the focus of medicine use is generally about risks. We need to balance evidence of danger with reassuring evidence. For example, while alerting health professionals about the need for caution with codeine in breastfeeding women, we can explain other options for analgesia and evidence for their compatibility with breastfeeding.

"Quality use of medicines" programs are active in many countries, yet have not addressed the use of medicines for women who are pregnant or breastfeeding. For example, in the UK, the National Collaborating Centre for Primary Care (NCCPC) has recently published a guideline on involving patients in decisions about prescribed medicines, yet fails to mention use of medicines in pregnancy or lactation. Similarly, the Canadian online database of interventions to promote evidence-based prescribing and medicines use makes no specific mention of issues relevant to women.

Women's perspectives: Women's perception of risk: A few studies have examined pregnant and breastfeeding women's risk perceptions of commonly used medicines. A Norwegian study found that most women overestimated the teratogenic risk associated with medicine use during pregnancy. Interestingly, they found that women with a high perception of risk were more likely to be older, more highly educated and primiparous, although over 80% of the women had used drugs during pregnancy (most commonly paracetamol, penicillin and medicine for reflux). Similarly, a study by Sanz et al concluded that overestimated risk perception among women and health professionals led to induced abortions of healthy and wanted babies. Women's perceptions of risk of the use of antidepressants during pregnancy has also been explored, with 87% of women mistakenly believing that antidepressant use during pregnancy increased the risk of congenital abnormalities.

Increasingly, it seems that our society expects a breastfeeding woman to be "pure": her body and her milk should be free from any form of contamination. It is not surprising then, that studies have found that prescribing medicine to breastfeeding women may lead to early cessation of breastfeeding or that a breastfeeding mother may be denied treatment due to the possible risk to her baby.

Women's decision-making during pregnancy and breastfeeding: Recently researchers have examined the complexities surrounding women's experiences of antenatal screening, for example pregnant women's decision-making processes with regard to antenatal screening for Down syndrome. The authors of this review of qualitative studies on the topic have dismissed the Theory of Planned Behavior as a particular decision-making trajectory and suggested that the decision-making takes place in a complex framework. They plan to test the framework using ethnography and choice modeling research. Pregnant women considering antenatal testing are often confused by the estimates of risks they are given: the risk of having a baby with Down syndrome, the risk for miscarrying secondary to testing, and so on. On the other hand, how much harder would it be to make decisions when the potential risk of taking medicine while pregnant or breastfeeding is not quantified? Furthermore, the risks of the alternatives are not stated; the potential hazards of infant formula are rarely considered. Often, formula feeding is such a cultural norm that health professionals and families have trouble recognizing that this is an artificial food, potentially contaminated with bacteria and potentially leading to adverse child health outcomes.

Public health discourse has increasingly framed personal health choices as social and moral issues and as one's own responsibility to sustain one's health. We would extend this to pregnant and breastfeeding women and suggest that many women now feel responsible for producing and maintaining a healthy child. This increased responsibility has resulted in hyper-vigilant women going out of their way to avoid any possible toxins while pregnant or breastfeeding. With increased awareness of environmental contaminants on health, the list of potential impurities continues to increase.

Areas for research: Decision-making around the use of medicines for pregnant and breastfeeding women is an under-researched area in both the biomedical/pharmacological as well as the social context. Although the importance of the health of mothers and babies should be self-evident, we believe this is a neglected area. Chris Mulford has argued that breastfeeding is invisible to the health care system and in her list of "blind spots" is medicine use for lactating women.

Pharmaceutical companies have traditionally avoided involving women of reproductive age in drug trials and, although women are now included in many trials, pregnant and breastfeeding women continue to be excluded. This appears to be an area that everyone wants to steer clear of. Yet, pregnant and breastfeeding women do have acute and chronic medical conditions that may require medicines. We can see at least three areas where research is needed: at the level of drug testing, at the level of health professionals who are responsible for prescribing and dispensing medicine and at the level of the general public – in particular the woman herself.

It is timely for pharmaceutical companies to consider ways of determining whether medicines are compatible with pregnancy and lactation. The US FDA has proposed major revisions to labeling of prescription drugs in order to provide better information about the effects of medicines used in pregnancy and breastfeeding. The current letter category for risks of drug use in pregnancy is inaccurate and overly simplistic.

We need a better understanding of the issues for health professionals faced with decision-making when the medicine is prescribed for one body, but may impact on two. Where do they get their information? How helpful do they find the information? How can this be improved? Similarly, understanding the ways in which pregnant and lactating women want to receive information about risks of taking medicines is crucial. For example, would women appreciate the quantification of the risks of each possible adverse outcome? Would presenting numerical risk information as a "thousand person" graphic be more useful than presenting as numbers or percent (such as 1 in 1,000; 0.1%)? Could the estimate of the chance of suffering no adverse outcome be more useful? Alternatively, would women prefer a description of the possible adverse outcomes (without quantification) or a comparison with everyday risks (such as the risk of a particular birth defect without any known exposure to a teratogen, or the risk of car accident)? Can we quantify the risks to the child for premature cessation of breastfeeding and the introduction of infant formula? Would women like to be provided with this information? In addition to what information and how women would like to receive it, who would they like to provide it? The general practitioner during the consultation? The pharmacist dispensing the medicine? Written information from a government department, health professional body or health institution? There is a dearth of knowledge about the type of information as well as the most appropriate and effective way to convey it to pregnant and lactating women but we would argue that information presented to women should be woman-centered.

Beyond prescribed medicine, little is known about how pregnant and breastfeeding women interpret risk and make decisions about the use of social substances such as nicotine and alcohol as well as illicit substances. Insight into the decision-making of pregnant and breastfeeding women can inform better public health messages, clinical practice and policy guidelines.

We suggest that qualitative methodologies are often appropriate to address many of these research questions. Best results will be achieved by conducting collaborative interdisciplinary research, combining medicine, pharmacy, public health, psychology, sociology and anthropology. We also need to include the woman herself, in conjunction with her family and consumer advocates. Women may wish to play a more active role in decision-making (the "patient-empowerment model," rather than the biomedical-educational model). Previous research has found that consumers value information that enables "an informed choice promoting their autonomy; [consumers reported that] it was reassuring and reduced concern, conflict and anxiety about whether the medicine was the right one for them; and it gave them confidence in taking medicines," and this may also be true for pregnant and breastfeeding women.

Summary

Health research in general focuses on the mother or the baby (usually it is the mother who gets lost). The complexity of living in a body where one's actions impact on another body has not

Continued on page 55…

Smoking in Preeclamptic Women is Associated with Higher Birthweight for Gestational Age and Lower Soluble Fms-like Tyrosine Kinase-1 Levels

Susan R. Kahn, Nisha D. Almeida, Helen McNamara, Gideon Koren, Jacques Genest, Jr, Mourad Dahhou, Robert W. Platt, Michael S. Kramer

Abstract

Background: Smoking paradoxically increases the risk of small-for-gestational-age (SGA) birth but protects against preeclampsia. Some studies have reported a "U-shaped" distribution of fetal growth in preeclamptic pregnancies, but reasons for this are unknown. We investigated whether cigarette smoking interacts with preeclampsia to affect fetal growth, and compared levels of soluble fms-like tyrosine kinase-1 (sFlt-1), a circulating anti-angiogenic protein, in preeclamptic smokers and non-smokers.

Methods: From a multicenter cohort of 5337 pregnant women, we prospectively identified 113 women who developed preeclampsia (cases) and 443 controls. Smoking exposure was assessed by self-report and maternal hair nicotine levels. Fetal growth was assessed as z-score of birthweight for gestational age (BWGA). sFlt-1 was measured in plasma samples collected at the 24-26-week visit.

Results: In linear regression, smoking and preeclampsia were each associated with lower BWGA z-scores (β= -0.29; p=0.008, and β= -0.67; p<0.0001), but positive interaction was observed between smoking and preeclampsia (β= +0.86; p=0.0008) such that smoking decreased z-score by -0.29 in controls but increased it by +0.57 in preeclampsia cases. Results were robust to substituting log hair nicotine for self-reported smoking and after adjustment for confounding variables. Mean sFlt-1 levels were lower in cases with hair nicotine levels above vs. below the median (660.4 pg/ml vs. 903.5 pg/ml; p=0.0054).

Conclusions: Maternal smoking seems to protect against preeclampsia-associated fetal growth restriction and may account, at least partly, for the U-shaped pattern of fetal growth described in preeclamptic pregnancies. Smoking may exert this effect by reducing levels of the antiangiogenic protein sFlt-1.

Background

Preeclampsia, a hypertensive disorder that occurs in 2-7% of pregnancies, is an important cause of fetal and maternal morbidity and mortality.[1] Paradoxically, while maternal cigarette smoking increases the risk of a number of pregnancy complications, including miscarriage, preterm birth and small-for-gestational-age (SGA) birth, smoking has consistently been shown to be associated with a ~30% reduction in the risk of preeclampsia.[2,3] The mechanism for this protective effect is unclear, but may involve direct effects of smoking byproducts nicotine or carbon monoxide in inhibiting placental cytokine production, placental vascular constriction or oxidative stress,[4,5] factors that have been implicated in the pathophysiology of preeclampsia.[6] Furthermore, it was recently reported that both in normal and preeclamptic pregnancies, smoking is associated with lower maternal plasma concentrations of soluble fms-like tyrosine kinase-1 (sFlt-1),[7] a circulating anti-angiogenic protein that induces endothelial dysfunction and is found in higher concentrations in pregnant women who subsequently develop preeclampsia.[8]

In preeclamptic pregnancies, fetal growth has been described as having a "U-shaped" distribution, with an increased risk of both low birthweight and high birthweight babies.[9] In a case-control study nested within a large multicenter cohort of pregnant women whose primary aim was to evaluate the link between thrombophilia and preeclampsia, we performed secondary, hypothesis-generating analyses to assess whether maternal cigarette smoking, measured by selfreport and by hair nicotine levels, modifies the association between preeclampsia and fetal growth. In addition, we examined the relationship between plasma sFlt-1 levels, smoking and preeclampsia.

Methods

The Montreal Preeclampsia Study[10] is a case–control study nested within a prospectively recruited cohort of 5337 pregnant women who were participants in the Montreal Prematurity Study, a large multicenter study on causal pathways of preterm birth.[11] At the time of providing informed consent for the preterm birth study, the preeclampsia study was explained and women were asked to provide signed informed consent on a separate consent form. Before both studies were started, they received approval by the research ethics committees of the four participating hospital centers (Hôpital St. Luc; Hôpital Maisonneuve Rosemont; Royal Victoria Hospital and Jewish General Hospital.

Recruitment of cohort and follow-up to time of delivery: Patients and study setting: Trained research assistants

Authors Kahn and Genest Jr are with the Department of Medicine; Almeida, Platt and Kramer are with the Department of Epidemiology and Biostatistics; McNamara is with the Department of Obstetrics and Gynecology and the Department of Pediatrics, McGill University, Montreal; Koren is with the Motherisk Program, Hospital for Sick Children, Toronto, Canada. Reprinted from BioMed Central, BMC Pregnancy and Childbirth © 2011 Kahn et al; licensee BioMed Central Ltd. This is an open access article distributed under the terms of the Creative Commons Attribution License.

Table 1 Classification of preeclampsia among cases (N = 113)

	Total	Early-onset[b]	Severe[c]
Canadian Hypertension Society classification[a]			
Gestational hypertension with proteinuria without adverse conditions	12 (11%)	3 (8%)	0 (0%)
Gestational hypertension with proteinuria with adverse conditions	49 (43%)	16 (46%)	19 (59%)
Gestational hypertension without proteinuria with adverse conditions	49 (43%)	14 (40%)	10 (31%)
Chronic hypertension with superimposed preeclampsia	3 (3%)	2 (6%)	3 (10%)
TOTAL	**113 (100%)**	**35 (100%)**	**32 (100%)**

[a] Diagnostic criteria used for preeclampsia and non-preeclamptic hypertensive disorders of pregnancy were adapted from the 1997 Report of the Canadian Hypertension Society Consensus Conference [12]. Gestational hypertension was defined as diastolic hypertension (≥ 90 mm Hg) on two occasions at least 4-6 hours apart that developed after 20 wks gestation. Proteinuria was defined as protein excretion of ≥ 0.3 g/day in 24-hour urine collection or positive dipstick result ≥ 2+. Adverse conditions were defined as convulsions (eclampsia), diastolic pressure > 110 mm Hg, platelet count < 100,000 × 10^9/L, oliguria, protein excretion ≥ 3 g/day, pulmonary edema, elevated liver enzymes, severe nausea and vomiting, frontal headache, visual disturbances, persistent abdominal pain in right upper quadrant, chest pain or shortness of breath, suspected abruptio placentae, HELLP syndrome, intrauterine growth restriction, oligohydramnios, or absent or reverse umbilical artery end diastolic flow, as detected by Doppler velocitometry. Chronic hypertension with superimposed preeclampsia was defined as known chronic hypertension associated with further worsening of blood pressure and protein excretion ≥ 3 g/day after 20 weeks gestation. Non-preeclamptic hypertensive disorders (criterion for exclusion as case or control) included gestational hypertension, defined as diastolic hypertension (≥ 90 mm Hg) that developed after 20 wks gestation but without proteinuria or adverse conditions, and chronic known hypertension, defined as diastolic hypertension (≥ 90 mm Hg) that predated pregnancy or was diagnosed before 20 wks gestation, with or without proteinuria.

[b] Early-onset preeclampsia defined as occurrence at < 34 weeks gestation [18]

[c] Severe preeclampsia defined as presence of any of the following: seizure, HELLP, proteinuria ≥ 3 g/24 hours or diastolic blood pressure > 110 mm Hg [18]

approached consecutive pregnant women at the time they presented for routine ultrasound examination (most subjects), prenatal blood drawing, or first- or second-trimester obstetric clinic visits at four large maternity hospitals affiliated with McGill University or l'Université de Montréal in Montréal, Canada. Women aged ≥18 year at the expected date of delivery who spoke and understood French or English and had a singleton fetus were eligible for enrolment in the study. Women with severe chronic illness (other than hypertension, asthma or diabetes) requiring ongoing treatment, placenta previa, history of incompetent cervix diagnosed in a previous pregnancy, impending delivery, or a fetus affected by a major anomaly were excluded. Among these excluded women, reasons for exclusion and data on maternal education were recorded whenever possible.

Study visit at 24-26 weeks: Women who consented to participate were asked to return for a study visit at 24-26 weeks of gestation to obtain data on sociodemographic characteristics, medical, obstetric and family history, and cigarette smoking. Subjects were asked if they had ever smoked, if they had smoked (defined as one or more cigarettes per day) during the pregnancy, and if so, the average number of cigarettes smoked per day.

After the interview, non-fasting blood samples were obtained by venipuncture and immediately placed on ice. Samples were centrifuged, and plasma was aliquoted into cryovials that were frozen at -80°C.

Identification of cases of preeclampsia and selection of control subjects: Cohort women were followed until delivery.

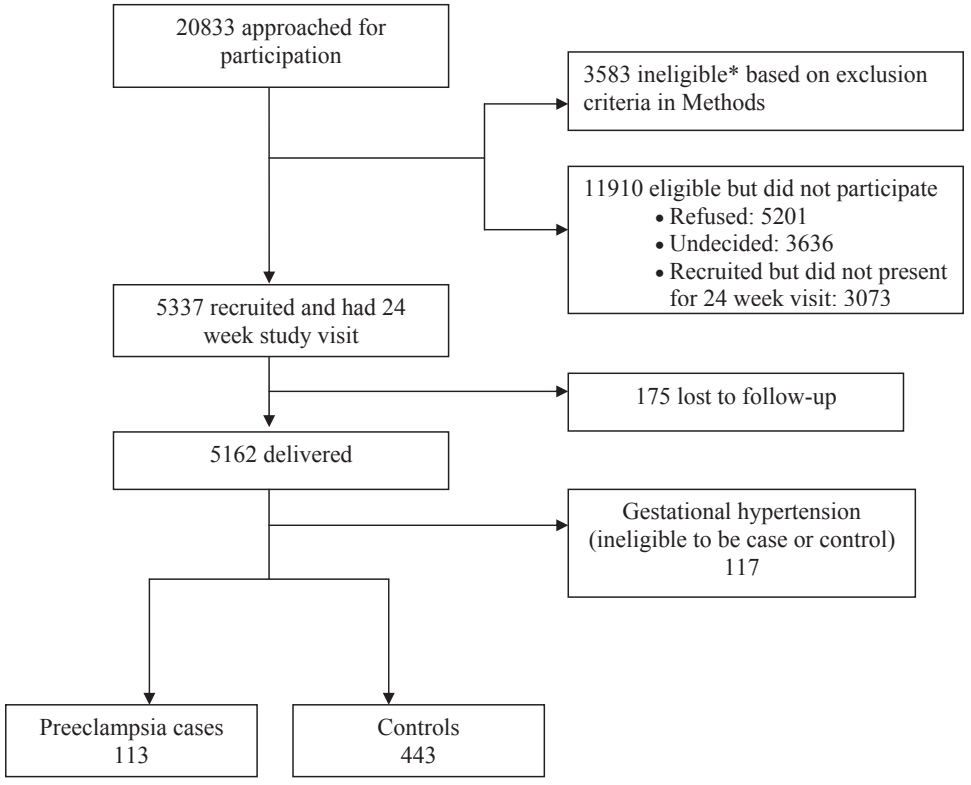

Figure 1 Study flow diagram. * data on reasons for ineligibility were available in 952. The most common reasons were lack of fluency in French or English (n = 321), plans to deliver in a non-study hospital (n = 272), severe chronic disease (n = 90) and gestational age at initial contact > 24 weeks (n = 62).

Table 2 Comparison of preeclampsia cases, non-cases and controls: demographic, medical and obstetric characteristics ascertained at 24-26 week study visit

Characteristic	Cases (n = 113)	Non-cases* (n = 5107)	Controls (n = 443)
Age category			
< 20 years	3%	3%	3%
20-34 years	78%	79%	79%
> 34 years	19%	18%	18%
Hospital recruited			
Hôpital St. Luc	15%	22%	24%
Hôpital Maisonneuve Rosemont	39%	36%	37%
Royal Victoria Hospital	22%	18%	17%
Jewish General Hospital	24%	24%	22%
Body Mass Index before pregnancy, kg/m^2			
< 18.5	2%	8%	9%
18.5 to < 25	52%	63%	60%
25 to < 30	27%	18%	18%
≥ 30	19%	11%	13%
Primigravida	40%	35%	34%
Use of prenatal vitamins	92%	92%	92%
Diabetes before pregnancy or prior to 24 weeks gestation	6%	2%	1%
High blood pressure before pregnancy	8%	4%	3%
Previous preeclampsia or eclampsia (among women with prior pregnancy lasting > 20 wks)	21%	3%	3%
Smoke currently	10%	16%	16%

* Non-cases = study cohort (n = 5337) excluding cases (n = 113) and women who developed gestational hypertension without preeclampsia (n = 117). Controls were selected from among non-cases as described under Methods.

During the admission for delivery, each study woman identified as having had hypertension or preeclampsia during pregnancy or after delivery underwent a detailed interview and chart review by trained study staff to assess whether diagnostic criteria for preeclampsia were met. Preeclampsia was diagnosed according to the 1997 Canadian Hypertension Society criteria and further classified as severe or early onset (Table 1).[12] All cases of preeclampsia (n=113) were independently verified by two study investigators (SK and HM).

Primarily for recruiting convenience, controls (n=443) were study women who delivered at the same hospital closest in calendar time to a case, but did not have preeclampsia. As controls partially overlapped with those of the concurrently running preterm birth study,[11] 3-4 eligible controls were available per case of preeclampsia. Study women who had onset of hypertension during pregnancy but did not meet criteria for preeclampsia were ineligible to be cases or controls and were excluded from all analyses.

Postpartum procedures for cases with preeclampsia and control subjects: After delivery, study staff collected data from the mother's and infant's hospital chart and by interview on infant birthweight, sex, placental weight, gestational age and pregnancy course since the 24-26 week study visit.

Infant birthweight and placental weight were recorded as the weights obtained in the delivery room. Gestational age was determined using both the subject's last menstrual period (LMP) as well an ultrasound estimate usually obtained at 16-20 weeks gestation. If the gestational age estimates using the two methods differed by more than 7 days, the ultrasound estimate was used; otherwise, the LMP estimate was chosen. During the postpartum interview, subjects were asked if they had smoked cigarettes (defined as one or more cigarettes per day) since the prenatal interview, and if so, the average number of cigarettes smoked per day.

Laboratory analyses: After delivery, cases and controls had a small amount of maternal hair cut from the posterior scalp, sealed in a labeled envelope and sent in batches to Dr. Koren's laboratory in Toronto to test for nicotine concentrations, using previously described techniques.[13] Results are expressed in nanograms of nicotine per milligram of hair.

Table 3 Gestational age and fetal growth among preeclampsia cases and controls

	Cases	Controls	P value
Gestational age at delivery, weeks; mean (SD)*	36.8 (3.5)	39.2 (1.4)	< 0.0001
Gestational age at delivery, weeks*			
< 32 weeks	8 (7%)	1 (0%)	< 0.0001
32-33 weeks	6 (5%)	0 (0%)	
34-36 weeks	23 (21%)	18 (4%)	
≥ 37 weeks	76 (67%)	415 (96%)	
Birthweight, grams; mean (SD)#	2834.4 (848.4)	3485.3 (500.2)	< 0.0001
Z-score birthweight for gestational age^; mean (SD)	-0.31 (1.0)	0.15 (0.9)	< 0.0001
Small for gestational age^	22 (21.6%)	32 (7.3%)	< 0.0001
Large for gestational age^	6 (5.9%)	50 (11.3%)	0.10
Z-score placental weight for gestational age+; mean (SD)	-0.01(1.13)	0.15 (0.98)	0.25

Values shown are n (%) unless otherwise noted

* data missing for 9 subjects;# data missing for 5 subjects;

^ Z-score birthweight for gestational age, small for gestational age, large for gestational age as defined in Kramer et al [14]; data missing for 13 subjects

+ Z-score placental weight for gestational age calculated as defined by McNamara [15,16]; placenta data missing for 186 subjects

Table 4 Self-reported cigarette smoking and hair nicotine levels in preeclampsia cases and controls

Variable	Cases N = 113	Controls N = 443	p-value
Smoked throughout pregnancy	10 (8.9%)	69 (15.6%)	0.07
Smoked steadily (within the same category of number of cigarettes) throughout pregnancy	4 (3.4%)	41 (9.3%)	0.05
Average number of cigarettes/day, mean (SD)*	1.20 (3.6)	1.91 (4.7)	0.08
Category of average number of cigarettes smoked per day			
0	90 (80.4%)	340 (77.3%)	0.69
1-10	16 (14.3%)	67 (15.2%)	
> 10	6 (5.4%)	33 (7.5%)	
Hair nicotine (ng/mg), mean (SD)#	1.29 (2.9)	1.94 (5.4)	0.10

Values shown are n (%) unless otherwise noted

* calculated as average of the number of cigarettes smoked per day in each of the trimesters.

Hair nicotine available for 99 cases and 398 controls

Table 5 Linear regression analyses: Relationship between maternal exposure to smoking, preeclampsia and fetal growth

Model	Unadjusted β (95% CI)	p-value	Adjusted β# (95% CI)	p-value
Model 1a **z-score BWGA = smoker + preeclampsia + interaction term**				
Smoker	-0.29 (-0.51,-0.08)	0.008	-0.38 (-0.61, -0.15)	0.0013
Preeclampsia	-0.67 (-0.91,-0.43)	< 0.0001	-0.67 (-0.93, -0.41)	< 0.0001
Smoker* preeclampsia	0.86 (0.36, 1.36)	0.0008	0.86 (0.33, 1.39)	0.0015
Model 1b z-score BWGA = smoker + preeclampsia + interaction term + z-score PWGA				
Smoker	-0.30 (-0.50, -0.09)	0.004	-0.32 (-0.54, -0.09)	0.0067
Preeclampsia	-0.61 (-0.86, -0.35)	< 0.0001	-0.60 (-0.87, -0.33)	< 0.0001
Smoker* preeclampsia	0.74 (0.25, 1.23)	0.003	0.69 (0.16, 1.22)	0.0112
z-score PWGA	0.56 (0.48, 0.65)	< 0.0001	0.52 (0.43, 0.61)	< 0.0001
Model 2a z-score BWGA = log hair nicotine + preeclampsia + interaction term				
Log nicotine	-0.12 (-0.16, -0.05)	0.0004	-0.086 (-0.16, -0.01)	0.0234
Preeclampsia	-0.31 (-0.55, -0.07)	0.011	-0.36 (-0.63, -0.09)	0.0087
Log hair nicotine * preeclampsia	0.28 (0.11, 0.46)	0.002	0.26 (0.07, 0.46)	0.0091
Model 2b z-score BWGA = log hair nicotine + preeclampsia + interaction term + z-score PWGA				
Log nicotine	-0.09 (-0.16, -0.03)	0.005	-0.06 (-0.13, 0.01)	0.0912
Preeclampsia	-0.31 (-0.54, -0.08)	0.009	-0.33 (-0.60, -0.07)	0.0131
Log hair nicotine * preeclampsia	0.25 (0.07, 0.42)	0.007	0.25 (0.06, 0.44)	0.0095
z-score PWGA	0.56 (0.48, 0.64)	< 0.0001	0.52 (0.42, 0.62)	< 0.0001

Dependent variable for all models: z-score birthweight for gestational age (BWGA), as defined in Kramer et al [14]

PWGA = placental weight for gestational age; z-score PWGA calculated as defined by McNamara [15,16]

analyses adjusted for age, pre-pregnancy body mass index, maternal language other than French or English, diabetes, chronic hypertension and parity (nullipara vs. other). For adjusted models 1a and 1b, diabetes was statistically significant (p = 0.03 and p = 0.03, respectively). No other variables were statistically significant in any of the models.

R-square for models: Model 1a unadjusted, 0.057, Model 1a adjusted, 0.096; Model 1b unadjusted, 0.388, Model 1b adjusted, 0.391; Model 2a unadjusted, 0.062, Model 2a adjusted, 0.100; Model 2b unadjusted, 0.395, Model 2b adjusted, 0.384.

Plasma samples of cases and controls were retrieved and thawed. sFlt-1 concentration was measured in Dr Genest's laboratory using commercial ELISA kits from R&D systems (Minneapolis, MN). Results are expressed in pg/ml. The sFlt assay is specific for human sFlt-1, with sensitivity of 5 pg/ml. As reported by the manufacturer, intra-assay and inter-assay coefficients of variation are 3.2% and 5.5%, respectively. All laboratory analyses were performed blindly without identifying the source of each specimen as a case or a control.

Statistical analysis: Data on demographic and medical characteristics, self-reported cigarette smoking, pregnancy outcome, and hair nicotine and plasma sflt-1 concentrations were compared in cases and controls using t-tests for continuous variables and chi-square tests for categorical variables. Hair nicotine and plasma sFlt-1 were examined both as continuous and quantile (divided at the median and by quartiles, respectively) variables. A P value of <0.05 was considered statistically significant.

Fetal growth was assessed on a continuous scale as the z-score of birthweight for gestational age (BWGA), using the following formula: z = (observed birthweight – mean birthweight)/ SD, where mean and SD were based on published Canadian population-based standards, stratified by infant sex and gestational age in completed weeks.[14] SGA and LGA births were defined as having birthweight below the 10th percentile and above the 90th percentile, respectively, using the same Canadian population-based standards used to obtain the BWGA z scores.

Multiple linear regression was used to test associations between measures of maternal tobacco smoke exposure, preeclampsia, and z-score of BWGA. Models were constructed in which the dependent variable was fetal growth represented by z-score of BWGA, and the independent variables were preeclampsia, maternal tobacco smoke exposure (self-reported smoking status, or log-transformed hair nicotine concentration), and an interaction term for preeclampsia and smoking exposure. As the distribution of hair nicotine was right skewed, this variable was log-transformed (natural log) to normalize the distribution. In order to retain 0 values, we added a constant (0.1) that best normalized the distribution after log-transformation.

Because birthweight and fetal growth are known to be influenced by placental weight, we also constructed models adjusted for placental weight, represented by the z-score of placental weight for gestational age (PWGA) using the following method, described by McNamara:[15,16] z = (observed placental weight at a given gestational age – mean placental weight for that gestational age)/SD, where mean and SD were based on singleton deliveries (excluding infants with congenital anomalies) between 1978 and 2001 in the McGill Obstetrical and Neonatal Database,[17] stratified by ultrasound-confirmed gestational age.

Finally, the above models were further adjusted for age, pre-pregnancy BMI, maternal language other than French or English, diabetes preceding or during pregnancy, chronic hypertension and parity (nullipara vs. other). All analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC).

Results

Of the 20,830 women who were approached for participation in the study from 1999 to 2003, 5337 were recruited and attended the 24-26-week study visit, and thus comprised the study cohort (Figure 1). Of these, 175 did not deliver at a study hospital and were lost to follow-up. Of 5162 study women followed to delivery, 113 developed preeclampsia (cases) (2.2%) (Table 1). Subsequent to identification of cases, 443 controls were chosen.

Characteristics of the study population are shown in Table 2. Controls had very similar characteristics to all non-cases (ie cohort women from among whom controls were selected). Women with preeclampsia had higher pre-pregnancy BMI than non-cases, were more likely to have a history of diabetes, prior hypertension and preeclampsia during a previous pregnancy and were less likely to be current smokers. Pregnancy outcomes are shown in Table 3. Cases with preeclampsia were significantly more likely than controls to deliver at earlier gestational age and to have a higher incidence of SGA birth, with correspondingly lower BWGA z-scores.

Maternal smoking and preeclampsia: Self-reported smoking and hair nicotine levels in cases and controls are shown in Table 4. While results did not achieve statistical significance, cases tended to be less likely than controls to report smoking throughout pregnancy ($p=0.07$) or to report smoking steadily within the same category of number of cigarettes throughout pregnancy ($p=0.05$). Cases also had lower mean hair nicotine levels ($p=0.10$) and reported smoking fewer cigarettes per day ($p=0.08$) than controls.

Effect of smoking on fetal growth in controls: Among controls, mean (SD) BWGA z-score was lower in self-reported smokers than in non-smokers (-0.26 (0.89) vs 0.22 (0.96); $p=0.0002$) and was lower in women with hair nicotine levels above vs. below the median (0.01 (0.99) vs 0.30 (0.95); $p=0.004$). Similarly, the risk of SGA birth was significantly increased in self-reported smokers vs. non-smokers (OR 2.28 [95% CI 1.01, 5.56]) and in women with hair nicotine levels above vs. below the median (OR 5.36 [1.99, 14.40]).

Association between smoking, preeclampsia and fetal growth: Consistent with the findings reported above, linear regression analysis showed that selfreported smoking and preeclampsia were each associated with lower BWGA z-scores ($\beta= -0.29$; $p=0.008$, and $\beta= -0.67$; $p<0.0001$, respectively). However, a significant positive interaction was detected between smoking and preeclampsia (interaction term $\beta= +0.86$; $p=0.0008$) such that being a smoker decreased the BWGA z-score by -0.29 in controls but increased it by +0.57 in preeclampsia cases (Model 1a) (Table 5). In clinical terms, this increase in z-score would translate into a 234g heavier weight for a male singleton born at 34 weeks, or a 255g heavier weight for a male singleton born at 38 weeks.[14] Results were similar after adjustment for age, pre-pregnancy BMI, maternal language other than French or English, pre-gestational diabetes, chronic hypertension and parity (nullipara vs other) (Model 1a adjusted), adjustment for PWGA (Model 1b), and adjustment for all of the above (Model 1b adjusted) (Table 5).

Similar results were obtained when log hair nicotine was substituted for self-reported smoking in the models (Models 2a and 2b) (Table 5). For example, in Model 2a, an increase in log hair nicotine by 1 unit decreased the BWGA z-score by −0.12 in controls, but increased the BWGA z-score by +0.16 in preeclampsia cases (ie βnic (log nicotine) + βinteraction (log nicotine*preeclampsia) = −0.12*1 + 0.28 (1*0) = −0.12 for controls, and −0.12*1 + 0.28 (1*1) = 0.16 for preeclampsia cases).

Due to the small numbers of smokers in subgroups of cases with early onset preeclampsia and severe preeclampsia, we were unable to examine the association between smoking, subtypes of preeclampsia and fetal growth.

Levels of sFlt-1 in association with preeclampsia and smoking: Mean (SD) plasma sFlt-1 was 761.5 (445.6) pg/ml in preeclampsia cases and 703.83 (358.8) pg/ml in controls (p=0.21), and cases were more likely to have sFlt-1 concentrations in the top quartile of values than controls (33.9% vs 21.9%, p=0.016). Among preeclampsia cases, women with hair nicotine levels above the median had significantly lower mean (SD) sFlt-1 levels than women with hair nicotine levels below the median (660.4 (377.2) pg/ml vs 903.5 (466.4) pg/ml, respectively; p=0.0054) and tended to be less likely to have sFlt-1 concentrations in the top quartile of control values (29.4% vs 44.7%, p=0.16). Among controls, sFlt-1 levels did not vary by hair nicotine level.

Discussion

We found that cigarette smoking was associated with reduced fetal growth restriction in preeclamptic women. This finding remained robust after adjustment for potentially confounding covariates. We further found that preeclamptic women who had higher levels of exposure to smoking, indicated by higher hair nicotine levels, had significantly lower plasma concentrations of the circulating anti-angiogenic protein sFlt-1 at 24-26 weeks gestation than preeclamptic women with lower levels of smoking exposure.

We also confirmed previous reports that smokers are less likely to develop preeclampsia than non-smokers and have lower birthweight for gestational age babies; that high BMI, diabetes, hypertension, primigravidity, previous preeclampsia and family history of preeclampsia increase the risk of preeclampsia; and that fetal outcomes are worse in preeclamptic vs non-preeclamptic women.

Our study has a number of strengths. Cohort women were recruited prospectively and consecutively at four large maternity hospitals in Montreal that serve a wide socioeconomic and demographic spectrum and are likely to be broadly representative of the general obstetric population. While the incidence of preeclampsia in our cohort (2.2%) was at the lower end of that previously reported in healthy pregnant women,[18] this likely reflects our use of strict, high-specificity criteria to diagnose preeclampsia. We are confident that we did not miss cases of preeclampsia as trained research assistants reviewed the delivery of each cohort woman to ascertain, using a detailed checklist, if criteria for preeclampsia were met. Our success in obtaining "true" cases of preeclampsia is shown by the differences in frequency of recognized preeclampsia risk factors and indicators of poorer pregnancy outcomes in cases and controls. Results were similar whether we assessed smoking exposure by self-report or using hair nicotine level, hence misclassification of smoking exposure is unlikely.[19] We used hair nicotine rather than hair cotinine as a measure of maternal tobacco smoke exposure because previous work by our group found that hair nicotine was a better predictor of reduced infant birthweight in control women, and hence a better measure of maternal smoke exposure.[20] The proportion of women who reported smoking during pregnancy was similar to that of other large cohorts of pregnant women.[21,22] We assessed fetal growth on a continuous scale adjusted for sex and gestational age, using Canadian population-based standards.[14]

As the sample size of our study was predetermined by the requirements of the Montreal Prematurity Study, precision was limited for estimates of association between smoking and preeclampsia. Furthermore, we could not perform analyses by preeclampsia subtype, which would have been of interest as severe, early-onset preeclampsia may be a different disease entity from milder forms of preeclampsia.[1] We did not have information on race/ethnicity of study women, hence could not examine potential effects on BWGA z-score, preeclampsia incidence or hair nicotine levels. Finally, we acknowledge that associations should be considered hypothesis-generating and do not prove causality.

Smoking has consistently been shown to reduce the risk of preeclampsia by ~30%.[2,3] The biological mechanism of this protective effect is uncertain, but may relate to inhibitory effects of smoking by-products such as nicotine and carbon monoxide on endothelial dysfunction and excessive maternal inflammatory response.[6] Nicotine acts on human placenta to release placental acetylcholine, which stimulates release of endothelium-derived relaxing factor and nitric oxide,[23] and in vitro studies show that nicotine selectively inhibits thromboxane A2 synthesis.[24] Both effects would be expected to reduce endothelial dysfunction and preserve placental blood flow. Nicotine also has anti-inflammatory activity and inhibits placental cytokine production.[4] Carbon monoxide has direct placental effects that could reduce the risk of preeclampsia, including promotion of trophoblast invasion, reduced decidual inflammatory response, increased uteroplacental blood flow, decreased hypoxia-induced apoptosis and upregulation of placental antioxidant systems.[5,25] Finally, findings of a recent Swedish birth register study suggest that tobacco combustion products rather than nicotine may be protective of preeclampsia, and it may be the smoking habits in middle or late gestation (rather than beginning of pregnancy) that influence the risk of developing preeclampsia.[26]

Our finding that smoking attenuated the relationship between preeclampsia and fetal growth restriction is intriguing, as some studies have reported a U-shaped pattern of fetal growth in populations of women with preeclampsia. In a population-based, retrospective Canadian study, Xiong reported that women with preeclampsia had a 2.6-fold higher risk of SGA birth than normotensive women, but also had a 1.8-fold higher risk of LGA birth.[9] While analyses controlled for self-reported smoking, potential interaction between smoking and preeclampsia on fetal growth was not examined. Similar results were reported in a population of Chinese women, for which information on maternal smoking was not available.[27] Based on our finding that preeclamptic women who smoked had infants with higher BWGA compared to preeclamptic women who were non-smokers, we suggest that smoking may account, at least in part, for the U-shaped pattern of fetal growth in preeclampsia.

In our study, plasma sFlt-1 levels were significantly lower in preeclamptic women with higher hair nicotine levels. This suggests that smoking may attenuate fetal growth restriction by reducing production of the anti-angiogenic protein sFlt-1. sFlt-1 is secreted by the placenta into the maternal circulation and adheres to the receptor-binding domains of placental growth factor and vascular endothelial growth factor (VEGF), preventing interaction with endothelial receptors, blocking VEGF-mediated vasodilation and inducing endothelial dysfunction,[8] considered to be key to the pathogenesis of preeclampsia.[6] Levels of sFlt-1 are elevated in preeclamptic women, and beginning at 21-24

weeks gestation, in pregnant women who subsequently develop preeclampsia.[7,8] Smoking increases placental expression of VEGF,[28] and plasma sFlt-1 levels have been found to be decreased in smokers.[29] Furthermore, carbon monoxide has inhibits sFlt-1 production in mice.[30] This effect of smoking on increasing pro-angiogenic factors and reducing anti-angiogenic factors may explain why preeclampsia occurs less frequently in smokers, and could also explain our finding that among preeclamptic women, smoking limits fetal growth restriction. A recent study of 58 preeclamptic women also reported a tendency to lower sFlt-1 levels in smokers vs. non-smokers.[7]

Finally, our finding of a protective effect of smoking on preeclampsia-associated fetal growth restriction corroborates that of a recent linked record study of >650,000 pregnancies, in which self-reported smokers who developed preeclampsia had a lower adjusted mean difference in birthweight compared to controls than would have been expected based on the independent additive effects of smoking and preeclampsia, and lower than expected rates of preterm delivery.[31] Furthermore, a secondary analysis of the Calcium for Preeclampsia Prevention trial reported that among 274 nulliparous women with preeclampsia, smoking did not act to further reduce infant birthweight, compared with non-smoking women.[32]

Conclusions

In conclusion, fetal growth restriction in preeclamptic pregnancies seems to be attenuated by maternal smoking. Smoking may account, at least in part, for the U-shaped pattern of fetal growth described in women with preeclampsia, and may exert this effect by reducing levels of the anti-angiogenic protein sFlt-1. Further exploration of the reasons why smoking may protect against preeclampsia-associated fetal growth restriction could increase understanding of the pathophysiology of preeclampsia.

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Prognosis and Long-term Neurodevelopmental Outcome in Conservatively Treated Twin-to-Twin Transfusion Syndrome

Xiangqun Li, MD; Seiichi Morokuma, MD, PhD; Kotaro Fukushima, MD, PhD; Yuka Otera, MD; Yasuo Yumoto, MD, PhD; Kiyomi Tsukimori, MD, PhD; Masayuki Ochiai, MD, PhD; Toshiro Hara MD, PhD; Norio Wake, MD, PhD

Abstract

Background: Amnioreduction remains a treatment option for pregnancies with twin-to-twin transfusion syndrome (TTTS) not meeting criteria for laser surgery or those in which it is not feasible. Amnioreduction is a relatively simple treatment which does not require sophisticated technical equipment. Previous reports of conservative management have indicated that major neurodevelopmental impairment occurs in 14.3-26% of survivors. The purpose of this study was to investigate long-term neurodevelopmental outcome in conservatively treated TTTS.

Methods: During the nine-year study period from January 1996 to December 2004, all pregnancies with TTTS who were admitted to our center were investigated. TTTS was diagnosed by using standard prenatal ultrasound criteria, and staged according to the criteria of Quintero et al. We reviewed gestational age at diagnosis gestational age at delivery, the stage of TTTS at diagnosis, and diagnosis to delivery interval. Neonatal cranial ultrasound findings were reviewed and the neurodevelopmental outcomes were evaluated.

Results: Twenty-one pregnancies with TTTS were included. Thirteen pregnancies (62%) were treated with serial amnioreduction. The mean gestational age at delivery was 28 weeks (22 - 34 weeks). The perinatal mortality rate was 42.9%. Twenty survivors were followed up until at least 3 years of age. The mean age at follow-up was 6.3 years (3 - 12 years). Six children (30%) had neurodevelopmental impairment. Four children (20%) had major neurodevelopmental impairment and two children (10%) had minor neurodevelopmental impairment. Children with neurodevelopmental impairment were delivered before 29 weeks of gestation.

Conclusions: Our study showed a high rate of perinatal mortality and a high rate of major neurodevelopmental impairment in conservatively treated TTTS. The long-term outcomes for the survivors with TTTS were good when survivors were delivered after 29 weeks of gestation.

Xiangqun Li is with the Department of Obstetrics and Gynecology, Graduate School of Medical Sciences; Morokuma, Fukushima, Otera, Yumoto and Wake are with the Department of Obstetrics and Gynecology, Kyushu University Hospital; Ochiai and Hara are with the Department of Pediatrics, Kyushu University Hospital; Tsukimori is with Fukuoka Children's Hospital, Fukuoka, Japan. Reprinted from BioMed Central, BMC Pregnancy and Childbirth, © 2011 Li et al; licensee BioMed Central Ltd. This is an open access article distributed under the terms of the Creative Commons Attribution License.

Background

Twin-to-twin transfusion syndrome (TTTS) complicates 9% of monochorionic twin pregnancies, and if untreated, is associated with a perinatal loss rate of over 80%.[1,2] Fetal interventions, such as repeated serial amnioreduction and laser surgery may reduce the perinatal mortality rate. A recent meta analysis has shown that the overall survival rate varies from 57% to 77% following laser surgery and from 38% to 81% following serial amnioreduction.[3]

The first randomized trial comparing amnioreduction with endoscopic laser surgery showed that endoscopic laser surgery resulted in higher survival rates and lower rates of neurologic complications at six months of age than did serial amnioreduction in severe TTTS presenting before 26 weeks of gestation. Therefore, endoscopic laser surgery has been adopted as the first-line treatment for TTTS diagnosed before 26 weeks.[4] As this technique interrupts placental vascular communication, it can potentially reduce neurodevelopmental impairment. Several studies, however, have reported that the incidence of neurodevelopmental impairment in TTTS survivors treated with laser surgery is still high.[5,6]

Although amnioreduction is no longer the only treatment option for TTTS, a subset of patients may still benefit from this intervention. Amnioreduction is useful in the setting of TTTS not meeting criteria for laser surgery and in patients in whom laser surgery is not technically possible. Amnioreduction is a relatively simple treatment which does not require sophisticated technical equipment. Previous reports of conservative management have indicated that major neurodevelopmental impairment occurs in 14.3%- 26% of survivors.[7-10] This study was undertaken to investigate the long-term neurodevelopmental outcome in conservatively treated TTTS.

Methods

We examined the prenatal records of all women and the medical records of children and neonates with TTTS admitted to the Maternity and Perinatal Care Unit of Kyushu University Hospital from January 1996 to December 2004. TTTS was diagnosed in all cases by ultrasound criteria of polyhydramnios (>8 cm, deepest vertical pool) in one twin sac and oligohydramnios (‹2 cm, deepest vertical pool) in the co-twin of a monochorionic, diamniotic pregnancy.[11] In our hospital, laser surgery was not performed, so cases with laser surgery were not included

The following data were obtained from the maternal medical record: gestational age at diagnosis, gestational age at delivery,

Table 1 Antenatal and delivery characteristics

Pregnancies(n)	21
Age (years)	28 (20-38)
Parity	0 (0-3)
Gestational age at diagnosis(weeks)	24 (18-34)
Gestational age at delivery(weeks)	28 (22-34)
Diagnosis to delivery interval(days)	25 (1-73)
Use of amnioreduction	13 (61.9%)
Amnioreduction per pregnancy	2.7 (1-6)
Cesarean section	13 (61.9%)
Gestational age < 30 weeks at delivery	15 (71.4%)
Quintero stage I	11 (52.4%)
Quintero stage II	4 (19%)
Quintero stage III	3 (14.3%)
Quintero stage IV	3 (14.3%)
Quintero stage V	0
IUFD of 1 twin	3 (14.3%)
IUFD of both twins	1 (4.8%)
0 survivor*	8 (38.1%)
1 survivor	4 (19%)
2 survivors	9 (42.9%)
Fetus(n)	42
Intrauterine fetal death (IUFD)	5 (11.9%)
Neonatal death	13 (35.1%)
Overall perinatal mortality	18 (42.9%)
Infant death	2 (5.4%)
Lost to follow-up	2 (5.4%)
Long-term survivors	20 (54.1%)
neurodevelopmental impairment	6 (30%)

Data shown as mean (range) or n (%) as appropriate.
*Survivor is defined as the survival of at least 12 months of age.

the stage of TTTS at diagnosis, diagnosis to delivery interval, and amnioreduction. TTTS was staged according to the criteria of Quintero et al.[12] The following neonatal data were extracted: birth weight and cranial ultrasound findings.

Cranial ultrasound scans were obtained in all neonates shortly after birth and further scans were carried out one, three, five, and seven days after birth, followed by weekly scans thereafter until discharge. Additional scanning was undertaken as clinically indicated. Abnormal cranial ultrasound findings in the neonatal period were reviewed for the presence of intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), and ventricular dilatation.

Intraventricular hemorrhage (IVH) was classified according to Papile et al.[13] Periventricular leukomalacia (PVL) was graded according to Vries et al.[14] Severe cerebral lesions on cranial ultrasound findings were defined as the presence of IVH grade III or IV, and/or PVL ≥ grade II.

All surviving children were offered care in our high-risk infant follow-up program. Repetitive examinations by experienced pediatric neurologists were performed. Their development was evaluated using the Enjoji Developmental Scale[15] before six years of age, followed by the Japanese Wechsler Intelligence Scale for hildren-Revised[16] (WISC-R) or Wechsler Preschool Primary Scale of Intelligence[17] (WPPSI). Children with normal development had a normal neurological evaluation and developmental quotient (DQ) or intellectual quotient (IQ) > 85. Minor neurodevelopmental impairment was defined as the presence of at least one of the following: mild cerebral palsy causing motor clumsiness or non-fluent gait, DQ or IQ between 70 and 85. Major neurodevelopmental impairment was defined as the presence of at least one of the following: cerebral palsy, DQ or IQ <70, deafness, or blindness. Cerebral palsy was classified as diplegia, hemiplegia, quadriplegia, dyskinetic or mixed.[6,8] Developmental or mental borderline was defined as DQ or IQ between 70 and 85. Developmental or mental retardation was defined as DQ or IQ <70.[15, 16, 17]

Statistical analysis: Analysis was performed with the SPSS statistical package 16.0 (SPSS Inc, Chicago, IL). Differences between categorical variables were analyzed using the chi-square test or the Fisher exact test as appropriate. Differences between continuous variables were tested using independent sample t-tests. A statistically significant difference was defined as $p<0.05$.

Results

Table 1 shows the pregnancy and fetal outcomes with TTTS. During the nine-year study, 21 pregnancies with TTTS were admitted to our center. The gestational age at diagnosis ranged from 18 to 34 weeks with a mean age of 24 weeks. The gestational age at delivery ranged from 22 to 34 weeks with a mean age of 28 weeks. Thirteen pregnancies (61.9%) were treated with serial amnioreduction, with the number of amniocenteses ranging from one to six per pregnancy (mean 2.7). In the eight pregnancies in which amnioreduction was not performed, one pregnancy was complicated by premature rupture of the membrane, two pregnancies presented with mild TTTS (stage I), and one pregnancy opted for delivery. There were two survivors in 42.9% of pregnancies, one survivor in 19% of pregnancies, and no survivors in 38.1% of the pregnancies. The Quintero stage at diagnosis showed 11 pregnancies to be stage I, four pregnancies to be stage II, three pregnancies to be stage III, three pregnancies to be stage IV, and none to be stage V. Intrauterine fetal demise occurred in five fetuses (11.9%), and all of these resulted from pregnancies not treated with amnioreduction. One pregnancy culminated in the intrauterine death of both fetuses, and three pregnancies resulted in the intrauterine death of one fetus. In the three neonates born after the intrauterine fetal demise of their co-twin, one neonate born at 22.4 weeks died soon after birth, one neonate died of heart failure at 75 days of age, and one survivor had mild cerebral palsy with epilepsy and mental retardation. Neonatal death occurred in 13 neonates (35.1%). The overall perinatal mortality rate was 42.9% (18/42). Two infants died after the neonatal period. Twenty-two survivors were followed to at least the age of 1 year corrected for prematurity. Two survivors were lost to follow-up. Neurological follow-up was available for the remaining twenty survivors. The mean age at follow-up was 6.3 years (range, 3-12 years). Fourteen children (70%) had normal neurological development. Six children (30%) had neurodevelopmental impairment.

Of 37 neonates, four died before the cranial ultrasound scan was performed. Abnormal ultrasound findings were present in seventeen (51.5%) of 33 neonates as follows: IVH grade I in five neonates; IVH grade I in three neonates; IVH grade I + III in two neonates; PVL grade I in three neonates; PVL grade I in two neonates; and mild ventricular dilatation in two neonates. Of seventeen neonates with abnormal cranial ultrasound findings, neonatal death occurred in five neonates; infant death occurred in two infants; one survivor was lost to follow-up; five of the

Table 2 Data of the 6 surviving twins with adverse neurodevelopmental outcomes

Case	D/R	Quintero stage	GA at diagnosis (weeks)	GA at birth (weeks)	AR (n)	Birth weight (g)	Neonatal cranial ultrasound findings	Follow-up age (years)	Neurodevelopmental Impairment	IQ	Outcome of co-twin	Severity
1	R	III	19	27	0	814	IVH I	6	Mild CP, epilepsy, Mental retardation	61(6 years)	IUFD	major
2	R	I	20	28	4	1018	PVL I	8	Mental retardation	69(6 years)	mental borderline	major
3	R	II	26	27	1	1130	mild bilateral ventricular dilatation	7	Mental retardation	54(6 years)	Infant death	major
4	D	I	21	28	0	865	IVH III	12	Mild CP, mental borderline hydrocephalus	70(12 years)	Mild CP, mental borderline	major
5	R	I	21	28	0	975	IVH I	12	Mild CP, Mental borderline	78(12 years)	Mild CP, mental borderline, hydrocephalus	minor
6	D	I	20	28	4	886	normal	8	Mental borderline	71(6 years)	mental retardation	minor

R = Recipient, D = Donor, GA = Gestational age, AR = Amnioreductions.

IVH = Intraventricular hemorrhage, PVL = periventricular leukomalacia; CP = cerebral palsy.

IUFD = intrauterine fetal death, IQ = intellectual quotient.

nine survivors had neurodevelopmental impairment. A severe cerebral lesion was present in four neonates (12.1%). One neonate born at 24 weeks died of heart failure at one day of age. One neonate whose co-twin died at 26 weeks of gestation died of heart failure at 75 days of age. Two survivors had major neurodevelopmental impairment. On 16 neonates with normal cranial ultrasound findings, neonatal death occurred in four neonates; one survivor was lost to follow-up; and one survivor had minor neurodevelopmental impairment.

Table 2 shows adverse neurodevelopmental outcomes with TTTS. Four children (20%) had major neurodevelopmental impairment. For case 1 (in which fetal death of the donor co-twin occurred at 25 weeks of gestation), birth occurred at 27 weeks of gestation. The child was found to have mental retardation (IQ 61) and epilepsy with mild cerebral palsy causing a non-fluent gait. Case 2 (PVL (grade I)) had mental retardation (IQ 69). Case 3 had mild bilateral ventricular dilatation and mental retardation (IQ 54). Case 4 had posthemorrhagic hydrocephalus and mild cerebral palsy causing motor clumsiness. Because the child's IQ was exactly 70, the case was classified as borderline mental impairment. However, we considered case 4 to have major neurodevelopmental impairment in this study on the basis of general clinical judgment. Two children (10%) had minor neurodevelopmental impairment. Case 5 had borderline mental impairment (IQ 78) and mild cerebral palsy causing motor clumsiness while case 6 had borderline mental impairment only (IQ 71). Case 2 /case 6 and case 4/case 5 comprised the pairs in two twin pregnancies. All of them were delivered before 29 weeks of gestation.

Table 3 shows antenatal and delivery characteristics in surviving cases without neurodevelopmental complications as well as those complicated by death or neurodevelopmental impairment. The mean gestational age for those surviving without complication at diagnosis and delivery was 28 weeks (range, 24 - 34 weeks) and 31 weeks (range, 27-34 weeks), respectively and the mean gestational age for those with death or neurodevelopmental impairment at diagnosis and delivery was 22 weeks (range, 19 - 27 weeks) and 27 weeks (range, 22 - 31 weeks), respectively. Overall, the mean gestational age for those with death or neurodevelopmental impairment was lower than surviving cases without neurodevelopmental impairment. The interval between diagnosis and delivery was significantly longer and the birth weight was significantly lower in those complicated by death or neurodevelopmental impairment. There was no difference in the ratio of Donors to Recipients between the groups. Table 4 shows perinatal outcomes and survivors' outcomes between amnioreduction and non-amnioreduction. There was no significant difference in the mean gestational age

Table 3 Comparison of normal development and death or neurodevelopmental impairment

	Normal development	Death or Neurodevelopmental impairment	*P* value
Number	14	26	
Gestational age at diagnosis (weeks)	28 (24-34)	22 (19-27)	< 0.001
Gestational age at delivery (weeks)	31 (27-34)	27 (22-31)	< 0.001
Diagnosis to delivery interval (days)	15 (2-34)	32 (1-50)	0.002
Birth weight (g)	1355 (750-2130)	812 (255-1970)	0.001
Donor/Recipient	7/7	13/13	0.999

Data shown as mean (range) or n as appropriate.

Table 4 Perinatal outcomes and survivor' outcomes between amnioreduction (AR) and non-amnioreduction (non-AR)

	AR	non-AR	*P* value
Number	26	16	*NS*
Gestational age at diagnosis (weeks)	25 (18-32)	23 (19-34)	*NS*
Gestational age at delivery (weeks)	28 (24-34)	27 (22-34)	*NS*
Diagnosis to delivery interval (days)	22 (4-56)	30 (1-73)	*NS*
Birth weight (g)	1124 (335-2222)	921 (255-2138)	*NS*
IUFD	0	5 (31.2%)	*NS*
Neonatal death	10 (38.5%)	3 (27.3%)	*NS*
Infant death	1 (3.8%)	1 (9.1%)	*NS*
Lost to follow-up	2 (7.7%)	0	*NS*
Long-term survivors	13 (50%)	7 (63.6%)	*NS*
Neurodevelopmental impairment	3 (23.1%)	3 (42.9%)	*NS*

Data shown as mean (range) or n (%) as appropriate.
NS, not significant; IUFD, intrauterine fetal death.

at delivery, diagnosis to delivery interval, or neurodevelopmental impairment.

Discussion

In this study, we reported that the overall perinatal mortality rate in conservatively treated patients with TTTS was 42.9%. The result was similar to the mortality reported by Mari et al,[18] Gray et al,[19] and Senat et al.[4] We found that 30% of surviving twins had neurodevelopmental impairment when TTTS was treated conservatively. Four children (20%) had major neurodevelopmental impairment. Two children (10%) had minor neurodevelopmental impairment. Cincotta et al. observed 17 pregnancies, of which 12 (71%) were treated with serial amnioreduction.[9] Twenty-three children were followed up at least two years. Five survivors (22%) had major neurological morbidity, which was similar to our results. Dickinson et al.[7] investigated 52 surviving infants from 31 pregnancies, with 22 pregnancies treated with serial amnioreduction. 49 children were followed up at a median age of five years. Major neurodevelopmental disability was present in seven children 14.3%. Minor neurodevelopmental impairment was not reported.

Mari et al investigated 42 survivors of TTTS after aggressive amnioreduction.[20] Cerebral palsy was diagnosed in two of 42 infants (4.7%). No developmental tests were used and the incidence of major neurodevelopmental impairment was lower. With regard to overall neurodevelopmental impairment, we found the incidence was lower than several studies previously reported in analyses of long-term neurological outcome.[8,10,21] Lopriore et al investigated 29 pregnancies, including 18 pregnancies (62%) with serial amnioreduction.[10] Twenty-nine children were followed up to a mean age of 6.2 years (4-11). Major neurodevelopmental impairment was observed in 21% of children, and minor neurodevelopmental impairment (mild speech delay) was seen in 17.2% (5/29). Haverkamp et al described 40 children who were followed up to a mean age of 24 months.[21] Majo neurodevelopmental impairment was seen in 23%, while minor neurodevelopmental impairment was found in 33%. Frusca et al investigated 31 children who were followed up to a mean age of 24 months.[8] Eight children (25.8%) had major neurologic disabilities; five children (16.1%) had minor neurologic disabilities. This discrepancy may be due to the heterogeneity within the neurodevelopmental impairment of TTTS and assessment of neurodevelopmental outcome.

Abnormal cranial ultrasound findings were found in seventeen cases (51.5%) of the 33 neonates who underwent cranial ultrasound scans. Denbow et al. reported an even higher incidence (58%) of neonates with abnormal cranial ultrasound findings.[2] Gestational age at delivery and birth weight were not associated with an incidence of abnormal cranial ultrasound findings. Cranial ultrasound scans at birth are commonly used as a surrogate marker for neurodevelopmental outcome in later life.[22] Periventricular white matter lesions (WMLs) and persistent ventriculomegaly in particular have been associated with an adverse neurodevelopmental outcome.[22, 23] In our patient group, five cases (15.2%) showed WMLs. Some studies have shown evidence of cerebral white matter lesions in one third of monochorionic twin infants at birth, particularly when the pregnancy was complicated by long-term coexistence with a co-twin intrauterine demise.[24, 25] Hecher et al.[26] reported a lower incidence (6%) of cerebral WMLs following laser surgery, compared with the cases treated by amnioreduction (18%). Results from observational studies[2, 10, 27] and an international multicenter registry[18, 28] of TTTS treated by amnioreduction suggest that the incidence of major cranial abnormalities ranges between 18 and 41%. Discrepancies among results may be due to differences in diagnostic criteria, disease onset, severity of the TTTS treatment modalities, and stratification of cranial lesions.

Since laser surgery for TTTS was introduced, survival rates have been increasing. Neurodevelopmental impairment, however, is still relatively common. Sutcliffe et al investigated 67 children with severe TTTS treated by laser surgery, and 9% had cerebral palsy.[29] They did not report the number of infants with developmental delay. Banek et al investigated 89 children after TTTS treated by laser surgery between 14 months and 44 months. Eleven percent of the children had minor neurologic deficiencies, and an equal portion had major neurologic deficiencies.[5] Graef et al investigated 167 children from TTTS treated by laser surgery and followed to a median age of 38 months (14 - 53).[30] In this group, 7.2% of the children showed minor neurologic abnormalities, and 6% showed major neurologic abnormalities. Both studies originated from the same research group in Germany. The largest analysis concerning long-term neurodevelopmental outcome after TTTS with laser surgery was published by Lopriore et al.[6] They investigated 278 children at two years of age (corrected for prematurity). The incidence of major neurodevelopmental impairment was 18%. They did not report minor neurodevelopmental impairment.

Whether TTTS is treated with laser surgery or managed conservatively, the incidence of major neurodevelopmental impairment is high. The pathogenesis of cerebral injury in TTTS is not clearly defined. Cerebral injury in TTTS may result from antenatal injury secondary to hemodynamic and hematological imbalance[21] and/or from postnatal injury associated with prematurity[31] and low birth weight.[8] In our study, the long-term outcomes for the survivors with TTTS were relatively good when survivors were delivered after 29 weeks of gestation. Mari et al found that long-term outcomes for the twins with TTTS were excellent when both fetuses were delivered alive after 27 weeks of gestation.[20] A research group from Germany reported that neurodevelopmental disability in infants who were born before

32 weeks of gestation was significantly higher.[5,30] Lopriore et al and Lenclen et al showed that early gestational age at delivery was a risk factor for neurodevelopmental impairment.[6, 32] It seems that prolongation of gestation is central in management strategies. The results of the present study suggest that the outcomes, particularly neurodevelopmental, resulting from the conservative management of TTTS are not markedly different from outcomes obtained with laser surgery. The strength of our conclusion is limited by the small study size and the preponderance of mild cases which presented later.[6] While immediate neonatal survival may be improved with laser surgery, this advantage may be lost with long term follow-up.

Conclusions

In conclusion, the primary predictor for neurodevelopmental impairment is gestational age, regardless of whether the management is conservative or by laser surgery. Therefore, prolongation of gestation is important. Additionally, we suggest performing a routine cranial ultrasound examination after birth as the results will be valuable in predicting long-term neurodevelopmental outcomes.

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Maternal Bodies…continued from page 41
been recognized and is under-researched. We are calling for the development of research that focuses on the maternal body. This is important because the themes of "purity" in pregnancy and breastfeeding, seem to be gaining momentum and increasing people's anxiety about what the maternal body is exposed to.

Women must deal with competing interests (hers and her baby's) when making decisions about medicine use in the pregnant and lactating body. However, when making such decisions, pregnant and breastfeeding women rely not only on the expert knowledge of their health care professionals but on their own experiences and socio-cultural understandings as well. Women are likely to be influenced by their families, partners, their cultural and societal norms and expectations, but also by discourses of risk, responsibility and good motherhood.

We argue that considering these issues in the complexity of maternal bodies can improve understanding of risk perception and decision-making concerning medicine use for the population as a whole as well as providing a better understanding of the decisions made by pregnant and breastfeeding women. In addition to research on the safe use of medicines during pregnancy and lactation, qualitative research is needed to explore in-depth the quandaries that women and their health care providers face when medicine is indicated for pregnant and breastfeeding women. Understanding decision-making by women and by health professionals requires suitable study methods (as recommended by the review of antenatal screening for Down syndrome).

While it may be helpful to conceptualize the "maternal body" when examining medicine use in pregnant and lactating women, it is over-simplistic to believe the issues are always the same. The answer is not one response for both pregnant and breastfeeding women. Responses must be considered separately for the pregnant woman and the breastfeeding woman. Research to help us understand the concerns of the women and health professionals will help with planning salient education programs for both groups.

Editorial…continued from page 4
helpful in the long term were explicit sharing of responsibility, clear expression of staff preferences, and respectful care and language toward the child.

Parents find it valuable to express their opinion in the EOL DMP of their child. Nonetheless, they do need continuous emotional support and an explicit share of the responsibility for the decision. As involvement preferences and associated feelings can vary, parents should be able to decide what role they want to play. However, our study suggests that fully autonomous decisions should be misadvised in these types of tragic choices.

The distribution of roles between physicians and parents as surrogates of the child in this process has raised questions for many years. Parents are naturally called on to participate in the decision because of their parental authority and because they are the persons besides the child most affected by the decision's consequences. The importance of involving parents is recognized by ethical guidelines in numerous countries. However, results from studies exploring caregivers' and parents' opinions on this topic are far from unequivocal. Some caregivers prefer to exclude parents from explicit participation or have them participate without making the final decision, to protect them from potential subsequent guilt. Others, on the contrary, consider parents to be the best placed to make these decisions, at least in some cases. On the other hand, some parents complain that they must live with the consequences of decisions made unilaterally by the caregivers. Parents do not want to be excluded; they frequently want to participate but not to decide, in view of the difficulty of the decision. Cultural context can nonetheless influence the preferred type of involvement.

A review of the literature shows that several aspects remain unclear: in studies involving parents, the notion of "taking part in a decision" seems to refer to diverse types of involvement, ranging from awareness of the decision to taking final responsibility for it. Other unclear issues include how end of life (EOL) decisions are taken, how parents construct and feel about those decisions, and what impact their type and content have on their future emotional well-being. This study sought to improve our knowledge of this area through an in-depth qualitative exploration of parents' experience of the EOL decision in the NICU. In particular, the study aimed to explore how parents described the decision making (DM), whether their feelings varied according to their perceived role in the decision process, the long-term impact of the experience in terms of guilt feelings and what they valued about physicians' attitudes in this situation.

The study included parents whose child died from 2002 through 2005 in one of 4 NICUs in different areas in France. All four units allowed unrestricted visiting for parents, and none had a specific protocol calling for family meetings for EOL decisions in clinical practice. Parents were contacted by letter about 2 years after the child's death and asked to participate in an interview.

In-depth face-to-face interviews lasted an average of 100 minutes. Parents were asked to speak freely about their own perspectives, concerns and feelings about the child's history and about their emotional condition and life following the death up to the moment of the interview. Interviewers paid special attention to the parents' perceived involvement in the end-of-life decision-making process (EOL DMP), which is the focus of this paper. Telephone interviews were less structured and limited to topics spontaneously chosen by the parents. This procedure was employed for ethical reasons because telephone interviews do not allow interviewers to provide the direct emotional support to parents possible in face-to-face interviews. The interviews were recorded. Eighty families agreed to telephone interviews and 53 to face-to-face interviews. In all 164 individual parents of 139 infants participated. Among the face-to-face respondents, 25 pairs of parents were interviewed simultaneously. Interviews were conducted between 2005 and 2008. Participants' mean age was 33.9 years at the time of the interview. Most were European women of high or middle socioeconomic status.

A third of the parents interviewed in person reported that *no decision* was made before the child died. In this case, the parent perceived that the child had died spontaneously without any discussion or any action by the staff (to withhold or withdraw treatments). "They *(the doctors) didn't even stop the machine; he died all alone; he fought for a day. He wanted to live. The machines were working as hard as possible. They couldn't do any more. So we were right to go all the way, to give him his chance.*" All the other parents reported a decision with a specific perceived role in the EOL DMP. We identified three types of decisions: shared decision, which was the most frequent, medical decision, and informed parental decision. We defined the decision as *medical* when it was perceived as made by the physician without explicit parental involvement. "*As doctors, they considered that at some point it was necessary to decide to pull the plug. Therefore at that point, they suggested we all go to the bedside.*" Medical decisions were the object of largely positive feelings. Many parents said that although they were not explicitly involved in the decision, they had reached the same conclusions as the medical team. Some spontaneously expressed relief that they did not have to decide, while others added that they found it impossible to express anything other than a desire for a healthy life for their baby: *"The doctor said to us: What do you want to do? We said to him: But you are the doctor, what would you do? Because what we want is for our child to be well."* The decision was defined as *shared* when it was made after a discussion with the physicians, during which each person explained what mattered from their perspective and each agreed with the decision. *The shared decision* was appreciated overall because it allowed the parents to express themselves without having to decide alone: *"The doctor said to me, 'your opinion is of course important, and your decision will be equally important, but you should know that the medical team also has an opinion and a decision.' That was good. I said to myself, Thank god, it isn't me who has to decide. Because I had just been thinking what a real, total fright it would be to decide alone."* A majority pointed out the possibility of protection against guilt: "*I have the impression that (the doctors) act so that you have the impression that you are not making the decision yourself, so that you cannot hold it against yourself later.*" All felt that confirmation by the doctors provided comfort and security: *"He said to us that the team would follow us in our decision, that he thought it was a good decision. That was great solace, because in fact it was our decision to make, and it was horrible to decide. At the time, it was great to be able to decide, that is, if a doctor had said to me, 'We are deciding this,' it would have been unbearable for me. Here, it was difficult but the fact of having support, and hearing that … yes it did me a lot of good."* A minority of parents also stressed the importance of respect for their personal values: "*I think it's very important to be involved. You know there are people who have convictions which don't disappear, even though their child*

has no cerebral activity that would allow him a minimum of life." None of these parents demanded greater involvement. Retrospective disagreement about the decision was found only once: a mother recently immigrated from Africa would have liked to oppose it. A minority of parents felt incapable of analyzing the situation and found this sharing artificial: "*It has a supernatural feeling. You don't really realize anything. Me, I said yes to everything. We were acted on, not actors.*" One mother felt obliged to state her agreement, although she would have preferred to accept in silence. Guilt feelings and the weight of a "life or death" decision persisted for many parents within this shared DM group, despite the perceived involvement and support of the staff. The decision was defined as *informed parental* when the parents considered the situation and made a decision without the doctors, after receiving full information about the medical data. *"They left us a full range of choices, based on our ethics, our morals, our religion."* The doctors applied the parental decision without influencing or reinforcing it. *Informed parental decision* was experienced negatively in most cases, largely because of a feeling of abandonment by the staff in a decision that involved the child's fate: "*They gave the choice to us, and it was difficult because they left us all alone, they left us really completely alone.*" Only a minority experienced it positively, sure that they had made the right decision to relieve their child's suffering.

On the whole, parents did not report the existence of an explicit discussion with the physicians on the distribution of roles in the DM. The parents most often accepted the role proposed by the doctor, without raising questions: "*They made us choose, a little, to say: I thus ask you not to keep this living creature alive.*"

Most parents described the decision as complex, neither chosen nor rational, and solitary. Complexity was linked to the effect it had on the family as a whole and to the sometimes contradictory interests involved, especially when based on the infant's future quality of life: "*It's selfish to say we are going to let her live for us. But it's also selfish to say that we are going to let her go to protect others.*" It often seemed imposed, constrained by the facts: "*They (*the doctors*) came to tell us that she was going to die, at the same time, it was our choice — but what choice? As if you can talk about a choice. It was surrealistic for me.*" Ambivalence was frequently suggested independently of the perceived role; although parents spoke about a "decision," they didn't describe it as a positive choice: they decided something but did not will it to happen.

Most parents described having made the decision in a less than rational way, sometimes hurriedly or intuitively: *"I did not want to think about it, for me it was clear; I never even asked myself the question."* Emotions blocked many mothers - more frequently than fathers - in their ability to analyze the situation: "*At the time, all the emotions were different. I would have accepted a child with all the handicaps in the world, although I know very well today that that would not have been good for anyone.*" For several parents the medical explanations were not sufficiently interpretable to serve as the basis for rational reflection: "*It was stories of percentages. Therefore in 50% of cases the children die of the side effects, and the 50% who remain, another 60% die. At the end, there was nothing. But I said, but what is she going to know about life?*" Several stressed the difficulty of having to decide alone. *"The doctors say to us: 'It's your choice. We are leaving the decision to you.' And finally, that is very very hard. I don't think it is a good thing."*

Of the parents interviewed in person, 48 of the 78 reported guilt feelings, 37 not related to the EOL DMP, 11 directly related to it. Among these 11 parents, 3 perceived an informed parental decision and the remaining 8 a shared decision. A mother who perceived she had decided without the doctors, reported: "*We are the ones who said, then, on such a day, we stop. It is difficult for parents to tell themselves that they are not (well let's say) 'killing' our child; it is that you stop, we stopped what was keeping her alive. You hate yourself.*" Persistent interrogations over the moral value of these past decisions were found among around half of the parents. This result was mostly observed in parents reporting an informed parental decision. Parents said they searched for arguments to make the decision acceptable and morally praiseworthy. However many found that to be difficult or impossible, especially those who thought that the decision was based on the child's future prognosis: "*Is it better to live with what we have now, or with an extremely handicapped child?*" Three years after the decision, half of the parents said they couldn't accept the past decision: *"It's not a choice; it's something that you never admit."* Many finally said they had to accept the decision, because its consequences were irreversible: "*After, you say to yourself, he is perhaps better off where he is than to live handicapped his whole life. In any case, you have to look at the positive side, or you will never get over it. You find reasons.*" Some supported the decision afterwards by concluding that God or Nature had finally made the decision.

Most of the parents used the interview to transmit messages to medical staff about improving the decision-making experience. Several points emerged as most important in helping parents to cope with this decision afterwards: some involved the development of a trusting relationship with staff members, and others how doctors should be involved in the DMP. The parents felt comforted in a protective, sympathetic and communicative ambience: *"They even asked me if I was hungry."* They appreciated dealing with the same caregivers the whole time: "*All 10 days, this pediatrician was there. She was really a person with whom we made decisions, choices, and she was there for us in the last seconds. She shared everything with us.*" Care and attention to the baby were important: "*The whole team was great, especially during the care, the procedures, the precautions they took with him, always extreme consideration. That was important.*" These factors gave them confidence in the staff and allowed some to express feelings that were difficult but determinative for the decision: "*I had a fear that I discussed with the doctors, in fact, I was afraid that she would live, to be honest. I said to myself that if they ever give us this, between quotations marks, 'gift' of the child, alive, it is going to be a nightmare for the entire family.*"

An interpersonal dialogue about the decision was praised; conversations with the doctor between humans on an equal footing made it possible to imagine the overall reasonableness of the choices. *"He explained that it was … I remember he said something: this isn't reasonable."* The family context and the realities of life had to be taken into account. "*The doctor left me the choice. He explained to me the risks of these choices. He told me, you already have a three-year-old daughter. He stayed in the context of our little family: for the child, for me, for my family. If something happens to you, who will take care of him? Very concrete questions.*"

Respectful language toward the child and the parents left a memory of the doctor's positive intentions: "*Doctor A*

always called the baby by her name: 'Lena has very serious sequelae'. She was a person, not an ordinary case." Inversely, a disagreeable, barely involved attitude encouraged subsequent questions about the decision taken: "*This doctor, I don't ever want to see him again. When he told us that it was no longer legitimate to continue the resuscitation, he said it to us casually, without emotion, as if that happened to him every day. He was not warm. So, was he telling us the truth? That's a question.*"

An expert medical explanation, transmitted frankly, not necessarily in detail, allowed the parent to understand the situation: "*The doctor had explained the severity of the sequelae to us. He said to us, do you understand what that means? But obviously we did not know what that meant.*" The doctor should translate, repeat and refine the medical data without creating false hopes or using incomprehensible metaphors. Consistency among the professionals was reassuring.

Parental desire for guidance in the DM varied among participants. More than half of the participants stated that the medical staff should express their opinions overtly and directively. These parents reported that they had felt overwhelmed by the situation (emergency, discovery of an unexpected malformation, or extreme prematurity) or by the exhaustion due to the baby's long hospital stay. Some mothers related this to their own weak health status in the post-partum. Other parents (approximately a quarter of the participants) preferred that the staff reveal its preference non-directively. Finally, a small minority reported that they did not need the staff opinion to decide.

Strong parental positions were in general not desired. For some, the decision was made by saying something to a given physician in an official setting. This gave them the impression of an action, a verbal action that could have been the cause of the child's death. Some had difficulty dealing with the fact that different doctors suggested different options: it made them feel obliged to take a position strongly and deliberately in favor of death. Many parents reported that doctors should explicitly involve themselves in the DM. *"Once we made our decision, it would have been best for the medical staff to be behind us, to tell us: you are right, this is what should be done, you've made the right choice."* The relief and security provided by the doctors' explicit position at least in supporting their choice was mentioned by many parents: "*Once we told them, they came to support our choice, saying, you've made the right decision. In fact they wanted to make us not feel guilty.*"

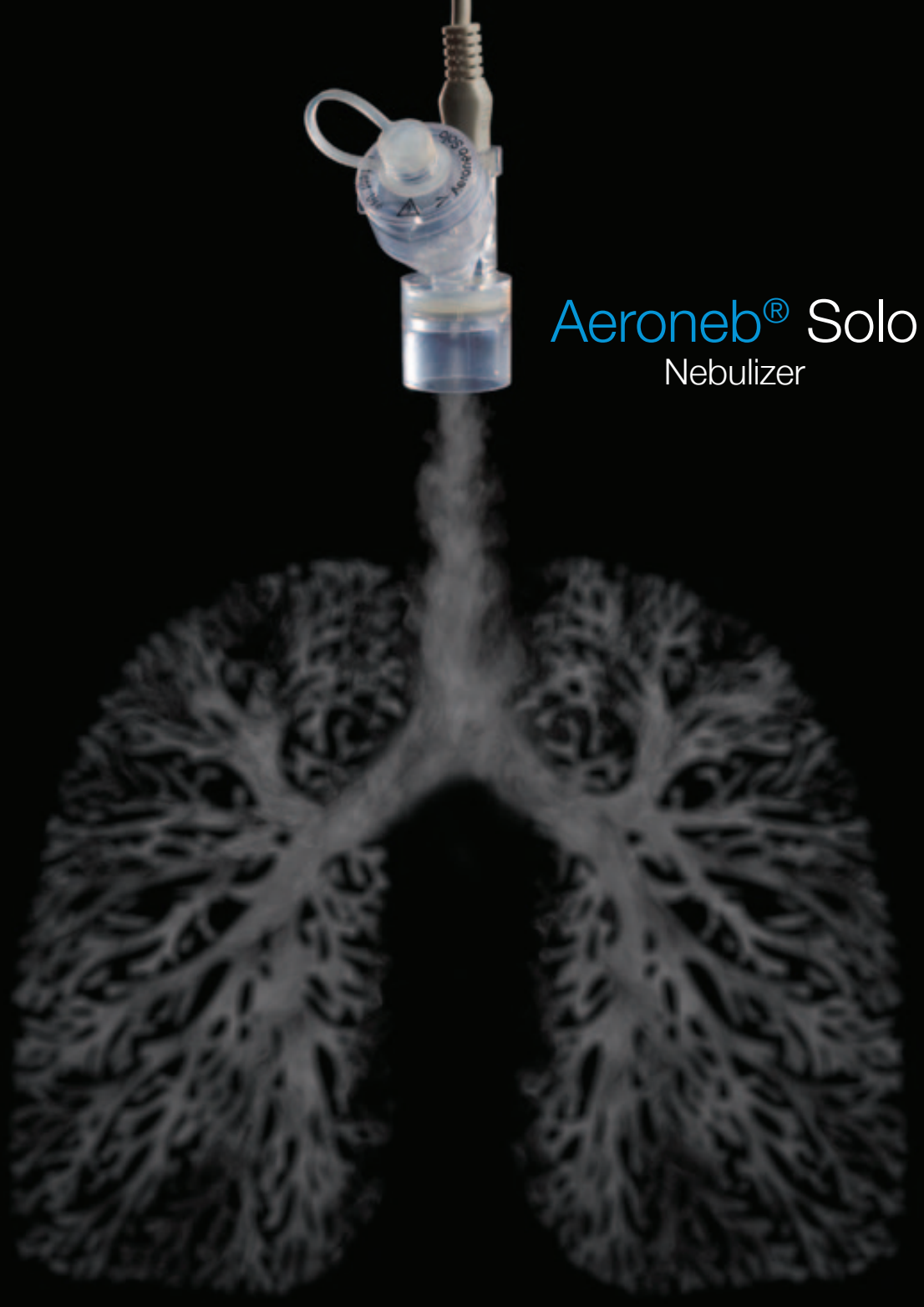
Overall, our study shows that the EOL decision is always complex, but often not really a choice for parents or rather, when the child is moribund, it is a Hobson's choice: if death can be prevented the step is nonetheless difficult to justify. Parents are tempted to flee such a stressful situation by making intuitive or rushed decisions, as shown in other stressful situations. Moreover, decisions are perceived as complex because they involve contradictory interests, making it difficult to define the child's best interests clearly.

The complex nature of such decisions affects how parents experience their involvement in the DM. Most parents explicitly preferred DM that they perceived as shared, which appears to offer a balance between the active position that parents seek and their fear of being wrong and overwhelmed by the future weight of responsibility.

Many parents, however, accept that doctors make the decision. In this case some parents stated their preferences and implicitly left to doctors the duty to make a decision in their place, as in a "doctor-as-agent" model. Others gave their assent to decisions already made by the team that they found appropriate, which allowed them to have their choice followed while avoiding responsibility for it. Finally, a small number of parents reported a decision made on their own without the doctors. The rarity of this autonomous decision might be related to the cultural context of the study: in France most neonatologists believe that parents in the NICU should not be required, or even allowed, to make the EOL decision alone. Although some could accept it, the majority strongly criticized precisely that aspect, being left alone to make the decision. They perceived it as isolation and abandonment. According to our data, parents need doctors to provide a supportive presence and to clarify the issues at stake. Those actions are necessary but not sufficient: it is at the moment of the decision that the presence and position of the doctor become essential. In the long term, this trusting environment reinforces the validity of the decision. In cases where parents perceived that they had decided without medical involvement, they often felt that the responsibility of having made a "life or death" decision was equivalent to a transgression: it belongs to God, nature, fate or possibly to the doctors but not to them.

In conclusion, many parents find it valuable to express their opinion in the EOL DMP of their child. Nonetheless, they do need continuous emotional support, a trusting relationship, and an explicit share of the responsibility for this decision. As involvement preferences can vary, real shared DM should also enable parents to decide the role they want to play in this crucial situation. It should be borne in mind that in these types of tragic choices, parents' subsequent coping would be aided by physicians' recommendations that the parents not take a fully autonomous decision. Deeper thoughts about the child's best interests might help to put these decisions into a clearer context. Concepts associated with communication and patient-centered medicine and parental insights could serve as a basis for training NICU professionals.

[Living with a Crucial Decision: A Qualitative Study of Parental Narratives Three Years after the Loss of Their Newborn in the NICU. Laurence Caeymaex, Mario Speranza, Caroline Vasilescu, Claude Danan, Marie-Michèle Bourrat, Micheline Garel, and Catherine Jousselme. Reprinted from PLoS, copyright Caeymaex et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License. The article has been edited for our readers. For the full article, with references and tables, please visit PLoS and type the full title.]



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1. Centers for Disease Control and Prevention. (2003) Guidelines for Environmental Infection Control in Health-Care Facilities. Recommendations of CDC and Healthcare Infection Control Practices Advisory Committee (HICPAC). MMWR, 52(RR10):1-42.

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