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References: 1. Carver JD, et al. *Pediatrics.* 2001;107:683-689. **2.** O'Connor DL, et al. *Pediatrics.* 2001;108:359-371. **3.** Groh-Wargo S, et al. *Pediatr Res.* 2005;57:712-718.

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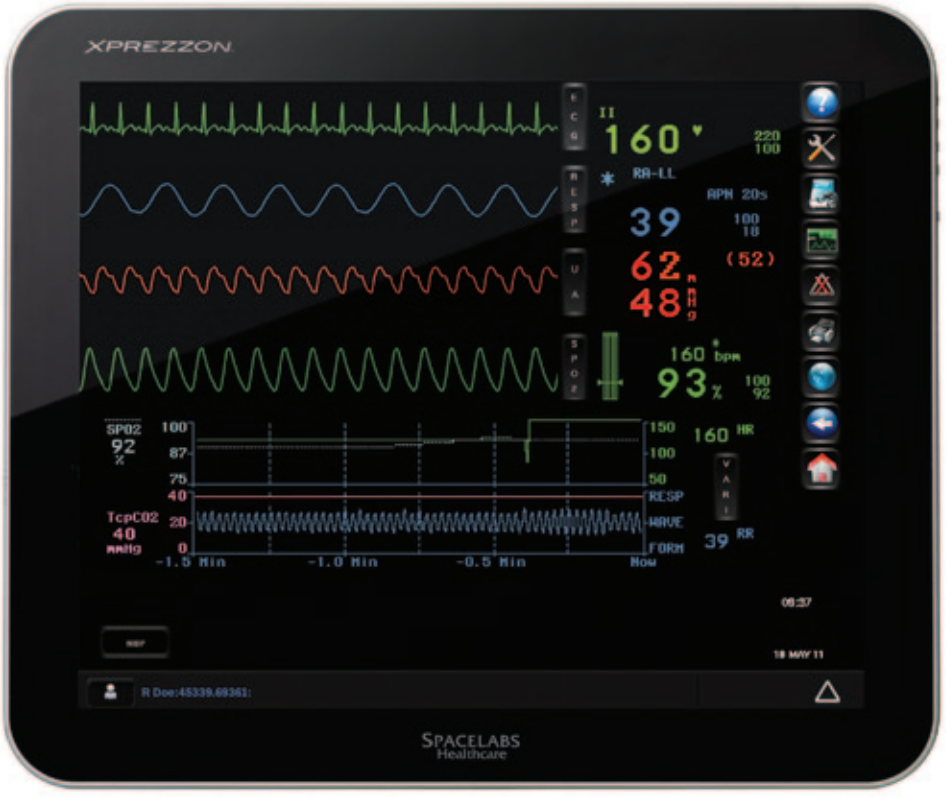

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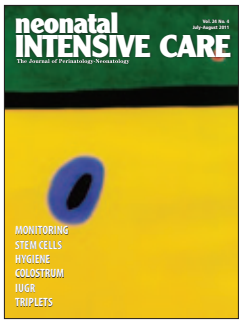

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INTENSIVE CARE

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Editorial

STEM CELLS – FROM JELLY TO GOLD

Boris M. Petrikovsky, Jeffrey Karsdon

Stem cell research is a controversial issue in the United States. These cells have the ability to differentiate into any type of cell and are ideal for repair of damaged tissues and organs eg Parkinson's disease, diabetes, heart disease, multiple sclerosis, burns and spinal cord injuries. Stem cells obtained from adults can only differentiate into different cell types of their tissue of origin while stem cell from the embryo (embryonic stem cells) can become all cell types of the body because they are pluripotent. Therein lies the rub. The embryonic stem cells are obtained from the destruction of the human embryo and here has great religious (fertilized egg is human) and political (violates the sanctity of life and is tantamount to murder) implications, which has hampered stem cell research in the United States compared to other industrialized nations.

To avoid these thorny issues attempts have been made to reduce the need for the embryo all together and some progress has been made. Kliminskya developed a stem cell line (Advanced Cell Technology, Worcester, MA) from a single blastomere obtained at the 8-10 cell embryo,[1] but still an "embryo" to some nonetheless. The embryo has been removed from the equation when stem cells are obtained either from the amnion[2] or amniotic fluid.[3] As politically correct as these techniques may be to the embryo, obtaining these stem cells is still difficult and invasive.

The answer to all these concerns may be the use of stem cells obtained from the Wharton's jelly of the umbilical cord after birth... or from the pulp of developing teeth (which would be your first choice).

Wharton's jelly is named for an English physician and anatomist, Thomas Wharton (1614-1673) who first described it in his publication Adenographia or "The Description of the Glands of the Entire Body," first published in 1656.

It is a gelatinous substance found within the umbilical cord as a mixture of water, gelatin, lipids, proteins, and enzymes. Wharton's Jelly is a rich source of stem cells, fetal specific proteins, fatty acids, and phospholipids, among other components. It provides protection to the blood vessels in the umbilical cord. In general, dry Wharton's Jelly is a composition of aminoacids mucopolysaccharides (35%), gelatin (25%), hyalaronan (15%), fetal-specific proteins and enzymes, (gelatinase A-meralloproteinase (MMP)-2, 72 KD and gelatinase B (MMP-9, 92 KD). It also contains a small amount of lipids (phospholipids and glycolipids). Wharton's jelly stem cells should be distinguished from umbilical cord stem cells.

Reports on trans-differentiation of mononuclear cells derived from human umbilical cord into immune response cells aroused great interest among investigators. Canque et al[4] reported their experience with human umbilical cord blood derived stem cells differentiation into dendritic cells/Langerhans cells responsible for initiating and maintaining the adaptative immune response.

The human umbilical cord has been a tissue of increasing interest in recent years. Many groups have shown the stem cell potency of stromal cells isolated from the human umbilical cord mesenchymal tissue, namely, Wharton's jelly.

Bakhshi et al[5] isolated and cultured mesenchymal stem cells from umbilical cord segments dissected after birth. These stem cells were grown in cell culture and allowed to divide and replicate. Morphology was documented and cell surface markers were determined by flow cystometry.

Stem cells obtained from Wharton's jelly have many advantages. It has low immunogenicity, easy to obtain (harvesting is non-invasive and in large numbers), and

Continued on page 25…

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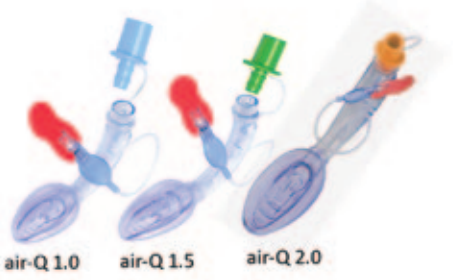

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News

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STRESS AND PROBLEMS

Research from Perth's Telethon Institute for Child Health Research has found a link between the number of stressful events experienced during pregnancy and increased risk of behavioral problems in children. Researchers found that it is the overall number of stresses that are most related to child behavior outcomes. Two or fewer are okay but three or more could mean trouble. Researchers also found that the type of stress was less important than the number. The scientists recruited 3,000 pregnant women and recorded stress events at 18 and 34 weeks, and recorded child behavioral assessments at various ages. The percentage of women with more than two stress events was 37.2%, while the percentage with six or more was 7.6%. The researchers said that as a result of the study, moms shouldn't stress about stress.

WHAT HAPPENED?

Researchers have taken a major step toward understanding exactly how thalidomide causes the birth defects. It's still used to treat multiple myeloma and leprosy. Researchers at the University of Toronto found that birth defects resulted not just from the thalidomide, but from the compounds that it breaks down to in the body, which last up to 40 times longer than thalidomide itself. These compounds lead to the production of highly toxic reactive oxygen species, (ROS) including hydrogen peroxide and free radicals that alter or disrupt normal embryonic development. Scientists developed an animal model for fetal thalidomide exposure by extracting rabbit embryos from pregnant mothers during the first trimester of pregnancy, when the limbs and other structures are developing. They cultured the embryos in dishes for one to two days, with or without exposure to thalidomide or one of its breakdown products. Front and hind limb deformities as well as other abnormalities were observed only in the embryos exposed to thalidomide or one of its products. DNA damage caused by ROS and free radicals was similarly increased only in the exposed embryos.

PRICE INCREASE

As a result of a barrage of bad publicity and press coverage, the FDA has altered its policy on use of the drug Makena, which we reported on in our May/June issue (page 19). As we previously noted, KV Pharmaceuticals had won approval to be the sole manufacturer and distributor of Makena, based on the drug 17P (hydroxyprogesterone caproate). The company had begun selling the drug at $1,500 per dose, as compared to $10 to $20, the previous price, and prohibited other companies from compounding it. Acceding to pressure by the Society for Maternal-Fetal Medicine and various others, the FDA revised its policy to continue to allow pharmacies to compound it. The FDA's policy adjustment came a day after The Washington Post reported the intense criticism that has arisen over Makena. After word of Makena's price began to spread, internet sites for pregnant women became filled with angry commentary. Some created Facebook pages lambasting KV. The price also drew harsh criticism from several members of Congress, as well as many doctors and medical groups. According to the SMFM, "This action will ensure that this life-saving treatment will continue to be available for all those who need it. Affordable access to hydroxyprogesterone caproate is critical in ensuring the health and full-term birth of babies in the US." Typically, once a drug is approved by the FDA, pharmacy compounding is no longer allowed. Critics of KV Pharmaceuticals noted that research for Makena was funded by taxpayer dollars which funded the initial clinical trial in 2003 under the auspices of the NICHD. Additional trials were funded by NICHD through its multicenter network of medical institutions over several years. An economic analysis authored at Case Western Reserve University showed that weekly injections of compounds similar to Makena, given to at risk women, would dramatically reduce the incidence of premature births, and moreover it could save the healthcare system at least $2 billion per year. The price increase of Makena would have meant that the cost of treatment could have grown to $30,000 per mom, which might have been an insurmountable barrier for many.

TIMING IS EVERYTHING

There appears to be a clear correlation between how early babies are born and their risk of being prescribed ADHD medications later in life, according to researchers from the Karolinska Institute, Sweden. The authors even found an elevated risk of developing ADHD among babies born at 36 weeks, just three weeks early. Or at least they found evidence of prescribing for the condition. Prior studies had shown an elevated risk for ADHD in follow-up studies of preemies. The researchers analyzed data from a Swedish database of over a million children between 6 and 19 years old, of which 7,506 had been prescribed ADHD drugs. Those with the highest risk of subsequently developing ADHD were born between 23 and 28 weeks of pregnancy, two and a half times higher than those born at 39 weeks. Fifteen in every 1,000 babies born at between 23 and 28 weeks went on to be prescribed ADHD drugs, versus 6 in every 1,000 born full term. Babies born at 37 weeks had a 20% higher risk of being prescribed ADHD later in life. Information is from Medical News Today, written by Christian Nordqvist, copyright Medical News Today.

YOU ARE WHAT SHE ATE

A mother's nutrition during pregnancy can strongly influence her child's risk of obesity many years later, according to researchers at the University of Southampton. A mother's diet can alter the function of her child's DNA through epigenetic change, which can lead to her child tending to lay down more fat. The effect is irrespective of the mom's weight or the child's weight at birth. Researchers measured epigenetic changes in nearly 300 children at birth and showed that these strongly predicted the degree of obesity at six or nine years of age. The epigenetic changes, which alter the function of our DNA without changing the DNA sequence inherited from the mother and father, can also influence how a person responds to lifestyle factors such as diet or exercise.

TOO SOON

More than 80% of preterm births can be spotted in advance with a blood test taken during the second trimester of a pregnancy, according to research at Brigham Young University, which looked at the naturally occurring molecules in women's blood to

identify the peptides and small proteins that are at quantitatively different levels in women who go on to have these complications. Three new peptide biomarkers in combination with a few other proteins can signal high risk of preterm birth, and can be identified by looking at just a drop of blood from a mother who is 24 weeks into a pregnancy. In this study, the researchers tested their method on blood samples from 80 women that went full-term and 80 women whose babies came prematurely. This method for predicting pre-term birth is patented by BYU and the University of Utah and has been licensed to a company called Sera Prognostics. The company hopes to have a diagnostic test on the market in the first half of 2012.

HAVE A HEART

Scientists at the Gladstone Institutes have identified networks of genes that play an important role in embryonic-heart development and offered clues about how to combat congenital heart disease, in which cells in the embryo fail to get the right instructions while the heart is being formed. One way cells control the amount of protein made from genes is through a recently discovered molecule called a microRNA, tiny strands of genetic material that inhibit other RNA molecules from producing protein. MicroRNAs provide an extra layer of regulation that helps ensure that the correct amount of protein is made from a particular gene at the right time. In the fetal heart, subtle changes in gene dosage and timing can yield heart defects in children. To find out the regulatory apparatus of microRNAs, researchers examined the impact of thousands of genetic mutations in fruit flies on the function of a muscle-specific microRNA, and were able to better understand how the fly heart develops and found that the same genes were important in the mouse heart. These results may provide insight into what happens in humans because genes common to mouse and fly hearts are also typically critical for heart formation in humans. The researchers identified genes that affected heart development. While the techniques used in this research revealed important information for heart research, a similarly structured experiment could also be used to reveal new knowledge about the function of microRNAs in other organs and tissues.

INFECTION CONTROL

The Journal of Perinatology recently published a paper on the changing spectrum of neonatal infectious disease. The article, by L.R.W. Plano, noted in its abstract: "To understand the changing spectrum of neonatal infectious disease, one must first be familiar with the history, the variety of organisms and the progression of change of neonatal infections over the years. As progressively more immature neonates are surviving, the spectrum of infectious disease has changed in response to current medical practice responsible for this success and to selective pressures on the microorganisms. The surviving very low birth weight infants are at a significant risk for contracting infections from this expanding repertoire of pathogens. Microorganisms once thought seemingly benign and nonpathogenic are now commonly accepted as pathogens and are among the most likely organisms to cause infections in this extremely vulnerable patient population. When considering the possible identity of infecting organisms and attempting to tailor specific therapies to decrease unwanted consequences, one must consider the level of maturity and the age of neonate, as well as the intensity of care necessary for a successful outcome." Neonatal Intensive Care will start a regular feature about this subject in our upcoming issues. Readers are invited to submit materials or sources for follow up on this vital subject.

BPD ROLE

A study in Pediatric and Developmental Pathology questions the role of dendritic cells in BPD. Postmortem lungs of preemies born between 23 and 29 weeks were examined to determine the early and late effects of ventilation on both the prevalence and the distribution of dendritic cells. These patients were grouped as short-term ventilated, infants 23 to 29 weeks at time of death and ventilated for at least four days; long-term ventilated, infants more than 30 weeks in total age, including at least six weeks after birth and dependent on a ventilator at least 75% of that span; early control; and late control. The control groups were age-matched infants who had lived less than 12 hours. The lungs of early and late control group infants with no evidence of antenatal infection showed scattered dendritic cells in the peripheral lung tissue. In contrast, the lungs of early control infants with a history of antenatal infection and the lungs of short- and long-term ventilated preterm infants displayed a threefold increase in dendritic cells. This study demonstrated that dendritic cells are a normal presence in the airways and tissue of more developed lungs. However, antenatal infection and ventilation with BPD are associated with excessive accumulation of dendritic cells in the lungs. This massive influx may play a part in the pathogenesis of BPD, and more clearly defining its role may lead to new therapeutic approaches to this disease. The article is: "Pulmonary Dendritic Cells in Lungs of Preterm Infants: Neglected Participants in Bronchopulmonary Dysplasia?" Pediatric and Developmental Pathology, Vol. 14, No. 1, 2011. Go to pedpath.org. From Newswise Pediatric Research and Children's Health Theme Wire, newswise.com.

LET IT GEL

The New York Times reported on a hormone treatment that could cut the number of premature babies born in the United States by 10,000 a year. Researchers at Columbia University have been looking at using a progesterone gel inserted vaginally every day during the second half of a pregnancy to reduce the risk of premature birth in women with a short cervix, which can soften too early. By doing this, the NIH estimated that as many as 2% of the US's 500,000 annual preterm births could be prevented. Screening all pregnant women and treating those found to have short cervixes would save the nation's health system $12 million a year. In the study, researchers gave sonograms to 32,000 women who were about halfway through their pregnancies. Doctors found 465 women with short cervixes. Half were treated with vaginal progesterone and the other half got a placebo. Using the progesterone gel, which women can self-administer, led to a 45% reduction in the rate of preterm birth before 33 weeks and to improved outcomes. Fourteen women with unusually short cervixes would need to be treated to prevent one preterm birth, the study found. Reported in the New York Times by Gardiner Harris.

FALSE POSITIVES

MSNBC reported on the false positives in genetic testing in a report that aired on its website recently. According to its report, only one in 50 "positive" newborn screening tests actually detect actual disease. For cystic fibrosis, about which the media outlet cited a specific case, for every 10 positive screening tests one child will actually have the disease. For congenital adrenal hyperplasia, there are 100 to 200 false positives for every child affected. In the news report, a mom said she was told to put her baby on a strict feeding schedule, which she said robbed her of enjoyment-time with her newborn. A physician noted that false-positives need to be given more attention in terms of fallout. The

report noted that newborn screening varies from state to state and there are widely ranging standards. "As it stands now," the report said, "parents in one state might find that false positives rates are as low as 0.01 percent of all newborn tests, while parents a few states over may find as many as 1.52 percent of those tests are false alarms. In a hypothetical state with 100,000 live births, that's the difference between 10 false positive results and more than 1,500 false positives." Also noted was that PPVs show a wide divergence as well. The field of genetic testing, MSNBC said, is "rife with turf battles over how newborn tests will be conducted, who will do it, and how to pay for it." One mom concluded, "There's a lot of false positives, so don't freak out until you have to freak out." Original report by JoNel Areccia, MSNBC.

GOIN' HOME

The Huffington Post reported that a child touted by international media as "the world's most premature baby" left the hospital after five months of neonatal care. The Associated Press reported that doctors at the Fulda Children's Clinic in Germany said Frieda was born at 21 weeks and five days. At the time, she weighed just 16 ounces, but had reached a weight of 7.7 pounds. The baby was kept in a completely sterile environment, with her breathing assisted, and fed through her navel. According to reports, Frieda was originally a twin, but the other child, a brother, died a few days after being born. The previous premature baby record was thought to be held by Canadian James Gill, who was also born 21 weeks and five days early, in 1987.

MIDWIVES NEEDED

Reuters reported that more than a million mothers and newborn babies are dying each year from easily preventable birth complications because of a chronic shortage of midwives across much of the developing world. Save the Children said that in the world's least developed countries, over half of mothers give birth without any trained help, compared with only one percent in Britain, and that some 2 million women face birth entirely alone. About a 1,000 mothers and 2,000 newborns die every day as a result. Another 350,000 trained professionals are needed to save their lives, the "Missing Midwives" report said. "It doesn't have to be complicated: someone who knows how to dry a baby properly and rub its back to help it breathe can make the difference between life and death," said Save the Children Chief Executive Justin Forsyth. Of the 8 million children who die each year before the age of five, one in ten do not even see the end of their first day. But midwives trained in just eight procedures, including keeping newborns warm and fed, could immediately cut newborn deaths by more than a third in the 68 countries with the worst neonatal mortality rates, the report said. Some countries report recent successes in this area. In Afghanistan, which has some of the highest risks to both mothers and children, the number of rural births attended by trained professionals rose from 6% to 19% between 2003 and 2006, Save the Children said, and about 2,400 midwives have joined the workforce, with 300 to 400 graduating each year. Save the Children noted that working as a midwife is not a very attractive profession in many areas. Despite demand for their services, midwives in the developing world are often poorly paid and overworked, or have to work in remote or even dangerous places. At the same time, rich countries drain healthcare workers from poor nations. Reported by Reuters, by Emma Graham-Harrison, edited by Sugita Katyal.

TWO FOR ONE

The March of Dimes and Stanford University are partnering to establish the first-of-its-kind Prematurity Research Center to discover the causes of preterm birth, develop new ways to identify pregnancies at risk and turn this research into effective clinical and policy-based solutions. The March of Dimes Prematurity Research Center at the Stanford University School of Medicine is adopting a transdisciplinary research method that will provide unique insights from scientists in different disciplines that will collaborate closely together to accomplish their common goal.

PLACENTAS WITH FTV

Pediatric and Developmental Pathology presented the results of a pathologic study of placentas with FTV and a control group without the lesion. Researchers sought to determine the prevalence of obstetric complications as well as adverse outcomes in the immediate neonatal period as they relate to placentas with FTV. Electronic medical records and pathology reports from an 18-year period were used to extract information about more than 300 cases. These details included maternal and gestational age, method of delivery, neonatal outcome (live birth, stillbirth, or neonatal death), lesions of the umbilical cord, obstetric complications, and fetal abnormalities. The authors examined placental slides of all cases. Patients in the FTV group differed from those in the control group in that they were older, had a higher rate of cesarean delivery, were more likely to have a preterm birth, and had a higher rate of obstetric complications. Additionally, FTV placentas were significantly smaller than the control placentas. The presence of FTV in the placenta greatly increases the risk of an adverse outcome for the fetus or newborn. This study found a nine-fold increase in the rate of stillbirth and a twofold increase in intrauterine growth restriction. A six-fold increase was documented for both oligohydramnios and fetal cardiac abnormalities. An association between FTV and obstructive umbilical cord lesions was also found. From Newswise Pediatric Research and Children's Health Theme Wire, newswise.com.

PROMISING

A study performed by University of Kentucky researchers shows promise for the use of azithromycin in treating Ureaplasma-colonized or infected premature infants to prevent BPD. The study showed that subjects colonized or infected with the Ureaplasma bacteria developed BPD or died 73% of the time in the azithromycin-treated group, compared to 94% of the time in the placebo group. The study was performed on a group of 220 infants admitted to the UK Neonatal Intensive Care Unit from September 2004 to August 2008. Enrollment criteria included a birth weight of less than 1,250 grams, the use of intermittent mechanical ventilation for fewer than 12 hours, and an age of under 72 hours. Infants were randomized to receive azithromycin or a placebo for a total of six weeks. Infants testing positive for Ureaplasma were placed in a separate subgroup of the study. The study didn't demonstrate a significant benefit to using azithromycin therapy to prevent BPD in preterm infants who were not colonized or infected with Ureasplasma. Reported by Newswise Pediatric Research and Children's Health Theme Wire. www.newswise.com.

STRESS REDUCTION

To prepare parents with preemies in the NICU, UC San Diego Health System provides programs to help relieve stress and anxiety. The program encourages parents to build a support circle that includes physicians and NICU nurses, social workers, occupational therapists, lactation consultants and volunteers. Family and friends are encouraged to prepare meals and clean the parents' house. The UCSD Health System launched CarePages (carepages.com/UCSD), a free site for patients to share their stories and build a support circle. The University also has an NICU Concierge Program where volunteers provide parents with services, such as checking in breastmilk, providing a rocking chair and other amenities, taking pictures of the family, creating bedside name cards and offering educational materials on support activities. UC promotes kangaroo care and offers a "Cuddler Program" where volunteers can comfort babies when the parents aren't around. The UC System also encourages breastfeeding in the NICU through its Supporting Premature Infant Nutrition (SPIN) program to help moms produce sufficient milk. More info is available at health.ucsd.edu/women/nicu. Reported by Newswise Pediatric Research and Children's Health Theme Wire.www.newswise.com.

PESTICIDE PROBLEMS

Environmental Health Perspectives (EHP) published three studies that linked prenatal exposure to organophosphate (OP) pesticides with IQ deficits in school-age children. The three studies were conducted at the University of California, Berkeley, School of Public Health; the Mailman School of Public Health at Columbia University; and Mount Sinai School of Medicine. The Berkeley and Mount Sinai investigators measured OP pesticide metabolites in pregnant women's urine, while the Columbia investigators measured the OP pesticide chlorpyrifos in umbilical cord blood. Intelligence tests were administered to children of these mothers between ages 6 and 9 years at Mount Sinai and at age 7 years at Berkeley and Columbia. Investigations found evidence linking prenatal OP pesticide exposures with adverse effects on cognitive function that continued into early childhood. From Newswise Pediatric Research and Children's Health Theme Wire, newswise.com.

EAR TO RESEARCH

The House Ear Institute Board of Trustees announced that the nonprofit has changed its name to House Research Institute. The change to Research in the name more accurately reflects the institute's expanded research mission. The Institute noted its finding that hearing dysfunction often goes beyond the ear. For example, medications to treat HIV/AIDS, cystic fibrosis, tuberculosis and cancer can be ototoxic, sometimes damaging the sensorineural hair cells in the inner ear, resulting in permanent hearing loss or even deafness to the patient. The change reflects the Institute's expansion into areas of research such as a project to study a gene associated with autism that may play a role in causing deafness. Contact houseresearchinstitute.org.

CLEFT REPORT

A 2010 study led by researchers at Johns Hopkins identified two genes that may be responsible for the development of oral clefts. Their work in this area continues. Hopkins experts offer the following tips to help prevent oral clefts: Women planning to become pregnant should take 400 micrograms of folic acid each day. The supplement reduces the risk of neural tube defects like spina bifida, and researchers believe it may also help reduce the risk of other birth defects, including oral clefts. Pregnant women should tell their physicians about any prescription and over-the-counter medications they are taking because certain medicines can cause birth defects or increase the risk of birth defects. They should discuss with their physician the need for a

genetic workup if family members have cleft lip/cleft palate as these conditions tend to occur either as standalone disorders or as symptoms signaling a complex genetic syndrome that affects several organs and systems. One in 940 babies is born with cleft lip with or without cleft palate, and one in 1,500 is born with cleft palate. From Newswise Pediatric Research and Children's Health Theme Wire.www.newswise.com.

THYROID PROBLEMS

One in 20 women who gives birth will go on to develop thyroid problems within two years, according to researchers at Charles University in Prague. Almost one woman in seven is known to test positive for antibodies to the enzyme thyroid peroxidase. TPO plays a major role in the production of thyroid hormones, and many women show an autoimmune response against the enzyme. Thirty-five percent of women who have TPO antibodies in their blood go on to develop abnormal thyroid hormone levels within two years of giving birth, a symptom indicative of thyroid disease. Testing positive for TPOAb in pregnancy is linked to obstetric and thyroid problems in some women. Researchers followed up 189 out of 822 women who had shown some form of thyroid disorder in the first trimester of pregnancy. One hundred of these women tested positive for the TPOAb antibody, but otherwise showed no thyroid problems. However, on retesting 22 months after delivery, 35% of these women showed abnormal levels of thyroid stimulating hormone. Roughly one in seven pregnant women will test positive for the TPOAb antibody, and more than a third of these will go on to develop thyroid problems within two years of giving birth.

THE BASICS

A program that teaches healthcare workers in developing countries basic techniques to resuscitate babies immediately after birth is saving lives, according to a study presented at the Pediatric Academic Societies (PAS) annual meeting in Denver. Helping Babies Breathe focuses on simple techniques such as rubbing the baby dry, keeping the baby warm and suctioning the baby's mouth, all within the first minute of life. If the baby does not start breathing at this time, the provider has been taught to initiate face mask ventilation. The program is designed to be implemented in settings where oxygen, chest compression, intubation and medications are not feasible or available. Nurse midwives, physicians, assistant medical officers, and medical and nursing students were taught the steps to take immediately after birth to evaluate babies and stimulate breathing. Four hospitals collected data for three months before and three to four months after the program was implemented. Results showed that the mortality rate dropped 50% after program implementation from 13.4 deaths per 1,000 births to 6.3 deaths per 1,000 births.

LITTLE TWEAKERS

A scale used to assess the behavior of newborns exposed to methamphetamine before birth might be able to identify those children who will develop problems later on, according to researchers at Warren Alpert Medical School of Brown University and Women & Infants Hospital. Methamphetamine has become the drug of choice for many pregnant drug users. The study looked at the neurobehavioral effects of prenatal meth exposure in 185 newborns at four clinical centers. A comparison group included 195 newborns who were not exposed to methamphetamine but were exposed prenatally to alcohol, tobacco or marijuana. This allowed researchers to tease out any effects due to methamphetamine exposure rather than effects that may have been due to other substances commonly used in conjunction with meth. Researchers used the NICU Network Neurobehavioral Scale (NNNS) to evaluate the newborns during the first four days of life and again at 1 month of age. Results showed that newborns whose mothers used methamphetamine while pregnant were hard to arouse, but once awakened, they could not be calmed easily. At 1 month, improvements were seen in arousal and total stress among the methamphetamine-exposed group.

WINTER THREAT

Women who contracted H1N1 were more likely to give birth to lower birth weight babies as compared with women who had "influenza-like illness" during the outbreak, according to researchers at Women & Infants Hospital of Rhode Island. The 2009 H1N1 influenza virus contained a unique combination of gene segments that had never been reported in human influenza cases in the United States. The researchers found that women who had H1N1 during pregnancy were more likely to have a lower birth weight baby. The average gestational age at delivery was less than 39 weeks and the babies born to women with H1N1 weighed an average of 285 grams less than other babies.

STURDY IMMIGRANTS

Immigrants living less than five years in Canada are less likely than their Canadian-born counterparts to have premature babies regardless of where they live, according to a new study by St Michael's Hospital. Living in poor neighborhoods has been linked with poor health outcomes, but this study showed that this is not always the case for new Canadians. However, the longer immigrants stay in Ontario cities, the higher the risk of premature delivery. Once immigrants have lived in Canada for 15 years or more, they have higher premature birth rates than Canadian-born residents living in the poorest neighborhoods. The study reviewed birth data from Ontario hospital records from 2002-2007 and were linked to an official Canadian immigration database for 1985 to 2000.

UNKIND CUTS

The use of episiotomy fell by 60% between 1997 and 2008, according to the latest News and Numbers by the Agency for Healthcare Research and Quality. However, the proportion of hospital stays of women who delivered via cesarean section increased by 72% during the same period. The use of forceps to aid delivery declined by 32% from 14 to 10%. The number of hospital stays for childbirth fell by 300,000 between 2007 and 2008, from 4.5 million to 4.2 million. In comparison, the annual number of childbirth stays had been increasing by an average of 2% a year starting in 1999. The average childbirth stay involving C-section with no complications cost hospitals an average of $5,700 and $7,600 when there were complications. By comparison, a vaginal childbirth stay without complications cost hospitals an average of $3,400 and $4,400 when there were complications. Forty percent of all childbirth stays were billed to Medicaid, 53% to private insurers, 4% were uninsured, and the rest were charged to other payers. About 36% of all childbirth hospital stays in 2008 occurred in the South compared to 16% in the Northeast. The West and Midwest accounted for 26% and 23% percent.

PRODUCTS

PEEP PLUS

Pediatric Research recently published a paper on increasing PEEP to recruit alveoli during HFJV, hypothesizing that

high PEEP would recruit alveoli and reduce lung injury but compromise pulmonary blood flow. The study was carried out using preterm lambs delivered after instillation of surfactant. The lambs either remained on constant PEEP of 5 cm H_2O or adjusted stepwise to 12 cm, then back to 8cm over an hour-long period. Pressure volume deflation curves were recorded postmortem and tissue assessed for inflammation. Lambs receiving increased pressure had lower pressure amplitude, fractional inspired oxygen concentration and PBF and more compliant lungs. Inflammatory markers were also lower. The study concluded that "adjusted PEEP during HFJV improves oxygenation and lung compliance and reduces ventilator requirements despite reducing pulmonary perfusion." The paper noted: "The current strategy recommended for treatment of RDS with HFJV is to commence HFJV early in the disease process with a PIP just below that being used during CMV (Bunnell Inc, How to use the LifePulse HFV: Seven Steps to Success)." Bunnell supplied the high frequency ventilators for the study. For the complete study, see High Positive End-Expiratory Pressure During High-Frequency Jet Ventilation Improves Oxygenation and Ventilation in Preterm Lambs, Pediatric Research, Vol 69 No 4, pages 319-324. Information above was provided by Bunnell. Contact bunl.com.

TO A TEE

Mercury Medical is pleased to announce the Neo-Tee, a new, single-use disposable infant T-Piece resuscitator. Neo-Tee is flow controlled, pressure limited and the only device on the market to offer a built-in manometer "on the Tee" for convenient, in-line viewing of delivered pressure to an infant/patient. Adding the Neo-Tee complements Mercury's product line with the infant size air-Q family of Masked Laryngeal Airways and the Neo-StatCO2, disposable colorimetric CO_2 detector available for babies below 1 kg. Contact mercurymed.com.

GLOBAL WARMING

The same conductive technology utilized to warm patients in the operating room is quickly becoming the preferred method to keep infants warm in the Labor & Delivery room. Koala Infant Warmer, by NovaMed USA, a worldwide leader in critical care and neonatal temperature monitoring products, is a uniquely designed warming system that specifically addresses the clinical issues of cold stress and hypothermia in newborn babies. Koala Infant Warmer is a patented, reusable conductive thermal mattress that provides continuous evenly distributed warmth to an infant, effectively simulating a mother's natural body heat. Unlike the traditional radiant warmer, Koala warms through direct skin to skin contact, and is therefore not subject to air currents within the room. Koala provides continuous gentle warmth at a controllable, pre-set temperature, making it safer and more effective than disposable heated gel pads. It addresses those infants prone to hypothermia outside the NICU and eliminates the need for intensive intervention and the complexity of an incubator or radiant warmer. This FDA-approved product can be utilized in the Delivery Suite, Newborn Nursery, Neonatal ICU, ER, and OR and can be configured for Intra-Hospital Transport. Contact novamed-usa.com.

TAPPING IN

HealthTap (www.healthtap.com), the first interactive Expert Health Companion, recently opened its public beta. Pioneering the field of Interactive Health, HealthTap brings interactive software to medicine. It uses expert knowledge from its network of more than 550 physicians, personal health data (such as age, weight, symptoms, etc), and community insight to tailor information to users. HealthTap's personalized, actionable information helps consumers make better decisions about their health and well-being. For physicians in its rapidly growing Medical Expert Network, HealthTap is a one-of-a-kind digital platform for growing their practices and improving the quality of care, while reducing costs. Initially focused on pregnancy and the first year of life, HealthTap will expand to cover health for all. Consumers on HealthTap can: • Create a Home for Health with personalized health feeds, a customizable checklist, and secure storage of health information. • Get succinct answers and tips from doctors, data from an extensive proprietary medical Knowledge-Base, and validated insight from community members similar to them. • Find doctors locally and nationally. by exploring their insight, expertise and care. US licensed physicians admitted to HealthTap's Medical Expert Network can grow their practices and improve the quality of care that they provide patients, while reducing costs through HealthTap's digital platform. They can also create their own Online Medical Home where they can easily store and share their medical wisdom, extending relationships with patients beyond office hours. Contact healthtap.com.

MILKING IT

Dr Sharon Groh-Wargo was recently interviewed by Cleveland media outlet WKYC-TV about MetroHealth Medical Center's use of a milk analyzing machine used to check the nutritional value of breast milk fed to premature infants. Metron Instruments makes a milk analyzer that can determine the protein, caloric, carbohydrate, lactose and fat content in breast milk. MetroHealth is testing the analyzer on the milk of 28 moms to see if they can create "designer" milk for their baby's individual needs. Paragon is a Cleveland company that makes software in parternship with NeoMed, that manages all the feedings of preemies in NICU's, called SafeBaby. SafeBaby tracks all expressed breast milk, donor milk, formula, and fortifiers; and then validates they are all correct for each patient prior to feeding. Paragon sponsored and funded this study because knowing what is in "mother's milk" is only half of the issue. Once the nutrient content is known, it must be correctly fortified. Paragon is making a product called SafeNutrition which will take the data from the study and create the best fortification recipe for that preemie's requirements. Paragon's research led them to Metron Instruments and Dr. Sharon Groh-Wargo, an expert in dietary requirements for preemies at Metro. Once the study is completed, the system of Metron's analyzer and Paragon's software hopes to be the most cutting edge feeding system for preemies in the country. Contact safebabybmt.com.

CERTIFIED

GE Healthcare's Centricity Perinatal 6.90 has received Modular EHR Certification. This solution enables eligible providers and hospitals to use the Centricity Perinatal solution as part of their efforts to meet meaningful use measures and qualify for federal health IT incentives. Centricity Perinatal, an EHR Module, is 2011/2012 compliant. It has been certified by InfoGard, an ONC-ATCB, in accordance with the applicable certification criteria adopted by the Secretary of HHS. (This certification does not represent an endorsement by the US Department of Health and Human Services or guarantee the receipt of incentive payments.) The Centricity Perinatal Clinical Information System supports efficient documentation of mothers and infants through the perinatal continuum, from prenatal management to intrapartum fetal monitoring surveillance through postpartum, nursery and

NICU, discharge documentation and patient education. Centricity Perinatal automates documentation of the full spectrum of perinatal care. Clinicians enter and access patient data quickly and easily right at the point of care. The result: a single, continuous file of the entire patient record to help you easily review and document care. GE Healthcare also announced that it will embed PeriGen, Inc's PeriCALM Patterns in its Centricity Perinatal solution, and offer it to clinicians seeking to help improve the quality of care delivered. Contact gehealthcare.com.

SENSITIVE

Spectros' T-Stat VLS Tissue Oximeter is the first device to be labeled as "sensitive to ischemia" by the FDA. The Neonatal Buccal Probe can be noninvasively placed on the cheek. The probe monitors the saturation of the buccal mucosa (inside the mouth) as a surrogate for gastrointestinal perfusion. GI perfusion is important, because the body's neuroprotection mechanisms will maintain brain perfusion until the limits of autoregulation are reached, but the GI tract will show decreased perfusion early, allowing the clinician to respond earlier, resulting in improved outcomes. T-Stat can be used for: hemodynamically unstable preterm babies with decreased flow; babies with congenital heart defects (HLCS, PDA, TGA or other mixing lesions); resuscitation, when treating with fluids or vaso-active drugs; and ventilator management. Contact spectros.com.

SPECIAL SCREENING

PerkinElmer, Inc announced that the company's Signature Genomics Laboratories has launched its new Signature Precision Panel Prenatal diagnostic test for rapid testing of 15 common and severe chromosomal disorders. The Signature Precision Panel Prenatal test is designed for pregnant women undergoing amniocentesis or CVS who have been determined by their physicians to require specialized screening due to clinical or parental factors, such as maternal age. The test quickly detects some of the most common and potentially severe chromosomal conditions that affect fetal health, allowing physicians to provide preliminary results to patients within one to two days of the sample receipt at the laboratory, followed by a comprehensive and confirmatory final report direct to physicians. The test is available to clinicians through PerkinElmer's Signature Genomics Laboratories to analyze placental tissue or amniotic fluid, extracted during a pregnant woman's chorionic villus sampling or amniocentesis procedures, to determine whether an abnormal number of chromosomes (aneuploidies) or small losses of chromosomes (microdeletions) are present during pregnancy. The prenatal panel tests for 15 common and severe microdeletion syndromes and aneuploidies of 5 chromosomes, including Down Syndrome, Trisomy 18, DiGeorge syndrome, Miller-Dieker syndrome, Prader-Willi syndrome, 1p36 microdeletion, and Wolf-Hirschhorn syndrome, among others providing early insight to parent and physicians regarding the overall health of the child. Signature Genomics offers a range of prenatal testing including karyotyping and microarray analysis. Contact signaturegenomics.com.

EMBRACEABLE

The Embrace Infant Warmer from GE is an affordable, portable and safe device that can reduce infant deaths from hypothermia. Developed in an Entrepreneurial Design for Extreme Affordability course at Stanford University, the device's technology bundles a sleeping bag with a warming pack and heater. By using a reverse-innovation design approach, and working with local teams in the field, the design was tested and refined. GE has partnered with Embrace to distribute the Infant Warmer in rural areas around the globe. The Embrace Infant Warmer has three components: a sleeping bag, a sealed pouch of phase-change material and a heater. The sleeping bag swaddles the child while the heater warms the pouch, located in an adjacent compartment. Its design is intuitive, versatile, can be deployed to remote locations, and promotes close interactions between mother and child. It has a retail price under $200, compared with up to $5,000 for a traditional warmer. Embrace is now a member of GE's Maternal Infant Care portfolio of Lullaby products, which serve low-resourced healthcare settings.

CEO NAMED

Siemens Healthcare has appointed Gregory Sorensen, MD, as chief executive officer of Siemens Healthcare in the US. Sorensen was Professor of Radiology and Health Sciences & Technology at Harvard Medical School; faculty member of the Harvard-MIT Division of Health Sciences and Technology; and Co-Director of the A.A. Martinos Center for Biomedical Imaging at Massachusetts General Hospital. He is a practicing neuroradiologist and active researcher with significant experience in clinical care, clinical trials, and translational research. At Siemens, Sorensen is responsible for leading the marketing, sales, service, and support functions for Siemens Healthcare in the US, including medical imaging, therapy, healthcare information technology, and laboratory diagnostics. He will be based in Malvern, PA. Contact siemens.com/healthcare.

MONITORING CASE STUDY

Reliable, Faster Measurement

Information for this case study was provided by Masimo.

A new study reported that the use of Masimo SET enables better adjustment during critical neonatal resuscitation situations, aiding in the prevention of damage caused by unnecessary exposure to high or low oxygen.

Masimo announced that a new study published in a recent issue of the European peer-reviewed journal Acta Paediatrica demonstrates that pulse oximetry makes a critical difference in neonatal resuscitation both in terms of reliability and speed of measurements. In comparing the measurement response times of three different pulse oximetry technologies, researchers found that the Masimo Radical-7 pulse oximeter with Masimo SET Measure-Through Motion and Low Perfusion technology displayed reliable oxygen saturation (SpO_2) measurements three to four times faster than competing pulse oximeters.[1]

Despite numerous advances to improve newborn care, oxygen is still used liberally during newborn resuscitation, unnecessarily exposing many newborns to potentially damaging hyperoxia. Although pulse oximetry is an important clinical tool for evaluating a patient's oxygenation status and guiding resuscitation, measurement failure rates due to motion artifact and low perfusion can be high – leading to inaccurate readings, failure to report readings, or freezing of displayed values. As a result, the time to obtain a reliable oxygen saturation reading during newborn resuscitation in the delivery room and during NICU care is a critically important consideration when choosing

a pulse oximetry technology. This is the first prospective observational study to compare pulse oximetry technology performance in detail during newborn resuscitation under unstable critical conditions.

The study was conducted at two health care centers in Barranquilla, Colombia (Clinica del Mar and Medicina Alta Complejidad SA) on 32 newborns (median gestational age of 32 weeks) receiving resuscitation as standard of care either in the delivery room or in the Neonatal Intensive Care Unit (NICU). Using the Masimo LNOP sensor with the Radical-7, the E630 sensor with the Ohmeda Biox 3700, and the OxiMax Max-N sensor for the Nellcor N395, the time to a reliable SpO_2 measurement was recorded post-ductally (one sensor placed on each foot) once an adequate pulse rate signal was displayed. Results showed that "the pulse oximeter with Masimo SET provided the fastest response time." In the first comparison of 17 infants, the median response time to obtain a reliable measurement for the Masimo Radical-7 was 20.2±6 (with a range of 18-26 seconds) versus 74.2±12 (with a range of 38-98 seconds) for the Ohmeda Biox 3700. In the second comparison of 15 infants, the median response time for the Masimo Radical-7 was 20.9±4 (with a range of 19-28 seconds) versus 67.3±21 (with a range of 40-90 seconds) for the Nellcor N-395.

Finding that "there are significant differences in the response of pulse oximeters during neonatal resuscitation," researchers concluded that "the speed and reliability of the Masimo SET technology can be of help for clinicians to more accurately adjust the fraction of inspired oxygen during newborn resuscitations, thus preventing or minimizing damage secondary to unnecessary exposure of oxygen and hyperoxemia and to wide fluctuations in oxygen levels."

The "gold standard" Measure-Through Motion and Low Perfusion of Masimo SET has been shown in over 100 independent clinical studies to provide the most accurate and trustworthy measurements – even under the most challenging clinical conditions, including patient motion and low perfusion. [Reference: 1. Baquero H, Alviz R, Castillo A, Neira F, Sola A. "Avoiding Hyperoxemia During Neonatal Resuscitation: Time To Response Of Different SpO_2 Monitors." *Acta Paed* April 2011 Vol. 100, Issue 4, pp 515-518. Published online.]

Abstract

Aim: To assess the time to obtain reliable oxygen saturation readings by different pulse oximeters during neonatal resuscitation in the delivery room or NICU.

Methods: Prospective study comparing three different pulse oximeters: Masimo Radical-7 compared simultaneously with Ohmeda Biox 3700 or with Nellcor N395, in newborn infants who required resuscitation. Members of the research team placed the sensors for each of the pulse oximeters being compared simultaneously, one sensor on each foot of the same baby. Care provided routinely, without interference by the research team. The time elapsed until a reliable SpO2 was obtained was recorded using a digital chronometer. Statistical comparisons included chi-square and student's *T*-test.

Results: Thirty-two infants were enrolled; median gestational age 32 weeks. Seventeen paired measurements were made with the Radical-7 and Biox 3700; mean time to a stable reading was 20.2 ± 7 sec for the Radical-7 and 74.2 ± 12 sec for the Biox 3700 ($p = 0.02$). The Radical-7 and the N- 395 were paired on 15 infants; the times to obtain a stable reading were 20.9 ± 4 sec and 67.3 ± 12 sec, respectively ($p = 0.03$).

Conclusion: The time to a reliable reading obtained simultaneously in neonatal critical situations differs by the type of the pulse oximeter used, being significantly faster with Masimo Signal Extraction Technology. This may permit for better adjustments of inspired oxygen, aiding in the prevention of damage caused by unnecessary exposure to high or low oxygen.

SPOTLIGHT ON MONITORING

HEARTBEAT

Cardiotronic, Inc specializes in 100% non-invasive cardiac output monitoring for the NICU. The compact/portable ICON monitor is FDA market released for use in the neonatal patient population and provides continuous estimations of stroke volume and cardiac output through the use of only 4 skin sensors. It has been shown that implementation of Cardiotronic EC monitors results in economical and operational benefits including reduction in costs, procedural risks, and medical staff time. Contact cardiotronic.net.

TAKING CARE

GE Healthcare announced that the University of Colorado Hospital (UCH) has installed the new CARESCAPE Monitor B850, the company's latest advance in bedside patient monitoring, to help enhance clinical decision making in the Neonatal Intensive Care Unit (NICU). Deployed in UCH's 50-bed NICU and Neonatal OR, the CARESCAPE Monitor B850 enables access to critical patient information from any bedside monitor anywhere in the unit. Additionally, UCH leverages the CARESCAPE Monitor B850 care area-specific monitoring features for more accurate NICU clinical measurements, and to help support its goal of aggressively addressing common premature infant complications. About 12.8% of all babies are considered pre-term, representing a 36 percent higher incidence than the 1980s. The CARESCAPE Monitor B850 is easily customized to address these growing NICU clinical demands, as well as the gestational age and weight of each patient. With the CARESCAPE Monitor B850, UCH staff can flex monitoring capabilities up or down depending on the patient's needs. Visual alarming can replace sounds to reduce disruptive bedside noise, helping support a developmentally appropriate environment. Large displays and remote controls enable caregivers to view monitoring screens from across the patient room. When an alarm occurs, nurses can remotely view the clinical information without leaving the patient's side, helping streamline workflow and making it easier to care for their patients. In addition to supporting caregivers, the CARESCAPE Monitor B850 helps keep parents informed of their baby's overall condition. Neonates are initially covered and protected in a setting that mimics the environment of the uterus, which means parents have limited ability to view or hold their child. The monitors can help parents watch their baby's clinical status, while the infant remains in an enclosed environment, shielded from disruptive lights and sounds. With the CARESCAPE Monitor B850, parameter and default alarm limits are pre-configured to help support priority NICU clinical initiatives, which include PDA and bradycardia. Interfacing with the CARESCAPE Monitor B850, Masimo technology provides enhanced sensitivity for SpO_2 measurements. Oxygen saturation measurements help clinicians

determine when patients can be weaned off ventilators. Additionally, UCH is the first hospital to leverage InSite, a GE Healthcare remote diagnostic and repair service, with the CARESCAPE Monitor B850. This means bedside monitors can maintain themselves through a remote serviceability feature, which enables remote diagnostics and predictive maintenance. This may help prevent system downtime and reduce overall servicing needs. The remote service feature also supports seamless upgrades, making the monitors easier to keep current. Contact gehealthcare.com.

VISIONARY
The MetaVision Suite of Clinical Information Systems from iMDsoft manages all of the clinical data in critical care environments, and is successfully implemented in NICUs worldwide. It automatically creates a complete electronic patient record, arming healthcare professionals with timely, accurate, and actionable information. MetaVision fully supports the unique workflows of high-need, data-rich NICUs. It seamlessly integrates data from bedside devices including IV pumps, hemodynamic monitors and incubators to create a single continuous patient record for NICUs and step-down nursery units. To learn more, visit imd-soft.com.

RAPID ANALYSIS
Whole Blood Total Neonatal Bilirubin testing is available on the RAPIDLab Blood Gas Analyzers from Siemens. Because when it comes to the smallest and most vulnerable of patients, fast results, delivered instantly, can make all the difference in the world. Neonatal Bilirubin offers the following features: • Immediate test results: 60 seconds; • Minimum sample volume requirements: 100uL; • All critical care test results, including nBili, from a single sample: 175uL; • No sample preparation required: whole blood; • Reportable range: 2.0–30.0 mg/dl; • No additional reagents are required. Contact siemens.com.

COMPANY PROFILE

Philips Mother and Child Care

Describe your neonatal/perinatal products and their features.
Philips has provided products and solutions for mother and child for more than 40 years, starting with the introduction of the world's first non-invasive fetal monitor in 1968. But this year the company has launched a renewed focus on supporting mothers and children from the early days of pregnancy through the early years of life by creating a business within its healthcare sector's Patient Care and Clinical Informatics business. The company provides a wide range of products and solutions to help ensure the health of mother and baby from pregnancy through delivery, as well as products and solutions to support developmental care from the obstetrician's office to the hospital's OB department, Well Baby Nursery and Neonatal Intensive Care Units through to care at home. Philips Mother and Child Care solutions focus on three areas of care: • Pregnancy and Labor & Delivery: Philips ultrasound imaging, fetal/maternal monitoring, and OB information systems allow clinicians to manage patient care for mothers and babies from the very first visit. These solutions deliver the clinical information clinicians need to help provide the best possible care to expectant mothers and their babies during this critical time of life. • Postnatal, Neonatal & Pediatric Care: Philips offers a wide range of products and educational services to support developmental care for premature babies, healthy newborns and hospitalized pediatric patients. The Philips Mother and Child Care solutions portfolio includes therapeutic support products, jaundice management, feeding and safety, respiratory products, neonatal and pediatric ICU monitoring and neonatal and pediatric clinical care systems to help improve and save lives of this critical patient population and encourage family-centered care. • Care at Home: New beginnings are both exciting and challenging. Philips delivers innovative solutions that make nurturing, feeding and caring for newborns simple. Philips provides both consumer and hospital-grade solutions including prescription home monitoring and therapy and feeding solutions help to ease the transition to home, helping parents and their babies get off to a healthy start. The Philips AVENT product portfolio is a broad offering for parents and babies to optimize the health and well being of mother and child. For a comprehensive list and description of Philips products available in the US, please visit Philips.com/motherandchild.

Tell us about the educational services you offer for neonatal caregivers.
Philips Mother and Child Care educational programs are developed to nurture high-risk infants and children by taking a holistic approach and facilitating delivery of developmental care and pertinent clinical decision support. Educational solutions are developed to account for the diversity of patients in the neonatal intensive care unit (NICU) and pediatric intensive care unit (PICU), and the seriousness of their conditions. Philips offers a range of educational services for expecting parents, health care staff, new parents and families of premature or ill infants – from workshops, to process improvement plans, books and products. These programs include: • "Wee Care" Training: Evidence-based best practices aimed at standardizing developmentally supportive care practices in the NICU and helping improve patient and financial outcomes. • "Cue- Based Feeding" Workshop: Innovative feeding program aimed at individualizing and optimizing the feeding experience for infants in the NICU. • "Preemie for a Day" Workshop: Interactive, multisensory training, which allows participants to experience an infant's journey, from birth through admission, and the opportunity to practice developmental care throughout their stay. • "Kangaroo Care" DVD: Benefits detailed in the "Kangaroo Care: Positive Touch in the NICU" interactive learning module range from cardio-respiratory stability, protected thermoregulation, better sleep patterns and decreased hospital stay.

Tell us about the latest neonatal advances germane to your product offering.
The Philips neonatal product offering includes innovative, advanced solutions that help health care providers deliver optimal care for infants and their families. The IntelliVue MX800 Neonatal Patient Care Solution is a combined patient monitor and informatics point-of-care product that allows critical neonatal and pediatric care monitoring while also accessing the EHR, PACS images, running clinical decision support applications and accessing most any informatics solution in the department. In November 2010, Philips Healthcare and Atom Medical Corporation in Japan announced an alliance to expand their relationship to serve customers with a more complete offering of perinatal care solutions. This new portfolio now includes neonatal incubators and warmers, and a high-end combined incubator and warmer product with developmentally friendly elements in their design.

Evidence-Based Recommendations for Breast Pumping Hygiene

Jean Rhodes, PhD, CNM, IBCLC

This article discusses the research evidence for best practices in breast pumping hygiene. Contamination of human milk can occur at any or all of several steps in the collection, storage, preparation and administration of human milk for infant feedings, however, for the purposes of this review we will focus specifically and sequentially on the processes involved in mother's own milk expression by breast pump.

Pathogens in human milk

Fresh human milk is not sterile but rather contains a wide variety of organisms including non-pathogenic or commensal bacteria, pathogenic bacteria, viruses, mycobacteria and fungi.[1-7] Studies vary on quantities of bacteria in human milk. In one study, 100% of collected human milk samples contained bacteria.[4] In general the majority of identified organisms are non-pathogenic commensal skin flora from the mother's nipple or breast, eg, coagulase-negative *Staphylococcus epidermidis*, diphtheroids, and *Streptococcus viridans* or are organisms which have migrated via the enteromammary pathway to the breast – such as *Bifidobacteria* or *Lactobacilli* – which protect the newborn's gastrointestinal system.[3,8] However, potentially pathogenic bacteria are also common in human milk. *Staphylococcus aureus* including MRSA, B-hemolytic *streptococci*, *Pseudomonas* species, *Klebsiella*, *Proteus* species, and enterobacteria are often cited as the most frequent.[2-5,9] Of interest to practitioners in the neonatal intensive setting, human milk from mothers of preterm infants has been found by Thompson *et al* to have higher bacteria levels – non-pathogenic and pathogenic – than human milk from term mothers.[1] Also of interest is a finding by Boo and associates that human milk pumped at home has higher contamination levels than milk expressed in the hospital.[7]

Breast hygiene

In the 1970s and 1980s, breast cleaning prior to pumping and culturing of breastmilk prior to its administration to NICU infants were common practices. Studies on the value of additional breast cleaning beyond daily hygiene prior to pumping are conflicting. Costa in 1989 found additional breast cleaning to be beneficial in reducing human milk bacterial colony counts[10] while Thompson et al in 1997 found breast washing with Phisoderm to be no more effective than water alone in reducing bacteria.[1] Currently, the Human Milk Banking Association of North America (HMBANA) and the Academy of Breastfeeding Medicine (ABM) recommend normal maternal body (breast) hygiene but no additional cleaning prior to human milk expression.[11,12]

Hand hygiene and cleaning

Adequate hand cleaning prior to breast pumping is, without a doubt, one of the most important factors in reducing bacteria and pathogens in human milk. Hand cleaning and drying options offer an interesting layer of complexity to the formation of recommendations for mothers. In terms of cleaning methods, we will first examine non-washing and washing methods of hand disinfection followed by issues related to drying options.

While the most frequent method of hand cleaning in a hospital setting is with alcohol rubs, there is insufficient data at this time as to how these methods might impact breast milk collection. Alcohol rubs have been implemented in hospitals and elsewhere for their convenience of use (no sink required) and are supported by the CDC for use in the health care setting for staff. Alcohol rubs are effective when used correctly,[13-15] may be more effective than hand washing in removing spores,[16] but are not as effective as hand washing in eliminating C difficile.[17] HMBANA guidelines acknowledge the use of alcohol rubs as a method to decontaminate hands in the hospital but do not explicitly state they are recommended for use before expressing or handling human milk or feeding equipment.[11]

Hand washing is often cited as the first line of defense against infection. In the present context, washing may be preferable to other forms of hand hygiene because it does not pose the risk of chemical (alcohol) contact with the breast and human milk. At this time, the literature is inconclusive in terms of results and recommendations for washing with non-antibacterial soap or antibacterial soap in breast pumping mothers. The general concern about antimicrobial soaps is the risk of bacterial resistance[18,19] the removal of commensal bacteria that serve a role in protecting skin surfaces[20] and the potential effect on T cell maturation.[20] For health care workers, the CDC guidelines for hand hygiene recommend hand washing with either non-antimicrobial soap or antimicrobial soap and water when hands are visibly dirty or soiled. Hot water should be avoided because it can damage skin. In addition, the CDC recommends using an alcohol-based rub or an anti-microbial soap to decontaminate health care worker hands between patients and prior to specific patient care activities.[14] Lactating mothers are not health care personnel, however, they are in contact with hospital

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pathogens as soon as they enter the hospital. Elevator buttons, door handles, intercoms, sink handles, objects in the infant's environment and waiting areas are just a few examples of potential fomites. Therefore, the use of antimicrobial soaps for hand washing might be of benefit prior to breast pumping in the hospital environment but use of antimicrobial soaps may not be necessary in the home.

Research of hand washing techniques with soap and water vary as to length of washing time and amounts of soap. The CDC guidelines for health care workers recommend applying an amount of soap as recommended by the soap manufacturer and washing for at least 15 seconds, covering all surfaces of the hands and fingers before rinsing and drying.[14] Fuls et al found improved cleaning with an increase in wash time to 30 seconds and use of approximately 3 grams of soap volume.[21] In situations where manufacturer recommendations are not known, longer times and generous amounts of soap may be prudent. Lastly, more research is needed in the area of hand washing soaps for health care situations. For example, Contreras et al found hand washing with dishwashing soaps to be 100 times more effective than antimicrobial hand soaps in inactivating respiratory syncytial virus.[22]

Hand drying presents a variety of options for consideration including paper towels, cloth towels, and forced-air dryers. Infection control literature suggests clean disposable paper towel, the most common source of hand drying in hospitals and frequently used in homes, are the most hygienic method of hand drying.[14,23-25] However, paper towels which may be wet or contaminated are not recommended. Literature comparing paper and cloth towels on dispenser rolls found cloth towels to be more at risk for contamination.[26] Data comparing individual cloth towels to paper towels used in the home is not available.

Forced-air dryers are available in hospitals, public locations and work environments. Hot forced-air hand dryers appear to be safe in most environments,[27] however, in hospital environments forced-air hand dryers may disperse bacteria, contributing to air borne contamination.[28] (Obviously, coughing, sneezing and expectorating in the process of hand washing and human milk collection can also introduce airborne pathogens in the equation.) More than one study suggests that when using forced-air dryers, hands should not be rubbed together as this increases the numbers of bacteria on dried hands.[29,30]

Lastly, in terms of hand hygiene, fingernails and jewelry have been found to be factors in post-cleaning bacterial colonization of hands. The evidence-based 2002 CDC recommendations for health care workers' hand hygiene include not wearing artificial fingernails or extensions, avoiding chipped nail polish, keeping nail tips to less than ¼ inch long, and subungual areas clean. Multiple studies also suggest the presence of rings can negatively impact attempts at hand cleaning. Ring wearing has been associated with 10-fold higher median skin organism colony counts, hand contamination with *Staphylococcus aureus*, gram-negative bacilli and *Candida* species.[31-33] Furthermore, the more rings an individual wears, the greater the contamination even after hand cleaning.[32] While these studies are on health care personnel, they present valuable information for mothers who are practicing hand hygiene prior to breast pumping.

Cleaning Pump Equipment

Breast pumps, like all hospital equipment, are potential carriers of pathogenic microorganisms. Improper cleaning of breast pumps and pump parts can increase the risk of expressed human milk contamination.[11,12] External surfaces of hospital breast pumps, particularly those touched by mothers or staff in the process of pumping, should be disinfected between users. At Rush Presbyterian, Meier has empowered NICU mothers to assume a primary role in their infants' care, including responsibility for cleaning hospital breast pumps before use with quick cleaning disinfecting wipes.[34,35] In addition to pumps, in the hospital and at home, the surface upon which cleaned pump parts are to be placed prior to drying should be disinfected with disinfecting solutions or wipes. If recommended by the solution's manufacturer, the surface should be rinsed after disinfection with clean water to prevent solution contamination of washed parts. Hands should also be washed after disinfecting pumps and surfaces to prevent breast or human milk contact with disinfectant chemicals.

Pump parts that come in contact with human milk should be completely separated and thoroughly cleaned after use. Even in the case of no human milk collection during a pumping session, pump parts should be cleaned. Washing is the most common method of cleaning in hospital settings. After the pump parts are disassembled, they should be rinsed in cool water to remove human milk residue, especially human milk proteins.[11] Parts should be washed with soap and water, either under running water or in a clean bowl or basin designated for this purpose.[11] Although not specifically mentioned in the lactation literature, clean paper towels or clean unused cloth towels can be used with soap and water to clean parts as they create friction and remove surface contaminants. Patient specific bottle and nipple brushes can be used to clean parts, especially tight crevices. Sponges are generally discouraged and not appropriate in hospital settings because they trap microorganisms. In the home environment, if they have to be used, sponges should be disinfected by microwaving them (damp) for 2-4 minutes.[36] Given the information above on hand washing, the use of antimicrobial soaps for pump part cleaning might be appropriate in some settings. Because of the high levels of bacteria in drains and sinks and on faucet handles, pump parts should not be placed in the sink for washing and faucet handles should be turned of with a clean paper towel.[11,14,37]

After washing, parts should be rinsed thoroughly then placed on a disinfected surface for drying. A clean paper or cloth towel may be placed on top of the surface to collect dripping water. If the pump parts came in a sterile hard plastic container, this packaging can serve as a temporary surface. As with hand washing, clean paper towels may be used for drying in the hospital or at home. Clean cloth towel drying may be acceptable providing the towel has not been used since laundering. Air-drying is another option but not realistic in some situations where mothers share pumping space with others or if mothers need to leave the cleaning area. Once clean and dry, pump parts should be removed from the sink area to prevent contamination. Reconnect and place with the pump, so parts are ready for the next use. HMBANA recommends cleaning pump parts after rinsing in the dishwasher as an alternative to washing by hand.[11] Most dishwashers now also have heat boost and air-drying options.

It is not necessary to clean tubing unless it comes in contact with human milk or other substances. In these cases, or if condensation appears in the tubing, the manufacturer's instructions for cleaning should be followed. Pump tubing,

connectors to the pump and all other pump parts, are not to be shared between mothers.

After cleaning pump parts you may sanitize in boiling water for at least 10 minutes or with microwave bags, following manufacturer's instructions. While there are no specific recommendations in the lactation research literature at this time regarding the use of these additional disinfecting measures, there are no known disadvantages. As data emerges about the bacterial growth on "cleaned" (or rather, inadequately cleaned) breast pump parts and in newly expressed human milk, these additional options may become recommended practices.

Expressing human milk as hygienically as possible will diminish the risk of pathogenic contamination and decrease microbial growth in stored human milk, however, the process is fragile and any break in technique can lead to undesired results. Unfortunately, health care workers themselves are often non-compliant with basic infection control practices such as proper hand cleaning, use of rings and fingernail condition.[14,38,39] Health education with rationale regarding pumping hygiene should be provided to mothers, fathers and other family members but also to health care staff. Observance of poor hygienic practices in staff caring for hospitalized infants can undermine infection control best practices.

Basic Recommendations for Pumping Hygiene

- Maintain short, clean natural fingernails with un-chipped polish. Avoid wearing rings.
- Prior to pumping, prepare a surface for cleaned pump parts: disinfect, rinse if necessary and cover with clean paper towel or freshly laundered cloth towel.
- Wash hands thoroughly with soap and warm water for 20-30 seconds.
- Turn the sink off with a clean dry paper towel.
- Dry hands with clean paper towels or a freshly laundered cloth towel.
- If soap is not available, use a generous amount of alcohol hand rub to clean all hand surfaces but avoid touching breasts or interior surfaces of clean pumping parts or rinse the alcohol off with water.
- Pump breasts.
- After pumping, wash all pump parts that would normally come in contact with human milk after every use whether was human milk was obtained or not.
- Separate pump parts, rinse with cool water, and then wash under warm running water or in a clean bowl/container specified for this purpose only.
- Dry pump parts with clean paper towels, cloth towels or air dry.
- Remove pump parts from sink area.
- Reassemble pump parts with clean hands.
- Store in a safe location.

Additional Recommendations for Initial Pumping in the Hospital

- Hospital staff should disinfect breast pumps between patients per infection control guidelines.
- Provide infant's mother and family education re: pumping techniques and hygiene.
- Mothers may need assistance with hand hygiene if they are confined to bed.

Additional Recommendations for Pumping at Home or Work

- Wash pump parts in the kitchen area, not in the bathroom.
- A dishwasher may be used for washing of pump parts. Some manufacturer's suggest top rack only, be sure to follow manufacturer's cleaning instructions. Use hot water boost and air-drying if available.

Additional Recommendations for Pumping in NICU/ Nurseries

- Mother or staff must disinfect pump before use with antiseptic spray or wipes per manufacturer recommendations.
- Do not use anyone else's pump parts including tubing and pump connectors.
- Notify nursery staff of problems with paper towels, soap or disinfecting materials.

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Importance of Brain Monitoring in the Neonatal Intensive Care Unit

Dr Anita Kharbteng

The overall aim of care for the sick newborn is survival with an intact neurological and development outcome. Brain injury is a serious and constant threat to the newborn. Neurodevelopmental disabilities and clinically silent seizures are estimated to affect more than 16% of the Neonatal Intensive Care Unit (NICU) patient population.

Increased understanding of the pathogenesis of neonatal encephalopathy indicates that it is much more complex than originally thought. Further it is becoming more evident that hypoxic-ischemic encephalopathy (HIE) is the final common endpoint for a complex convergence of events. The knowledge that HIE is a process that evolves over hours to days provides a "window of opportunity" for interventions.

The electrophysiological brain activity as reflected by electroencephalography (EEG) is well established as a tool for providing information about the current metabolic state of the brain and the occurrence of epileptic seizure episodes. In neonatal care, EEG has been extensively used for estimation of the degree of cerebral maturation in preterm infants, and for detection of abnormal patterns indicating focal and global cerebral lesions. However, interpretation of neonatal EEG is

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considered among neurologists as a demanding task considering the different specific EEG features related to different gestational age, activity state and medication.

In the neonatal setting as well as in intensive care in general, EEG has been recorded intermittently, at best serially rather than continuously. The main disadvantage with intermittent conventional EEG during neonatal care is the difficulty in discriminating emerging trends of development of the electrocerebral activity over hours and days. If at all possible, it takes special skills not usually available at the NICU to identify such long term changes of EEG patterns. In order to have an impact on the intensive care, monitoring of the electro cortical activity would have to be continuous and simple in terms of recording equipment and number of recording electrodes. Furthermore, EEG features which are immediately relevant for clinical decisions should be continuously available at the bedside and made possible to interpret by the attending physician day and night.

In the 1970s, data compression techniques were introduced in an attempt to simplify EEG interpretation. Pamela Prior and Douglas Maynard developed a device in the 60s/70s called Cerebral Function Monitor (CFM) which is a single channel analog EEG machine that processes the EEG in such a way that seizure and EEG background activity can be recognized on a time scale that is much more compressed than a conventional EEG. This method has been described as "Amplitude Integrated EEG" or aEEG. This original CFM device, however, has struggled to gain acceptance in the field of neurology as it has been criticized for its limitations in channels as well as for the lack of sophisticated raw EEG data.

Neonatologists however found aEEG very useful and have used it widely in the NICU. The aEEG background gives valuable information of the neurological outcome of the infant. The aEEG is very useful to simplify and speed up seizure detection. The finding that the aEEG is suitable for very early prediction of outcome after perinatal asphyxia is presently being used as an inclusion criterion in studies of therapeutic hypothermia, and has resulted in spreading use of the technique. The clinical experiences with neonatal aEEG monitoring have been exemplified in an "Atlas of Amplitude Integrated EEG in Newborns" by Lena Hellström Westas, Linda de Vries and Ingmar Rosen.

It is, however, important to be aware of the limitations and risks of over-interpretation when using aEEG. The raw EEG data should always be used to interpret the aEEG trends. The possibility of extracting detailed information from the EEG is also lost. Therefore, continuous aEEG does not replace but is complementary to standard EEG.

Quantification of interburst intervals, ie, the time between bursts in burst-suppression EEG or counting of bursts per hour, may also provide additional information on neonatal brain development and prediction of outcome. Identification of sleep-wake cycles in infants in the NICU can be of great value. In addition to giving prognostic information, indication of quiet sleep periods can guide routine patient care.

The need for a brain monitoring device is clear and for devices that offer the user (both the neonatologist and the neurologist) a fully functioning recording, with multiple data analyzing tools.

With new advances in digital technology, many of these impediments have been overcome, making bedside EEG a clinically relevant tool. New trend analysis packages have been developed to make EEG easier to analyze for non-experts and they sometimes give more information than the raw EEG data.

With the advent of new technology, continuous EEG monitoring in the NICU is feasible. This allows for better evaluation of cerebral function, faster time to treatment and better prognostic information which results in quality care for the NICU patient, and better neurodevelopmental outcomes.

Editorial…continued from page 4

multi-functional providing both stem cells and a stromal support structure or an extracellular matrix. All of these properties makes Wharton's jelly an ideal source for tissue repair, regeneration and commercialization.[6]

A lucrative area of research is Wharton's jelly's potential source of specific skin protection and rejuvenation proteins as a method to combat skin aging.

Many research laboratories, both public and private, are in the race to develop the potential of stem cells derived from Wharton's jelly. Wharton's jelly may not yet be the "silver bullet" for medicine but it may be the "golden egg" for others.

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Electronic Fetal Monitoring

A fairly recent article in the journal Obstetrics and Gynecology made the following claim: "Electronic fetal monitoring has failed as a public health screening program... Because of low-prevalence target conditions and mediocre validity, the positive predictive value of electronic fetal monitoring for fetal death in labor or cerebral palsy is near zero. Stated alternatively, almost every positive test result is wrong..." [Electronic Fetal Monitoring as a Public Health Screening Program; The Arithmetic of Failure, by Drs David Grimes and Jeffrey Piepert.]

The website Dr Amy (SOB) The Skeptical OB, made the following comments: It is critical to note that the authors are not claiming that fetal monitoring is a failure, merely that electronic fetal monitoring fails to provide additional benefits over monitoring by intermittently listening to the fetal heart rate. The authors provide a breathless analysis of the causes for this purported failure, implying that basic statistical analysis made this failure easily predictable.

In my judgment, the authors commit two serious, and inexplicable, errors: 1. Although, the authors provide a detailed statistical analysis of the limited ability of electronic fetal monitoring (EFM) to detect fetal death (stillbirth), such an analysis utterly misses the point. The purpose of electronic fetal monitoring is not to detect fetal death, but to prevent it. The primary purpose of fetal monitoring (whether by auscultation or electronic) is to diagnose fetal distress in progress, not to diagnose death, the end point of severe fetal distress. Curiously, the authors give short shrift to this. And since the authors virtually ignore the primary purpose of the test, their analysis, while sure to garner headlines, is not particularly compelling.

2. The authors complain that screening for rare events leads to tests with poor predictive value. Fortunately, adverse outcomes in labor are relatively rare. That's why neonatal deaths are expressed per 1,000 births. Therefore, it is not a surprise that screening for poor fetal outcomes has a poor predictive value. But if our goal is to prevent rare events, that is virtually inevitable.

The authors explain the nature of screening tests and the measurements that determine the validity of a screening test, including positive predictive value, negative predictive value and the impact of prevalence. I performed a similar analysis in a post written 2 years ago (HYPERLINK "http://homebirthdebate.blogspot.com/2008/10/sensitivity-specificity-and-fetal.html" Sensitivity, specificity and fetal monitoring). I used round numbers to illustrate the concept and it may helpful to read my post before reading the actual paper.

The key finding of the Grimes, Piepert paper is this: Here, electronic fetal monitoring is assumed to have a sensitivity of 57% and specificity of 69%, and the prevalence of fetal death is low: 50 per 100,000... [T]he predictive value of a positive electronic fetal monitoring screen [is] 29/31,013, which rounds off to zero percent. Because of poor test specificity, more than 30,000 false-positive tests ... overwhelm fewer than 30 true-positive results ... Given a worrisome tracing, the probability of fetal death is, rounded to percent, nil.

In other words, if EFM is used to predict which babies will definitely die, only 1/1000 will actually die. That seems compelling until you consider that EFM is not used to identify babies who will definitely die, it is used to identify babies who are not getting enough oxygen and therefore may suffer permanent brain damage or die. As the authors briefly acknowledge in what is virtually an aside, EFM performs very differently in that situation.

More common but less serious, fetal acidemia at birth [as a result of low oxygen in labor] may provide the most charitable assessment of electronic fetal monitoring. In a large randomized controlled trial with a frequency of fetal acidemia at birth (umbilical cord artery pH less than 7.15) of 10%, nonreassuring fetal heart rate patterns had a positive predictive value of 37%. Even for this common outcome, most positive tests were wrong.

Yes, the majority of babies identified as suffering from oxygen deprivation turn out to be fine, but 37 out of 100 (more than 1/3) are suffering from oxygen deprivation so severe that it may result in brain damage or death. That's a number too large to ignore.

For perspective, it helps to consider a real world example, like mammography. The positive predictive value of mammograms is low. Most abnormal findings on mammography turn out to be benign. The positive predictive value for screening mammography in detecting breast cancer is in the range of 10%, considerably less that the PPV for electronic fetal monitoring in detecting oxygen deprivation (37%).

Moreover, routine mammographic screening of women under 50 saves only 1 life per 1,400 women screened. That's a PPV for preventing death of 0.07%, nearly zero using the methodology that Grimes and Piepert applied to EFM. Nonetheless, the recent recommendation to suspend routine screening of women under 50 met with a firestorm of protest.

The bottom line is that obstetricians are well aware of the serious limitations of electronic fetal monitoring. For every neonatal life saved, for every case of brain damage averted, hundreds if not thousands of monitoring strips falsely predict fetal oxygen deprivation. The issue is not whether fetal monitoring is a good screening test; everyone knows that it is a bad screening test. The problem is that there is no screening test

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Home Cardiorespiratory Monitoring: caring for the medically compromised infant in the home

Sharyn Gibbins, NNP, PhD

Introduction

Over the past two decades, the survival of infants with complex medical needs has increased. In conjunction with this increase is the number of medically fragile infants who are cared for in the home environment as opposed to the hospital setting. Traditionally, infants were deemed stable for discharge home from the NICU if there was (a) sustained weight gain, (b) physiologic stability as defined as the ability to coordinate suckle feeding, swallowing and breathing while maintaining normal body temperature, (c) active parental involvement in the discharge planning process, and (d) adequate follow-up after discharge.[1] Although interrelated, these infant discharge competencies are usually reached between 34 and 36 weeks post conceptual age (PCA). The pace of maturation, however, is influenced by gestational age at birth, severity of illness while in the hospital, and co-morbid factors such as chronic lung disease or unresolved apnea. As a result of improved technology, nutritional science, developmental care, inter-professional practice, and the knowledge that shortening the length of hospital stay reduces hospital-acquired morbidities, NICU infants are sicker, smaller and more complex than any other decade to date.[1-2] Hospital discharge, therefore, requires a balance between the complex needs of the infant and those of the family who are prepared to care for the infant at home. A single set of criteria for discharge readiness is no longer adequate and careful consideration for who can be discharged home, and what cardiorespiratory monitoring is required to assure safety, is now under consideration. For select infants with delayed physiological maturity or those who require technological support, home cardiorespiratory monitoring has been suggested as an intervention that allows infants to remain at home while promoting family participation in their care. What is needed, however, are clear guidelines as to who would benefit from home monitoring, and the responsibilities of policy makers, caregivers and industry leaders when home cardiorespiratory monitors are prescribed.

History of cardiorespiratory monitors

Apnea monitors were introduced more than 25 years ago for the management of apnea of prematurity in the hospital setting.[1] Since then, apnea monitors have been used throughout the world to monitor the respiratory status of acute and chronic infants in the NICU. In the 1970s, home apnea monitors were seen as a logical extension of in-hospital technology as a solution for infants with delayed respiratory maturity who were otherwise stable enough to be discharged home.[3] Home cardiorespiratory monitoring became a common practice to facilitate early hospital discharge, with the assumption that they detected apnea and thus prevented sudden infant death syndrome (SIDS). Controversy over these claims, due in part to the failure to show a link between apnea and SIDS, led the American Academy of Pediatrics (AAP) to recommend cautious use of home monitoring.[4] A Task Force on Prolonged Infantile Apnea in 1980 further stated that a "causal relationship between prolonged apnea and SIDS has not been established and use of home monitoring should be reserved to individual situations and physician judgment."[5] Although these recommendations initially ran the risk of banishing home cardiorespiratory monitoring for all infants, they served as a catalyst to re-visit past practices. Rather than vague statements about who should be monitored and how individual situations and physician judgments are formed, systematic approaches to home monitoring based on current best evidence and fiscal responsibilities are proposed.

Why should infants be monitored?

The association between apneas in preterm infants, poor neurodevelopmental outcomes, and use of home cardiorespiratory monitoring warrants review. It is plausible that frequent hypoxic events and bradycardic spells during critical periods of brain growth lead to re-oxygenation injury and resultant negative sequelae.[6,7] In one study, 239 preterm infants born at less than 32 weeks gestation were followed to determine whether there was a correlation between the number of days during hospitalization that apnea spells occur and the neurodevelopmental outcome at three years of age 8 (see Figure 1). Forty-one infants had impairment, as defined by motor or cognitive delay, cerebral palsy, or blindness; with an increasing number of days on which at least one apnea occurred, total apnea days, and male sex as predictive factors for poor outcome. Gestational age at birth was not a predictor. Although it is not clear whether the apnea was a precursor to neurological injury or a symptom of a pre-existing injury, these data indicate the need for early apnea recognition and prompt intervention to prevent impairment.

Who should be monitored?

Early studies suggest that certain categories of infants may benefit from home cardiorespiratory monitoring.[2,9,10]

These categories include: (1) infants with a history of apparent

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life-threatening events (ALTE), (2) former premature infants with persistent apnea and bradycardia, (3) siblings of victims of sudden infant death syndrome (SIDS), and (4) infants who have anxious parents following a non-significant event. Logic would dictate that other infants at risk include those with tracheostomies or anatomic abnormalities that make them vulnerable to airway compromise, those with neurologic or metabolic disorders affecting respiratory control, and those with chronic lung disease requiring supplemental oxygen, continuous positive airway pressure or mechanical ventilation, or those receiving respiratory stimulants such as caffeine. These infant categorizations, however, have not been systematically examined for candidates for home cardiorespiratory monitoring. In a large study, 718,000 hours of documented monitoring of 1,079 infants (infants with idiopathic ALTEs, siblings of infants who died of SIDS, symptomatic [having clinically apparent apnea/bradycardia episodes] and asymptomatic preterm infants weighing less than 1750 g at birth, and healthy term infants) were analyzed.[11] The only groups with an increased risk of extreme events at home compared to healthy term infants were the preterm infant groups, up to approximately 43 weeks postmenstrual age. Infants being monitored for ALTEs had an increased risk of repeated extreme episodes, but the difference was statistically significant only for the preterm ALTE group. The risk of a recurrent extreme episode increased with each subsequent recurrence for all infants who had a single extreme episode.

In a later study, 1058 preterm infants (25-34 weeks GA) who had an abnormal polysomnography at the time of discharge were sent home with a cardiorespiratory monitor (see Figure 2). Abnormal events were defined by one of the following: (i) a heart rate less than 50 beats per minute (bpm) for more than three seconds, (ii) apnea lasting more than 15 seconds with a heart rate less than 60 bpm and (iii) peripheral oxygen saturation of less than 88%.[12] Ninety-six infants (9.6%) had abnormal events while at home, and ten of them required resuscitation following a serious event. The median age in which monitors were deemed no longer necessary was 44 (42–46) weeks PCA. However, 17 of the infants continued to have serious events after 50 weeks PCA. The results of this study suggest a significant negative correlation between the GA at birth and the PCA at which serious events occur (i.e., the more immature at birth, the longer time the infant is at risk for serious events). As more extreme preterm infants are surviving the neonatal period and being cared for in the home, careful assessment for when to discontinue monitoring is required.

In an attempt to understand the risk factors for the occurrence and severity of ALTE and predict who would benefit from close monitoring, one study examined all infants readmitted to the hospital for ALTE.[13] Of the 625 infants who appeared well on presentation to the emergency department, 7.5% had extreme cardiorespiratoy events recorded on the SmartMonitor 970S or SmartMonitor 2 within 24 hours of hospital admission. The most frequent events were extreme desaturations below 80%, preceded by a central apnea. Infants at highest risk for extreme events were those born prematurely, those less than 43 weeks PCA and those having symptoms of an upper respiratory tract infection. No infant more than 48 weeks PCA had an extreme event. The authors recommend that irrespective of how well the infant appears on physical examination, cardiorespiratory monitoring for a minimum of 24 hours following hospital admission should be instituted. Although this study addressed infants readmitted to the hospital for an ALTE, the results have implications for home monitoring because they highlight specific high-risk infants who experience significant cardiorespiratory compromise that may go unrecognized.

In another study describing infants who would benefit from close cardiorespiratory monitoring, the frequency and timing of apneic events following discharge from a NICU were examined.[14] Thirty-six percent of former preterm infants discharged home experienced a significant event as defined as central apnea longer than 20 seconds; central apnea of less than 20 seconds associated with bradycardia; or a bradycardic event (age-corrected and more than 5 seconds) without central apnea. Of the events, 85% occurred within the first month of monitoring and 69% within the second month. When significant events were recorded in hospital, the events were likely to recur at home, further supporting the need for ongoing cardiorespiratory monitoring in infants who have had a history of apneas and bradycardias while in the NICU. The link between apnea and SIDS is poorly substantiated. The risk of sudden death in siblings of infants who died of SIDS is even more unclear. The lack of association is due in part to the rarity of a SIDS death and the more extreme rarity of a subsequent SIDS death of a sibling.[15] It is hypothesized that the studies that reported an increased risk for siblings were performed before full understanding of the epidemiology evolved. The roles of infant sleep position and sleeping environment, smoking in the household, and death scene investigation to exclude infanticide are now recognized as significant factors in understanding the causation of SIDS.[15,16,17] Given the lack of evidence that home cardiorespiratory monitoring has had any impact on SIDS, prevention of SIDS is not an acceptable indication for home cardiorespiratory monitoring.

The efficacy of home cardiorespiratory monitoring for infants whose parents are anxious has not been fully explored, but rather extrapolated from studies indicating the NICU experience causes significant stress.[2,18] There are no data to support the use of monitors simply to alleviate parental concerns and caution is advised for those who recommend its practice for this reason alone. Although the infant-risk categories are derived from old studies, the categorization system (with the exception of infants who have anxious parents) continues to be relevant in today's NICU. Based on these data, the following 2002 AAP guidelines for the use of home monitors are proposed:[19]

Figure 1. Total number of infants with and without neurodevelopmental impairment at 3-year follow-up, by gestational age.

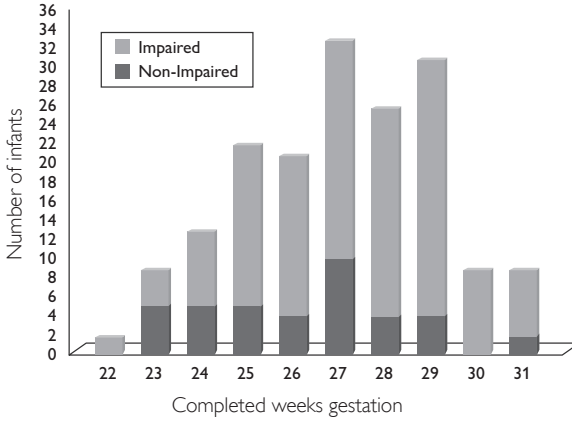
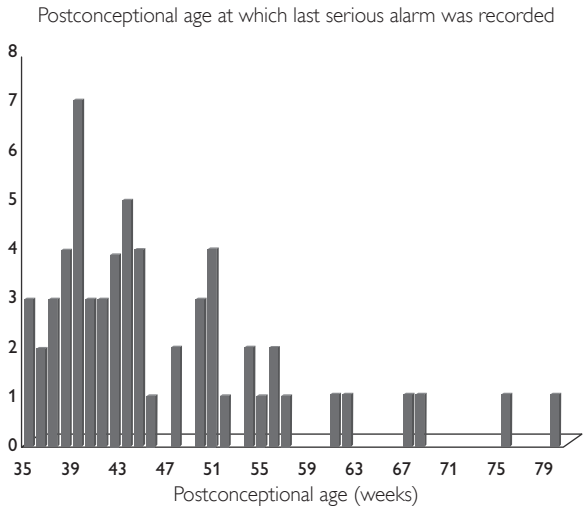


Figure 2.



Recommendations for use

Home cardiorespiratory monitors may be warranted for premature infants who are at risk of recurrent episodes of apnea, bradycardia and hypoxemia after hospital discharge.

Home cardiorespiratory monitors may be warranted for infants who are technology dependent (tracheostomy, continuous positive airway pressure), have unstable airways, have rare medication conditions affecting regulation of breathing, or have symptomatic chronic lung disease.

If home cardiorespiratory monitoring is prescribed, the monitor should be equipped with an event recorder.

Parents should be advised that home cardiorespiratory monitoring has not been proven to prevent sudden unexpected deaths in infants.

Pediatricians should continue to promote proven practices that decrease the risk of SIDS–supine sleep position, safe sleeping environments, and elimination of prenatal and postnatal exposure to tobacco smoke.

Responsibilities of policy makers, healthcare providers and industry leaders

While it is known that monitoring does not prevent adverse events in preterm or medically fragile term infants, they do alert caregivers to potential problems such as apnea recognition, airway obstruction, respiratory failure, interruption of supplemental oxygen supply, or failure of mechanical respiratory support.[3] The decision to discharge infants from the NICU is multifactorial, but usually coincides with physiological maturity and parental readiness. Rather than one-size-fits-all practices that suggest that home monitoring prevents adverse events such as SIDS, policy makers need to hold physicians and healthcare systems accountable for safely discharging infants home. Policies that combine risk factors such as PCA and NICU history, coupled with careful assessment of risk factors for respiratory fatigue or oxygen deprivation, should be used to determine which infant is discharged home with a cardiorespiratory monitor. Infants with specific neurologic or airway risk factors, or those requiring respiratory support, however, warrant home monitoring irrespective of what other risk factors exist.[3] Data to advocate the use of home monitoring for infants who have had a sibling succumb to SIDS or whose parents are anxious are less clear, and cannot be supported in the current healthcare climate. Exploration of family's feelings regarding discharge home should be considered before arbitrarily prescribing home monitors to this group.

When an infant is discharged home with a cardiorespiratory monitor, the family's stress is heightened because of the increased safety concerns of a high-risk infant.[18] As a result, healthcare providers must assess the level of stress, coping patterns, and existing support systems prior to discharge home. Anticipatory guidance by the healthcare team may allow the family to easily transition to life at home with medical equipment, while ensuring safe practice. Appropriate teaching is imperative and should include safety information for the use of the monitor, safe sleep practices, minimizing activity around the monitor that may result in accidental disconnection, checking that the monitor and alarms are in working order, performing self-tests according to manufacturers' directions, and keeping the monitor away from sources of electrical interference such as heated waterbeds, radios, televisions, and other appliances.[18] Families must also be taught what to do in the event of a true cardiorespiratory event. Appropriate cardiopulmonary resuscitation (CPR) teaching, 24-hour-a-day contact information, and knowing who to call for specified signs and symptoms are the responsibility of the healthcare team.

Industry leaders have a responsibility to create devices that can accurately distinguish between true cardiorespiratory events and artifacts. There are three types of monitors that need to be considered in light of the infant's medical needs. These include monitors that (a) detect infant gross motor movement, (b) detect respiratory and cardiac signals, and (c) record respiratory and cardiac signals and oxygen saturation. While the first two types of monitors may have served a purpose in previous decades where medically complex infants were less likely to be cared for in the home, the latter more recent models have broader applications because of the ability to record the time the monitor is turned on and off, ensure accuracy in reporting to healthcare professionals, and examine electrocardiography waveforms, heart rate trend, respiratory effort waveforms, oxygen saturation levels and pulse waveforms. Leaders in monitor development also have a responsibility to inform stakeholders of what monitors "can" and "cannot" do, whether in the hospital or home environment. Factual data that presents both the sensitivity (measures the proportion of actual positives which are correctly identified as such) and specificity (measures the proportion of negatives which are correctly identified) of the monitor must be included in educational materials, marketing strategies, and parent handouts. Moreover, data supporting the monitors' efficacy for specific infant categories rather than making claims that medical conditions can be managed with monitors are required. A collaborative approach with policy makers, healthcare providers, and industry leaders will increase the safety of high-risk infants receiving medical care in the home.

Summary

There has been a tremendous shift in the use of home monitors – from the belief that they prevent SIDS to the understanding that they provide warning to caregivers when a select group of infants is experiencing a cardiorespiratory event. There are studies to support home monitoring for preterm infants with a history of apnea or bradycardic events and those who have had an ALTE. Although not supported in large studies, but intuitively

recognized as significant risk factors for cardiorespiratory events, are technology-dependent infants, infants with airway anomalies that predispose them to oxygen deprivation, and neurologically or metabolically impaired infants with a dysfunctional respiratory drive. Less data support the use of home monitors for infants whose sibling died of SIDS and those whose parents are anxious. When advocating the use of monitors for these infants, parents need to be fully informed that prevention of SIDS is not possible. Rather, practices known to decrease the risk of SIDS should be instituted. Many types of monitors are available, and it is the responsibility of the healthcare team to not only prescribe the appropriate device but inform parents of its strengths and limitations. As more and more medically fragile infants are cared for in their homes, it is our professional obligation to fully inform them of the discharge process and adequately prepare them for life at home with a cardiorespiratory monitor as per the AAP recommendations. Once these discharge goals are met, safe home care of medically compromised infants can ensue.

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Fetal Monitoring…continued from page 26

that's better. The question we face is not whether EFM is highly effective, the question is whether EFM is worth it. That's an ethical issue, not an arithmetic one.

Here's the abstract of the article:

Electronic fetal monitoring has failed as a public health screening program. Nevertheless, most of the four million low-risk women giving birth in the United States each year continue to undergo this screening. The failure of this program should have been anticipated and thus avoided had the accepted principles of screening been considered before its introduction. All screening tests have poor positive predictive value when searching for rare conditions such as fetal death in labor or cerebral palsy. This problem is aggravated when the screening test does not have good validity as is the case with electronic fetal monitoring. Because of low-prevalence target conditions and mediocre validity, the positive predictive value of electronic fetal monitoring for fetal death in labor or cerebral palsy is near zero. Stated alternatively, almost every positive test result is wrong. To avoid such costly errors in the future, the prerequisites for any screening program must be fulfilled before the program is begun.

A Randomized Controlled Trial of the Oropharyngeal Administration of Mother's Colostrum to Extremely Low Birth Weight Infants in the First Days of Life

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Abstract

Background: Own mother's colostrum (OMC) provides immune protection to extremely low birth weight (ELBW) infants in the immediate post-birth period, however clinical instability typically precludes enteral feedings. Oropharyngeal administration is an alternative; however it is uncertain whether OMC would be immunostimulatory using this route.

Objective: The purpose of this study was to determine whether OMC has an immunostimulatory effect when administered via the oropharyngeal route to ELBW infants in the first days of life and to track clinical outcomes of subjects.

Methods: Sixteen ELBW infants were randomly assigned to receive either 0.2 mL of OMC or sterile water (placebo) oropharyngeally every 2 hours for 48 consecutive hours; beginning at 48 hours of life. Secretory immunoglobulin A (sIgA) and lactoferrin (Lf) were measured in tracheal aspirates and urine, and interleukin-10 (IL-10) was measured in tracheal aspirates and serum, pre and post-treatment.

Results: No statistically significant differences in immune markers were found between or within groups. A large and moderate effect size was noted for urine Lf (1.30) and urine sIgA (0.51) respectively, for OMC-treated infants which suggest that results may have reached statistical significance if a larger sample had been used. The most compelling finding was that infants in the OMC group reached full enteral feedings (150 mL/kg/day) 10 days earlier (M= 14.3 ± 5.7 vs 24.2 ± 8.7 days; p=0.032) compared to those in the placebo group.

Conclusion: OMC may have maturational effects on the intestine, and potentially an immunostimulatory effect, and when administered oropharyngeally to ELBW infants.

Introduction

Human milk (HM) feedings have been consistently associated with a lower incidence and severity of nosocomial infection,[1-4] enteral feed intolerance,[4-6] and necrotizing enterocolitis (NEC),[4,7-9] in premature infants when compared with formula-fed cohorts. These outcomes are attributed to the presence of protective factors in HM which modulate immunity, protect against infection, and promote intestinal maturation,[10-17] and recent evidence suggests an inverse relationship between the concentration of many of these factors and the duration of pregnancy.[18-22] Thus, the milk produced by mothers of extremely low birth weight (ELBW; BW<1000g) infants contains the highest level of protection, particularly during the colostral phase,[18-22] which suggest an important biological function for own mother's colostrum (OMC) feeding in the first days post-birth. Unfortunately, clinical instability precludes enteral feeding during this time and the inability to feed leads to intestinal atrophy[23] which increases the risk for enteral feed intolerance and necrotizing enterocolitis.[24] An alternative method of administering OMC during this critical post-birth period is needed.

Oropharyngeal administration is a feasible approach[25] and is hypothesized to protect infants via three distinct mechanisms: the potential interaction of OMC cytokines with lymphoid cells within the oropharyngeal associated lymphoid tissue (OFALT) system;[17,26,27] the mucosal absorption of immunologically-derived factors;[28] and the barrier protection afforded by human milk oligosaccharides against respiratory pathogens that can penetrate the oropharyngeal mucosa.[29,30] OFALT stimulation is particularly important because it may potentially lead to systemic immunostimulatory effects. However, with current standard practice in neonatology, the opportunity to use OMC to stimulate OFALT is often delayed for up to eight weeks post-birth for ELBW infants until "per oral" feeds can be safely introduced. During this prolonged period, enteral feedings are administered via a gavage tube that bypasses OFALT structures and OMC cytokines never come in contact with lymphoid cells within OFALT. Oropharyngeal administration of OMC potentially stimulates the OFALT system, and previous pilot studies[31,32] have established feasibility, however the immune effects and clinical outcomes of this new intervention have not been investigated. The purpose of this study was to determine whether OMC has an immunostimulatory effect when administered via the oropharyngeal route to ELBW infants in the first days of life and to track clinical outcomes of subjects. An immunostimulatory effect was determined by measuring concentrations of secretory immunoglobulin A (sIgA; marker for mucosal immunity) and lactoferrin (Lf; a glycoprotein) in tracheal aspirates and urine, and interleukin-10 (IL-10; anti-inflammatory cytokine) in tracheal aspirates and serum.

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Table 1. Characteristics by study group (n=15).

Characteristics		Colostrum (n=9)	Placebo (n=6)	*p*-value
Maternal age (yr)				0.606 [a]
	Mean ± SD	27.33 ± 5.24	28.83 ± 5.6	
	Median (range)	27 (18-35)	30 (21-36)	
Infant birth weight (g)				0.168 [a]
	Mean ± SD	776.11 ± 231.73	940.83 ± 181.34	
	Median (range)	800 (410-1120)	915 (690-1250)	
Infant gestational age at birth (wk)				0.148 [a]
	Mean ± SD	25.97 ± 1	26.77 ± 0.97	
	Median (range)	25.6 (25-27.5)	26.45 (25.6-28.3)	
Apgar 1 min				0.172 [b]
	Mean ± SD	4 ± 2.24	5.83 ± 1.47	
	Median (range)	3 (2-7)	5.5 (4-8)	
Apgar 5 min				0.092 [b]
	Mean ± SD	6.67 ± 1.22	7.83 ± 0.98	
	Median (range)	7 (5-8)	8 (6-9)	
		N (%)	N (%)	
Maternal race				0.866 [d]
	White (non-Hispanic)	5 (55.56)	4 (66.67)	
	African American	1 (11.11)	1 (16.67)	
	White (Hispanic)	2 (22.22)	0 (0)	
	Other	1 (11.11)	1 (16.67)	
Maternal race				1.0 [c]
	White (non-Hispanic)	5 (55.56)	4 (66.67)	
	All other	44.44 (9)	33.33 (6)	
Cesarean birth		6 (66.67)	5 (83.33)	0.604 [c]
Prolonged rupture of membranes (>24 hr)		0 (0)	1 (16.67)	0.400 [c]
Antenatal antibiotics		7 (77.78)	5 (83.33)	1.0 [c]
Antenatal steroids		8 (88.89)	5 (83.33)	1.0 [c]
Birth weight				0.580 [c]
	<750 g	4 (44.44)	1 (16.67)	
	≥750 g	5 (55.56)	5 (83.33)	
Gestational age (wk)				1.0 [c]
	24-25	4 (44.44)	2 (33.33)	
	26-28	5 (55.56)	4 (66.67)	
Gender				0.329 [c]
	Male	7 (77.78)	3 (50)	
	Female	2 (22.22)	3 (50)	

[a]: independent two sample t test; [b]: Wilcoxon two sample test; [c]: Fisher's exact test; [d]: exact Pearson Chi-square test

Methodology

Design: This study was a blinded, placebo-controlled, randomized controlled trial. Infants in the experimental group received OMC while those in the placebo group received sterile water during the treatment period. Dependent measures were collected at baseline and at the completion of the 48-hour treatment protocol.

Subjects and Site: Sixteen ELBW infants, hospitalized in a 44-bed level III neonatal unit, who met the following inclusion criteria served as subjects: birthweight <1000 g and/or gestation < 28 weeks; and appropriate weight for gestational age. Exclusion criteria were: presence of congenital anomalies, gastrointestinal or renal disorders; receipt of vasopressor medications at a dosage >10 mcg/kg/min; maternal chorioamnionitis, history of substance abuse, or positive HIV status. The study was approved by the institutional review board (IRB) of the institutions where the data collection took place and the home institution for the investigators.

Procedures: Maternal informed consent was obtained prior to the birth of the infant. Once informed consent was obtained, the infant was randomly assigned to either the experimental (OMC) group or the control (placebo) group. The PI was present at the time of delivery and a baseline tracheal aspirate specimen was obtained immediately after birth, before the administration of surfactant. Mothers began breast pumping within 24 hours after delivery, using a hospital-grade electric double breast pump (Symphony, Medela, Inc, McHenry, IL, US). Colostrum samples were placed in sterile, Volu-feed containers (Abbott; Columbus, OH, US) and immediately refrigerated.

The protocol for the administration of colostrum drops to the oropharyngeal area described by Rodriguez and colleagues[31] was followed. Wearing sterile gloves, 24 needleless tuberculin syringes were each filled with 0.2 mL of OMC or sterile water (placebo) based on the infant's group assignment. Colostrum samples for placebo group infants were immediately frozen and stored until enteral feedings were started. The syringes were labeled with the infant's preprinted hospital label, date and time of preparation, and were covered with an opaque tape as a blinding procedure. The treatment protocol was initiated immediately after baseline blood and urine specimens were collected and after the syringes were prepared. The colostrum or placebo was administered by placing the tip of the syringe into the infant's mouth, alongside the right buccal mucosal tissue, and directing it posteriorly towards the oropharynx. A volume of 0.1 mL was slowly administered over a period of at least two minutes. Without removing the syringe from within the infant's mouth, the tip was re-directed alongside the left buccal mucosal tissue, with the tip directed towards the oropharynx. An additional 0.1 mL was administered in the same manner. The infant's vital signs were monitored throughout the procedure. This procedure was started within 48 hours of life and carried out every two hours over a treatment period of 48 consecutive hours. Tracheal aspirate, urine and blood specimens were collected within 6 hours of completion of the treatment period. Minimal enteral feedings were started immediately after the study protocol was completed, which corresponded to DOL# 3 or 4, as per standard clinical practice.

Measures: sIgA and Lf concentrations were measured in duplicate in tracheal aspirates and urine using enzyme-linked immunoassay (ELISA) kits (ALPCO Diagnostics, Windham, NH, US; Calbiochem-EMD Biosciences Inc, San Diego, CA, US). IL-10 concentrations were measured in duplicate in serum and tracheal aspirate specimens using a human cytokine multiplex immunoassay kit (Linco Research, St Charles, MO, US). Blood samples were centrifuged at 3800 rpm for 25 minutes to separate plasma, while tracheal aspirates and urine samples were centrifuged at 1500 rpm for 15 minutes. All samples were immediately stored in a -80 degree Celsius freezer until biochemical analysis. Concentrations of sIgA and Lf were determined from a standard curve generated with known standards. Data were graphed using the Prism GraphPad program (GraphPad Software Inc, San Diego, CA) using a cubic spline procedure for converting optical density into concentration. The concentrations of IL-10 in serum and tracheal aspirate specimens were determined using a human cytokine multiplex immunoassay kit (Millipore, Billerica, MA, US) in which polystyrene beads are coated with capture antibody to the analyte of interest and incubated with 25 ul of plasma in a 96 well filter bottom plate, washed, and then incubated with detection antibody and finally incubated with added streptavidin-phycoerythrin. The median fluorescent intensity (MFI) of the beads is determined through a standard curve reading, in the range of 1.6 to 10,000 pg/mL, on the Luminex multiplex analyzer. Low and high controls were used to verify accuracy of the results. MFI was converted to concentration using a 5 parameter logistic curve.

Statistical Analysis: A paired t test or a signed-rank test was used to detect pre- vs post-treatment difference within each group. A two sample t test or a Wilcoxon two sample test was used to detect between-group difference at pre- and post-treatment. A repeated measures analysis of variance (ANOVA) was used to assess between-group difference over time. Optical density values were used for sIgA and Lf comparisons because some results fell above or below the limits of detection for the assay and extrapolation was not possible. The normality assumption was assessed via a Shapiro-Wilk's test or visual inspection. Variables were log-transformed if the normality assumption was violated. Cohen's effect size, (d), (small: 0.2, moderate: 0.5,

Table 2. Descriptive statistics of pre-and post-treatment infant immune markers by group, within- and between group comparison.

		Pre-treatment			Post-treatment						
		N	Median	Range	N	Median	Range	p^a	p^b	p^c	*Pre-post Effect size*
Serum IL10	Colostrum	9	108	63 – 247	9	57.3	5.27 – 242	0.803	0.072	0.780	-0.79
	Placebo	6	79.8	65.3 – 1913	6	81.34	21.3 – 180.7				-0.76
TALf	Colostrum	9	0.38	0.16 – 1.72	9	1.18	0.49 – 1.50	0.405	**0.005**	0.252	1.01
	Placebo	6	0.36	0.09 – 0.63	6	1.178	0.84 – 1.63				1.65
TA IL10	Colostrum	8	14.7	0 – 10000	7	6.65	0 – 20.5	0.270	0.431	0.222	-0.25
	Placebo	4	0	0 – 2.3	5	5.05	0 – 134.3				1.14
TAsIgA	Colostrum	9	0.15	0.09 – 0.81	9	0.20	0.13 – 0.56	0.572	0.154	0.385	0.25
	Placebo	6	0.19	0.09 – 0.30	6	0.23	0.11 – 1.57				0.81
Ulf	Colostrum	9	0.17	0.11 – 0.56	9	0.69	0.13 – 0.93	0.313	**0.047**	0.137	1.3
	Placebo	6	0.31	0.21 – 0.60	6	0.47	0.12 – 0.77				0.35
UsIgA	Colostrum	9	0.24	0.12 – 1.08	9	0.40	0.13 – 1.15	0.590	0.503	0.472	0.51
	Placebo	6	0.52	0.12 – 1.78	6	0.52	0.09 – 1.17				-0.07

[a]: overall group difference; [b]: overall pre-to post-treatment change; [c]: between-group change difference

large: 0.8) was calculated as the mean difference divided by the common standard deviation.[33] A Fisher's exact test, an exact Pearson's Chi-square test, or an exact Mantel-Haenszel test was used to assess the association between categorical covariates and treatment. All statistical analyses were conducted using SAS 9.2 (Cary, NC). A p value < 0.05 was regarded as statistically significant.

Results

All subjects tolerated the intervention and there were no recorded episodes of apnea, bradycardia, hypotension, desaturation or other adverse effects during the treatment protocol. Many infants began to suck on the endotracheal tube during the administration of the drops. This is consistent with our previous pilot study of five ELBW infants which demonstrated no untoward effects.

Characteristics of Subjects: The characteristics of mothers and their infants are summarized in Table 1. There were no statistically significant differences in the following maternal and infant characteristics: maternal age, race, infant birth weight, gestational age, gender, cesarean birth, prolonged rupture of membranes, antenatal antibiotics, or antenatal steroids.

Changes in Concentrations of Immune Markers: The pre- and post-treatment measures (median and range) of immune markers are summarized in Table 2. When analyzing pre- and post-treatment separately, no significant between-group (colostrum vs placebo) differences were found. When analyzing each of the two groups separately, in the colostrum group serum IL-10 significantly decreased from pre- to post-treatment (median: 108.4 to 57.4, p=0.039), whereas urine Lf significantly increased from pre- to post-treatment (median: 0.17 to 0.69, p=0.027); of note, in the placebo group, serum IL-10 did not decrease and urine Lf did not increase. Table 2 also presents p-values for pre and post between- and within-group comparison revealed from repeated ANOVA. Overall between-group comparisons were not statistically significant (all p>0.05). When using effect sizes to quantify the magnitude of change from pre- to post-treatment for each of the two groups separately, in the colostrum group, a large effect size (>0.8) was found for tracheal aspirate Lf (1.01) and urine Lf (1.30), and a moderate effect size (>0.5) was found for urinary sIgA (0.51) and serum IL-10 (-0.79). For the placebo group, a large effect size was noted for tracheal aspirate Lf (1.65), tracheal aspirate IL-10 (1.14) and tracheal aspirate sIgA (0.81), and a moderate effect size for serum IL-10 (-0.76).

Clinical Outcomes: Table 3 summarizes the clinical outcomes for infants in both groups. Despite higher acuity, infants in the colostrum group reached full enteral feedings (150 mL/kg/day) sooner at an average of 14.3 ± 5.7 (range 9-25) days compared to 24.2 ± 8.7 (15-37) days for the placebo group, and this was the only characteristic that was statistically significant (p=0.032). Infants in the colostrum group were smaller and younger (mean BW: 776.1g vs 940.8g, mean GA 25.9 vs 26.8) compared to those in the placebo group (Table 1). Nonetheless, despite a higher incidence (22% vs 16.7%) of chronic lung disease (CLD), bacteremia (33% vs 0%), and pneumonia (33% vs 0%) for infants in the colostrum group compared to placebo, these differences were not statistically significant and clinical outcomes for both groups were similar

Sixteen subjects were enrolled and fifteen completed the study. One subject, randomized to the placebo group, was withdrawn from the study due to a protocol violation because he received OMC instead of placebo. Two subjects, randomized to the OMC group, died from prematurity-related diseases and septic shock during their second week of life and their deaths were deemed to be not associated with the treatment, and consistent with expected high mortality in this high-risk population.

Discussion

Oropharyngeal administration of OMC to ELBW infants is a new intervention and to date, only two pilot studies[31,32] have reported its use, however both examined feasibility but did not measure specific outcomes. One study examined the feasibility, safety and infant's response to the oropharyngeal administration of OMC.[31] In that study, five ELBW infants received 0.2 mL of OMC administered oropharyngeally every 2 hours for a treatment period of 48 consecutive hours starting before 48 hours of life. The intervention was well tolerated by all of the infants. No adverse effects were noted and all infants began to suck on the breathing tube during the administration of the colostrum drops. A more recent study examined the feasibility of administering small volumes (0.2 mL) of OMC every three hours via oropharyngeal swabbing to very low birth weight infants for seven consecutive days.[32] Results demonstrated that 80-90% of mothers were able to supply the colostrum, although the initial colostrum was typically not available until the infant's second day of life. Once started, approximately 75-80% of the planned swabbings were administered as planned.[32]

This is the first study to examine immune effects and clinical outcomes of this intervention and despite a small sample size for this pilot study, findings will inform future research. The between group comparisons did not reveal statistically significant differences for the immune markers, however the study may have lacked sufficient power to achieve a significant result.

Serum concentrations of IL-10 correlate with severity of illness, meaning that infants with more severe respiratory distress syndrome may have higher serum IL-10 levels.[34] Thus the lower serum IL-10 concentrations at post-treatment for infants in the colostrum group may simply reflect a decrease in severity of illness over the first days of life or an appropriate balance between pro and anti-inflammatory processes due to immaturity of the cytokine response. This difference was not noted for infants in the placebo group.

Tracheal aspirate concentrations of Lf increased from pre to post for infants in both groups, which suggests this may reflect a maturational effect as opposed to an effect of the intervention. The change in concentrations of IL-10 in tracheal aspirates

Table 3. Clinical outcomes by study group.

		Colostrum	Placebo	*p*-value
Time to full enteral feeds (day)				**0.032** [a]
	N	7	6	
	Mean ± SD	14.29 ± 5.74	24.17 ± 8.66	
	Median (range)	11 (9-25)	24 (15-37)	
Time to full per oral feeds (day)				0.124 [b]
	N	7	6	
	Mean ± SD	69.86 ± 19.33	55.83 ± 12.97	
	Median (range)	57 (53-96)	53 (39-78)	
Time to full per oral feeds since start of enteral feeds (day)				0.125 [b]
	N	7	6	
	Mean ± SD	62.43 ± 17.58	49.83 ± 12.86	
	Median (range)	52 (48-90)	47.5 (34-73)	
Length of hospital stay (day)				0.780 [b]
	N	7	6	
	Mean ± SD	101.43 ± 44.26	85.33 ± 32.96	
	Median (range)	80 (57-172)	72 (64-151)	
Corrected gestational age (CGA) at discharge (wk)				0.732 [a]
	N	7	5	
	Mean ± SD	40.39 ± 5.73	39.23 ± 5.49	
	Median (range)	37.6 (34.1-49.4)	36.9 (35-48.3)	
		N (%)	N (%)	
Respiratory distress syndrome		9 (100)	6 (100)	NA
*Bacteremia		3 (33.33)	0 (0)	0.229 [c]
Pneumonia		3 (33.33)	0 (0)	0.229 [c]
Necrotizing enterocolitis		0 (0)	0 (0)	NA
Chronic lung disease		2 (22.22)	1 (16.67)	1.0 [c]
*Death		2 (22.22)	0 (0)	0.486 [c]

*Two subjects diagnosed with bacteremia later died from prematurity-related diseases and septic shock.
SD: standard deviation; Min: minimum; Max: maximum;
[a]: independent two sample t test; [b]: Wilcoxon two sample test; [c]: Fisher's exact test

for both groups is also difficult to interpret because the volume of tracheal aspirate obtained from the subjects was variable, with some samples being insufficient for laboratory analysis of IL-10 concentrations. It is difficult to obtain an adequate volume of tracheal aspirate in an ELBW infant immediately after birth. Additionally, amniotic fluid contains cytokines and other immune factors such as sIgA and Lf,[35] which makes interpretation of results for changes in tracheal aspirate Lf, IL-10 and sIgA problematic.

The main distinction between the two groups was that urine Lf and urine sIgA increased from pre to post for infants in the colostrum group but did not change in the placebo group. The large and moderate effect size results for urine Lf and urine sIgA, respectively, for OMC-treated infants suggests that results may have reached statistical significance if a larger sample had been used. This finding also suggests that these two factors may be systemically absorbed and excreted in urine when OMC is administered oropharyngeally. This is consistent with literature that shows that sIgA and Lf are excreted in urine at higher levels in infants who are fed HM compared to those that receive only formula feedings.[36] In addition, research has shown that the Lf present in the urine of HM-fed infants is of maternal origin[37] although the precise mechanism of entry into the urine is currently unknown. Thus, when OMC is administered oropharyngeally, it is plausible that sIgA and Lf may be absorbed locally, as previous research has demonstrated that numerous HM factors can be systemically absorbed including immunoglobulins such as sIgA, glycoproteins such as Lf, cytokines and fatty acids.[38] The fact that these macromolecules are absorbed intact into the circulation suggests an important biological function and possible protection against systemic infection.

The most compelling finding was that OMC-treated infants, although smaller and sicker, reached full enteral feedings (150 mL/kg/day) an average of 10 days earlier than those in the placebo group. The mechanism for this is unclear, however while oropharyngeally-administered OMC is intended to remain in the oropharynx to be absorbed by the oral mucosa, it is possible that factors that enhance intestinal motility and promote maturation including growth factors and enzymes contained in OMC,[13,14,38-40] may have been absorbed mucosally and/or traveled to the gastrointestinal tract providing local maturational effects at the mucosal surface. This finding has important clinical significance given the high incidence of enteral feed intolerance in ELBW infants[41] and is consistent with published research that reports enhanced intestinal maturation, a lower incidence of enteral feed intolerance, and an earlier achievement of full enteral feeds[4-6] in HM-fed preterm infants compared to formula-fed cohorts. Thus, clinically unstable ELBW infants who are unable to feed enterally would potentially receive this important protection from OMC when it is administered oropharyngeally.

The potential benefits of early OFALT stimulation when OMC is administered oropharyngeally are yet to be determined. With our current standard of care in neonatology, an ELBW infant's OFALT would not be exposed to the potential immunostimulatory effects of OMC factors until at least 8 weeks post-birth. Early post-birth OFALT stimulation may have important immune effects and future studies should investigate these outcomes. Additionally, developmental outcomes of ELBW infants who receive this intervention should be followed as subjects appeared to "taste" the OMC, as evidenced by sucking on the breathing tube, and this may potentially lessen the risk for future oral aversion and have developmental implications.

Conclusions

This study was the first to investigate the immune effects and clinical outcomes of oropharyngeal administration of OMC to ELBW infants. Although between-group comparisons for immune markers did not reach statistical significance, we found a statistically-significant reduction in time to reach full enteral feedings for OMC-treated infants. Despite a small sample, this study provides preliminary data for future research, which should measure the health outcomes for ELBW infants who receive this easy and inexpensive intervention.

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Screening and Triage of Intrauterine Growth Restriction (IUGR) in General Population and High Risk Pregnancies

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Abstract

Background: There is a strong association between stillbirth and fetal growth restriction. Early detection and management of IUGR can lead to reduce related morbidity and mortality. In this paper we have reviewed effectiveness of fetal movement monitoring and Doppler velocimetry for the detection and surveillance of high risk pregnancies and the effect of this on prevention of stillbirths. We have also reviewed effect of maternal body mass index (BMI) screening, symphysial-fundal height measurement and targeted ultrasound in detection and triage of IUGR in the community.

Methods: We systematically reviewed all published literature to identify studies related to our interventions. We searched PubMed, Cochrane Library, and all World Health Organization Regional Databases and included publications in any language. Quality of available evidence was assessed using GRADE criteria. Recommendations were made for the Lives Saved Tool (LiST) based on rules developed by the Child Health Epidemiology Group. Given the paucity of evidence related to the effect of detection and management of IUGR on stillbirths, we undertook Delphi based evaluation from experts in the field.

Results: There was insufficient evidence to recommend against or in favor of routine use of fetal movement monitoring for fetal well being. (1) Detection and triage of IUGR with the help of (1a) maternal BMI screening, (1b) symphysial-fundal height measurement and (1c) targeted ultrasound can be an effective method of reducing IUGR related perinatal morbidity and mortality. Pooled results from sixteen studies shows that Doppler velocimetry of umbilical and fetal arteries in 'high risk' pregnancies, coupled with the appropriate intervention, can reduce perinatal mortality by 29 % [RR 0.71, 95 % CI 0.52-0.98]. Pooled results for impact on stillbirth showed a reduction of 35% [RR 0.65, 95 % CI 0.41-1.04]; however, the results did not reach the conventional limits of statistical significance. This intervention could be potentially recommended for high income settings or middle income countries with improving rates and standards of facility based care. Based on the Delphi, a combination of screening with maternal BMI, Symphysis fundal height and targeted ultrasound followed by the appropriate management could potentially reduce antepartum and intrapartum stillbirth by 20% respectively. This estimate is presently being recommended for inclusion in the LiST.

Conclusion: There is insufficient evidence to recommend in favor or against fetal movement counting for routine use for testing fetal well being. Doppler velocimetry of umbilical and fetal arteries and appropriate intervention is associated with 29 % (95 % CI 2% to 48 %) reduction in perinatal mortality. Expert opinion suggests that detection and management of IUGR with the help of maternal BMI, symphysial-fundal height measurement and targeted ultrasound could be effective in reducing IUGR related stillbirths by 20%.

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Background

Intrauterine growth restriction (IUGR) represents pathological inhibition of fetal growth and failure of the fetus to attain its growth potential.[1] There is a strong association between stillbirth and fetal growth restriction.[2] The etiology and risk factors for stillbirth and IUGR largely overlap. Both the conditions are the result of complex[3,4] pathology resulting from a recognizable interaction among maternal conditions, placental dysfunction and hormonal regulation.[2,4] For example, maternal smoking, low educational level, advanced maternal age, nulliparity, and black race are associated with increased risk of fetal growth restriction and stillbirth.[2,4,5] The same is the case for maternal medical conditions like gestational hypertensive disorders, pre and gestational diabetes, systemic lupus erythematosus, chronic renal disease, and thyroid disorders.[2,3,6] Further evidence of strong association between IUGR and stillbirth comes from the fact that prior delivery of a growth restricted infant is among the strongest risk factors for stillbirth, comparable to the history of prior stillbirth.[3]

IUGR has been used as a marker to assess complications of pregnancy.[7] There is however, no standard definition of IUGR. It has been defined as a birth weight < 2 standard deviations below the median for gestational age, whereas others use a threshold of 3rd or 5th percentile of weight for age for the given population.[7,8] The term small for gestational age (SGA), usually defined as having a birth weight below the 10th percentile of an accepted reference standard, is often used as a proxy measure for IUGR.[8] These two terms are however not synonymous as some SGA infants may merely represent the lower tail of the "normal" fetal growth distribution, while others who have been affected in utero by an inadequate nutritional milieu or other growth-inhibiting influences may nevertheless have a birth weight that is

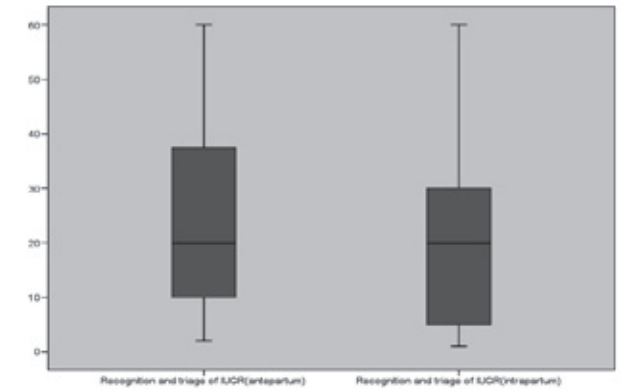

Figure 1. Box plots of the Delphi results on detection and management of IUGR compared to no identification or action for IUGR.

'appropriate' for gestational age (AGA).[8] Even though the terms SGA and IUGR are not synonymous, there is correlation between the two and the higher the SGA rate, the greater the likelihood that SGA is a result of IUGR.[9]

According to an estimate, approximately 30 million newborns per year are affected with intrauterine growth restriction in developing countries.[4] This rate is six times higher than that in developed countries. The highest burden of prevalence of SGA/IUGR babies lies in Asia (75%), mainly South East Asia, followed by Africa (20%) and Latin America (5%).[4]

In order to prevent complications associated with intrauterine growth restriction, it is important to first detect the condition and once detected, institute appropriate surveillance to asses fetal well being coupled with suitable intervention in case of fetal distress (for example early delivery).[1,10] The primary purpose of this paper is to assess screening and surveillance interventions that can help prevent stillbirths associated with IUGR. In this paper we review the methods used to detect IUGR followed by the methods used for surveillance of such high risk

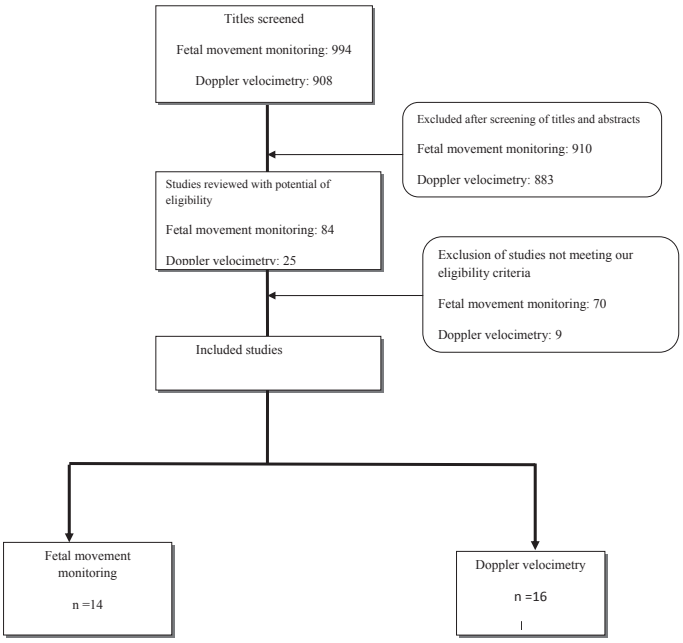

Figure 2. Synthesis of study identification in review of screening and triage of intrauterine growth restriction in general population and high risk pregnancies.

pregnancies. This paper is part of series of papers to estimate effectiveness of an intervention for input to Lives Saved Tool (LiST) model.[11] An intervention is currently included in the LiST if there is evidence that it reduces maternal mortality, infant/child mortality (<5 years) and/or stillbirths. The process of generating recommendations for an intervention involve qualitative evaluation of available evidence according to GRADE criteria[12] and quantitative evaluation according to Child Health Epidemiology Reference Group (CHERG) rules.[11] For more details of the review methods, the adapted GRADE approach or the LiST model see the methods section and the CHERG method paper.[11] For the purpose of simplicity, we will divide this review into parts: 1. The detection of IUGR; 2. Surveillance of high risk pregnancies.

Methods

Search strategy: We systematically reviewed all published literature to identify studies evaluating role of (1) fetal movement monitoring and (2) Doppler ultrasound in high risk pregnancies in reducing perinatal mortality and stillbirths. We searched PubMed, Cochrane Library, and all World Health Organization Regional Databases and included publications in any language. Last date of search was 3rd March 2010. We scanned the titles and abstracts of the studies identified to exclude those that were obviously irrelevant, retrieved the full text of the remaining studies, and identified relevant articles. We also reviewed the reference lists of identified articles, existing reviews and meta-analyses and looked for studies that were not picked up in the main search. Authors were contacted for any additional data, if required.

Inclusion/exclusion criteria: For Doppler velocimetry, only randomized trials and quasi-randomized studies addressing the use of Doppler ultrasound in high risk pregnancies were considered for inclusion in the review. Women with high risk pregnancies were defined as those women with singleton or twin pregnancy in which the maternal or fetal condition could be expected to lead to fetal compromise, eg identified intrauterine growth restriction, post-term pregnancies, previous pregnancy loss, women with hypertension, diabetes or other maternal pathology (eg thrombophilia).[13] Only those studies have been considered for inclusion in the review in which Doppler ultrasound of fetal and umbilical vessels was performed. Studies addressing utero-placental circulation were excluded however where umbilical artery or fetal Doppler was combined with utero-placental Doppler, the study has been included in this review.

For the fetal movement monitoring, we included randomized controlled trials, quasi-randomized and observational studies. The included studies either compared different methods of fetal movement monitoring vs no fetal movement monitoring, mixed or undefined monitoring. Studies addressing effectiveness of fetal movement counting in high risk pregnancies and/or unselected populations were considered.

Data abstraction and validity assessment: All relevant data from final studies were abstracted on a standardized Excel spreadsheet. Key variables extracted included study design, setting, allocation concealment, blinding, loss to follow-up, details of the intervention and comparison groups and the outcomes. The studies were assessed and graded according to the CHERG adaptation of the GRADE technique.[12] This method of assessment is based on strengths and limitations of individual

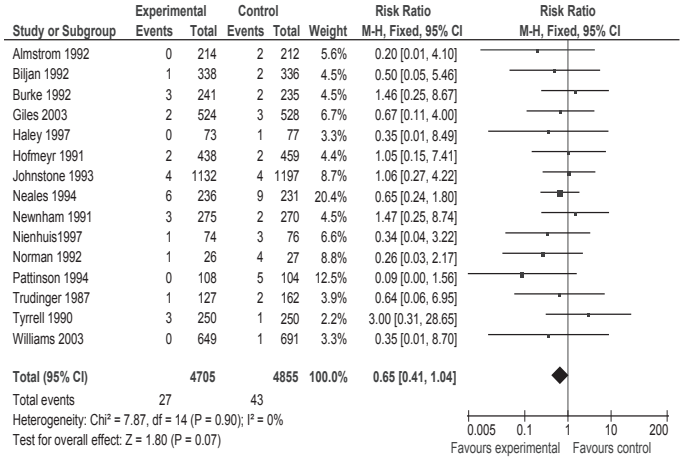

Figure 3. Forest plots for impact of Doppler ultrasound versus no ultrasound on stillbirths.

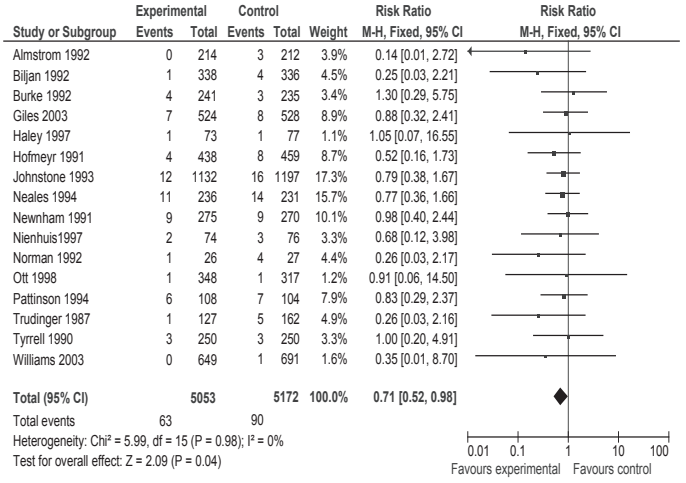

Figure 4. Forest plots for impact of Doppler ultrasound versus no ultrasound on perinatal mortality.

studies. The studies are graded as high, moderate, low, or very low quality based on study design, study quality, relevance to the objectives of the review and consistency across studies.[11] A randomized or cluster randomized trial initially received a high score which was downgraded to moderate if study design limitations or biases were present. In addition, studies having intent-to-treat analysis or a statistically significant strong association received 1-2 grade increases. Any study with a final grade of 'very low' was excluded from the analysis.

Quantitative data synthesis: We generated meta-analyses where data were available from more than one study and intervention and control groups did not have gross clinical heterogeneity. The primary outcome was stillbirths and/or perinatal death. The main comparison for Doppler velocimetry studies was Doppler ultrasound of fetal vessels versus no Doppler ultrasound of fetal vessels (including comparisons of Doppler ultrasound of fetal vessels concealed versus Doppler ultrasound of fetal vessels revealed). For cluster randomized trials, we used the stated cluster adjusted relative risk and 95% confidence interval, irrespective of the method used. We adjusted the results for cluster design if not stated in the study. The assessment of statistical heterogeneity among trials was done by visual inspection ie the overlap of the confidence intervals among the studies, and by the Chi square (P-value) of heterogeneity in the meta-analyses and I^2 value. A low P value (less than 0.10) or a large chi-squared statistic relative to its degree of freedom (I^2 >50 %) was considered as providing evidence of significant heterogeneity. In situations of substantial or high heterogeneity being present, causes were explored by sensitivity analysis. Fixed models were used for the primary analysis. All meta-analyses were conducted using software Review Manager Version.[5,14]

For recommendations to the LiST model, we summarized the evidence for each outcome including qualitative assessment of overall evidence according to GRADE criteria and quantitative measures according to standard guidelines of Child Health Epidemiological Review Group (CHERG) group.[11] The qualitative evaluation of the overall (pooled) evidence was based on the volume and consistency of the evidence across studies, the size of pooled relative risk and the strength of the statistical evidence for an association between the intervention and the health outcome as reflected in the p-value.[11]

Delphi process for establishing expert consensus: We did the Delphi process for generation of effect estimates for detection of IUGR by a proposed package that includes i) maternal BMI screening, ii) symphysis-fundal height measurement and iii) targeted ultrasound. This process involves consultation with experts in the field and asks their opinion about the effectiveness of an intervention.[11] The panel invited to participate were experts in newborn health and sepsis representing six WHO regions (South Asia, Africa, Western Europe, Eastern Europe, North America, Australia), and including multiple disciplines international health, obstetrics/gynecology/midwifery etc. Thirty-one experts agreed to participate in the Delphi process. The questionnaire was developed by MYY and ZAB, and refined after several rounds of pilot testing. The questionnaire was sent by email and included the background and aims of the Delphi and estimates of effect that were available from the literature for different scenarios. The median response and range were determined for each question. Consensus was defined a priori as an interquartile range in responses of < 30% for each question. For those estimates not reaching consensus, the plan was for results to be electronically distributed to the panel, virtual discussion allowed, and a second round of email questionnaires sent. However, consensus was achieved after one round of questionnaires and subsequent rounds were not considered necessary.

Results

The detection of IUGR. (This section will summarize the previous evidence and selection of interventions for detection of IUGR in the general population.) Some of the methods used to predict and monitor growth of the fetus include maternal BMI screening, symphysis-fundal height measurement and routine ultrasound.[15] Maternal BMI screening had been proposed as an effective method of predicting fetal growth by a group of experts.[16] Two Cochrane reviews on routine ultrasonographic evaluation in early (before 24 weeks of gestation) and late pregnancy (after 24 weeks) showed no effect in reducing overall peri-natal mortality.[17,18] Early pregnancy ultrasound (before 24 weeks) however was beneficial in detecting multiple pregnancies and reducing rates of induction of labor for post-term pregnancies.[18] Another Cochrane review on effectiveness of symphysis-fundal height measurement was inconclusive as only one trial was included and no recommendations in favor or against of the intervention were made.[19]

Table 1. Qualitative assessment of overall evidence for Doppler velocimetry and fetal movement monitoring according to CHERG rules.

Quality Assessment						Summary of findings		
				Generalizability		Number of events		Pooled Effect
No. of studies	Design	Limitations	Consistency	Generalizability to Population of Interest	Generalizability to intervention of Interest	Intervention	control	RR (95 % CI)
Effect of surveillance of high risk pregnancies with Doppler velocimetry: Outcome perinatal mortality: Grade quality of evidence 'Moderate'								
16	RCT	Methods of sequence generation and allocation concealment were not adequate in most of the studies	No heterogeneity (I^2=0%)	All the studies from developed countries except one which is from South Africa	Doppler velocimetry of umbilical and fetal arteries for surveillance of high risk pregnancy	63	90	0.71 (0.52-0.98)
Effect of surveillance of high risk pregnancies with Doppler velocimetry: Outcome stillbirth: Grade quality of evidence 'Low'								
15	RCT	Methods of sequence generation and allocation concealment were not adequate in most of the studies	No heterogeneity (I^2=0%)	All the studies from developed countries except one which is from South Africa	Doppler velocimetry of umbilical and fetal arteries for surveillance of high risk pregnancy	27	43	0.65 (0.41-1.04)
Effect of fetal movement monitoring on stillbirths: Grade quality of evidence "very low"								
14	RCT, quasi experimental and observational studies	Most of the evidence from observation studies. Of the four RCTs, only one compared fetal movement monitoring versus no fetal movement monitoring. This RCT showed no effect of fetal movement monitoring on stillbirths	Data not pooled due to gross clinical heterogeneity	Most of the studies from developed countries	No consensus on single counting method. Cardif method (Count to ten) was the most widely used method	Data not pooled		

For detection of IUGR, our approach was based on the results of a previous review conducted by us on different screening interventions during pregnancy.[15] On the basis of this review and other related evidence, a set of three interventions was proposed.[15,16] These interventions include (a) maternal BMI screening, (b) symphysis-fundal height measurement and (c) targeted ultrasound. The current evidence for these interventions is described based on our previous review and a summary of results is presented below.

Maternal anthropometry can be used to help predict adverse perinatal outcomes including low birth weight and preterm birth.[16,20] Appropriate detection and management of maternal malnutrition can significantly reduce the occurrence of IUGR and related perinatal adverse outcomes.[21] One of the nutritional interventions that have a proven effect in reducing incidence of SGA/IUGR is balanced protein energy supplementation.[5] A Cochrane review by Kramer et al on protein energy supplementation during pregnancy had shown that balanced protein energy supplementation can reduce occurrence of small for gestational age births by 32% [RR 0.68 (95 % CI 0.56, 0.84)].[22]

A Cochrane review by Nielson on effectiveness of symphysis-fundal height measurement was inconclusive as there was only trial that included 1,369 women.[19] None of the outcomes measured was statistically significant. Even though there was no conclusive evidence from the only randomized trial, some observational studies report that symphysis-fundal height measurement can be a cost effective and relatively accurate method for measurement of gestational age and subsequently fetal growth. A recent cohort study conducted in Pakistan compared fundal height measurement with recall of last menstrual period (LMP) to assess gestational age.[23] The effectiveness of both the interventions was compared with ultrasound. The results showed that symphysis-fundal height measurement was a better method of assessing gestational age compared to recall of LMP, however accuracy of both the methods was less than that of ultrasound. Authors suggested use of symphysis-fundal height measurement as a cost effective and relatively reliable method of gestational age assessment and fetal growth monitoring. Another study reported that weekly self-administered symphysis-fundal measurements can be used to monitor fetal growth.[24] Similar results were found in an observation study from Brazil[25] where 753 low risk women were followed with periodic symphysis-fundal height measurement and the results were plotted to obtain a curve. Results showed a sensitivity of about 86% for detection of SGA infants.

Even though routine ultrasound early (< 24 weeks of gestation) or late (> 24 weeks) in pregnancy have not been shown to decrease perinatal mortality,[17,18] repeated ultrasound estimation of growth can be used to detect abnormal fetal growth.[10] We propose that if this is combined with monitoring of fetal growth by symphysis-fundal height measurement and coupled with appropriate management (eg early delivery), it can substantially reduce perinatal mortality and stillbirth. We did a Delphi process to get an estimate for effectiveness of detection and management of IUGR for inclusion in the LiST.[11] In this process we contacted experts in the field and took their opinion on the effectiveness of IUGR screening using the above mentioned three methods (a-c) coupled with the appropriate management. The process revealed an estimated reduction of 20% each in antepartum and intrapartum stillbirths (Figure 1). This estimate had been recommended for inclusion in the LiST.

Surveillance of high risk pregnancies: (1) Fetal movement monitoring: During the literature search, a total of 994 titles were identified (Figure 2). After an initial screening of titles and abstracts, 84 were found to be appropriate and finally 14 studies were chosen for final data extraction. We evaluated studies on the basis of antepartum or intrapartum stillbirth and perinatal mortality as outcomes. There were four randomized controlled trials assessing fetal movement counting.[26-29] Three of these trials were conducted in developed countries[26,28,29] and one in a developing country.[30] Data were not pooled due to gross clinical heterogeneity in the assessment of fetal movement monitoring and the comparison group. Two of these trials compared different fetal movement counting methods, and measured the acceptability, the compliance and other outcomes.[29,30] No intrauterine death was reported in any of these

two trials. In another trial fetal movement counting (modified Cardiff method) was compared with hormonal analysis. Only one stillbirth was reported (in the fetal counting group). However the fetal movement counting group had significantly fewer visits to the hospital antenatally compared to the group undergoing hormone analysis (RR 0.26, 95% CI 0.20 to 0.35). The fourth and largest trial, was a cluster randomized study by Grant et al[26] involving 68,654 women comparing fetal counting (Cardiff method) versus no instruction to monitor fetal movements. There was no significant difference in the mean antepartum stillbirth rate per cluster in the intervention versus control group (2.90/1000 vs. 2.67/1000). The routine antenatal care guidelines of the UK National Institute for Health and Clinical Excellence (NICE)[31] that do not recommend fetal movement monitoring in uncomplicated pregnancies were largely dictated by the findings of this trial.[32]

In addition, we identified four other intervention studies[33-36] and six observational studies.[37-42] A quasi-randomized trial by Neldam showed a statistically significant difference in antepartum stillbirth rates among women told to monitor fetal movements compared to those not being asked to monitor movements (0/1125 vs 8/1125).[34] The three before-after studies all showed a significant decline in stillbirth rates after formal introduction of fetal movement monitoring into clinical practice.[33,35,36]

According to the observational study by De Muylder, high-risk women whose previously normal kick charts became abnormal had significantly higher antepartum stillbirth (194/1000 vs 7/1000) and perinatal mortality (222/1000 vs 27/1000) rates compared to women whose kick charts remained normal till delivery.[37] Other observational studies have mixed data regarding stillbirth outcome. Lema showed that poor fetal monitoring results had higher rates of stillbirths (5/27 vs 1/83),[40] while a recent study by Sinha[42] found no deaths in the two groups of women with decreased and normal fetal movements (0/90 vs. 0/90) similar to the result of the study by Romero Gutierrez on perinatal mortality.[41]

(2) Doppler velocimetry: Our literature search yielded 908 titles (Figure 2). Initially 25 studies were considered for inclusion in the review. Seven of these studies were excluded because the trial participants were described as unselected population or of low risk.[43-49] Two studies were excluded due to insufficient data.[50,51] Finally 16 studies were included in the review.[52-67]

All the studies were conducted in high income countries except one that was conducted in South Africa.[64] Pooled results for impact on stillbirth showed a reduction of 35% [RR 0.65, 95 % CI 0.41-1.04]; however the results did not reach the conventional limits of statistical significance (Figure 3). Pooled results from sixteen studies showed that Doppler velocimetry of umbilical and fetal arteries in high risk pregnancies leads to a reduction of 29 % [RR 0.71, 95 % CI 0.52-0.98] in perinatal mortality compared to no Doppler velocimetry (Figure 4). There was no heterogeneity (I^2 =0) in both the pooled estimates.

Recommendations for LiST model: Table 1 gives an overall qualitative assessment of studies addressing fetal movement monitoring and Doppler velocimetry. Data were not pooled for fetal movement monitoring due to gross clinical heterogeneity in the intervention and control groups of the included studies. We have not recommended fetal movement monitoring for inclusion in the LiST model due to insufficient data in favor or against the use of intervention (GRADE quality very low).

For Doppler velocimetry, there was a significant reduction of 29% in perinatal mortality and non-significant reduction of 35% in stillbirths in high risk pregnancies. The results across studies were consistent in both estimates and there was no significant heterogeneity in the pooled data (I^2 =0). The overall grade quality for reduction in perinatal mortality was that of 'moderate' level due to inadequate methods of sequence generation and allocation concealment in some of the included studies. Although the direction of effect (ie towards reduction) was similar for stillbirths, the overall grade quality of evidence for reduction in stillbirths was that of "moderate" level. Keeping in mind the magnitude and direction of effect of these estimates, we recommend reduction in perinatal mortality [29 % (95 % CI 2% to 48%)] as a proxy for reduction in stillbirths with conversion of its overall quality grade from moderate to low level. This was to follow the theme of CHERG guidelines ie to select the most conservative estimate from the available data. The effect size for perinatal mortality (29%) was more conservative than that of stillbirth (35%). These recommendations can be interpreted as "Surveillance of high risk pregnancies with Doppler velocimetry of umbilical and fetal arteries with appropriate timely obstetric intervention leads to a reduction of 29 % (95 % CI 2% to 48%) in stillbirths."

Discussion

Detection and management of IUGR: Maternal BMI screening is one of the methods that have been suggested to predict growth of fetus and related occurrence of low birth weight, and other perinatal adverse outcomes.[16,20,21,68-73] A Cochrane review on effectiveness of measurement of symphysis fundal height for detecting IUGR was inconclusive due to lack of RCTs.[19] Observational studies however suggest that it is a cost effective and fairly accurate tool to detect or at least suspect abnormal fetal growth.[15,23] In case of clinical suspicion and/or existing risk factors, repeat ultrasound can assess fetal growth and a judgment can be made about optimal or suboptimal growth.[15] However, routine ultrasound for every woman irrespective of indication or risk factor does not help to reduce perinatal mortality.[17,18]

Keeping in mind the existing literature reviewed elsewhere by us,[15] we propose a model to detect and manage IUGR with an expected reduction in stillbirths. This model consists of three screening interventions i.e. maternal BMI, symphysis-fundal height measurement and targeted ultrasound coupled with management of cases identified. As there are currently no studies evaluating this combination, we consulted experts in the field to give us their opinion on the expected benefit of these combined interventions in reducing IUGR and stillbirths. Delphi consensus (medians) determined the effect to be 20% reduction in ante-partum stillbirth with an inter-quartile range of 10% to 37.5% and 20% reduction in intra-partum stillbirth with an inter-quartile range of 5% and 30% (Figure 1).

Surveillance of high risk pregnancies: Several surveillance methods have been proposed to detect and manage high risk pregnancy during the antenatal or intrapartum period.[6] These methods involve assessment of fetal well-being by taking into account measures such as fetal movement, fetal heart rate pattern, and/or growth; and feto-placental and/or uteroplacental circulatory dynamics.[15]

There are no clearly identified criteria to distinguish between a high or low risk pregnancy; however, pregnancies in which the maternal and/or fetal condition pose a threat to life of the mother or fetus are considered as high risk.[13] Maternal conditions most commonly associated with adverse perinatal outcomes include conditions such as diabetes (chronic and gestational), hypertensive disorders (chronic hypertension and pre-eclampsia) and cardiac, renal, autoimmune and thrombophiliac disorders.[74-76] Fetal conditions associated with 'high risk' pregnancy include fetal growth restriction, and placental insufficiency.[77-79]

Doppler velocimetry is considered as one of the most objective methods to assess fetal wellbeing in cases of intrauterine growth restriction (IUGR).[13,15] It provides information on fetal and placental cardiovascular function on the basis of the blood flow dynamics measured in uterine, umbilical and fetal arteries.[80] A Cochrane review by Alfirevic et al. comprising of 16 studies and involving 10, 225 babies had shown that fetal and umbilical artery Doppler ultrasound in high risk pregnancies can decrease the perinatal mortality by 29 % (RR 0.71, 95 % CI 0.52-0.98), when obstetric services were in place to ensure safe and timely delivery of the baby when needed. Uterine artery Doppler waveform analysis on the other hand, may identify compromised fetuses at risk of stillbirth, especially in cases of placental underperfusion associated with preeclampsia and/ or growth restriction; however published literature does not show its effectiveness of subsequent intervention to prevent stillbirths.[15] We had therefore focused on effectiveness of Doppler velocimetry of fetal and umbilical arteries for the fetal wellbeing in case of surveillance of IUGR.

According to CHERG rules, we recommended a reduction of 29 % (95 % CI 2% to 48%) in stillbirths for high risk pregnancies if these are identified, followed by Doppler velocimetry of fetal and umbilical arteries and managed with the appropriate intervention (eg early delivery). This estimate was the most conservative of the estimates for reduction in perinatal mortality and stillbirths. The results for reduction in stillbirths did not reach statistical significance. The overall grade quality for the pooled estimate for still births was "low." This was because the quality of methods of sequence generation and allocation concealment was inadequate in some of the included studies. We therefore propose to take reduction in perinatal mortality as a proxy for reduction in stillbirths. Our results are in accordance with the previous meta-analysis done on this topic.[13] It is important to take into account that Doppler ultrasound is used as a diagnostic assessment method and the clinical outcomes depend on availability of and implementation of timely interventions such as early delivery eg via cesarean sections.

Fetal movement counting is a simple, inexpensive and the oldest way to monitor the condition of the baby during pregnancy and is considered to be an indirect measure of central nervous system integrity.[42,81] Fetal movements in the womb can be felt by the mothers from around 16 to 20 weeks of gestation.[82] A reduction in fetal movements is associated with decreased oxygenation, which may lead to fetal growth compromise or stillbirth.[83] A review based on twenty-four Western studies demonstrated that reduced fetal movements were associated with adverse pregnancy outcomes, both in high and low risk pregnancies.[84] Therefore, decreased fetal movements may be a sign of fetal compromise or impending fetal demise. Other causes of reduced fetal movements include decreased amniotic fluid, drugs, sedatives and sleep state in the fetus.[85] A Cochrane review by Mangesi and Hofmyer, comprising four randomized controlled trials and including 71,370 women, found no convincing evidence to recommend in favor or against routine fetal movement monitoring in unselected or high risk pregnancies.[86]

In developing countries, where advanced facilities are not available, fetal movement monitoring may be feasible, but its use is currently not supported by scientific evidence. We have graded the current evidence as "very low," which means that there is not sufficient evidence to include this intervention in the LiST model. We however consider it important to study this simple and oldest intervention in more detail to assess if it is useful to detect and follow high risk pregnancies especially in developing countries.

Conclusions

In conclusion, detection and management of IUGR using maternal BMI screening, symphysis-fundal height measurement and targeted ultrasound could be effective method of reducing IUGR related stillbirths. There are currently no studies available to assess the effect of these methods. Based on the opinion of experts in the field, this combination coupled with effective management could reduce IUGR related antepartum and intrapartum stillbirth by 20% each.

Doppler velocimetry of umbilical and fetal arteries for surveillance of identified high risk pregnancies leads to a reduction of 29% (95 % CI 2% to 48 %) in perinatal mortality. The direction of effect on the incidence of stillbirths was also similar but not statistically significant [RR 0.65, 95 % CI 0.41-1.04]. We recommend an estimate reduction of 29 % (95 % CI 2% to 48%) in stillbirths for inclusion in the Lives Saved Tool on the basis of rules developed by Child Health Epidemiology Reference Group. There is insufficient evidence to recommend in favor or against of fetal movement counting. More research is needed to study this method especially in developing countries.

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Individual Exposures to Drinking Water Trihalomethanes, Low Birth Weight and Small for Gestational Age Risk: a prospective cohort study

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Abstract

Background: Evidence for an association between exposure during pregnancy to trihalomethanes (THMs) in drinking water and impaired fetal growth is still inconsistent and inconclusive, in particular, for various exposure routes. We examined the relationship of individual exposures to THMs in drinking water on low birth weight (LBW), small for gestational age (SGA), and birth weight (BW) in singleton births.

Methods: We conducted a cohort study of 4,161 pregnant women in Kaunas (Lithuania), using individual information on drinking water, ingestion, showering and bathing, and uptake factors of THMs in blood, to estimate an internal dose of THM. We used regression analysis to evaluate the relationship between internal THM dose and birth outcomes, adjusting for family status, education, smoking, alcohol consumption, body mass index, blood pressure, ethnic group, previous preterm, infant gender, and birth year.

Results: The estimated internal dose of THMs ranged from 0.0025 to 2.40 μg/d. We found dose-response relationships for the entire pregnancy and trimester-specific THM and chloroform internal dose and risk for LBW and a reduction in BW. The adjusted odds ratio for third tertile vs. first tertile chloroform internal dose of entire pregnancy was 2.17, 95% CI 1.19-3.98 for LBW; the OR per every 0.1 μg/d increase in chloroform internal dose was 1.10, 95% CI 1.01-1.19. Chloroform internal dose was associated with a slightly increased risk of SGA (OR 1.19, 95% CI 0.87-1.63 and OR 1.22, 95% CI 0.89-1.68, respectively, for second and third tertile of third trimester); the risk increased by 4% per every 0.1 μg/d increase in chloroform internal dose (OR 1.04, 95% CI 1.00-1.09).

Conclusions: THM internal dose in pregnancy varies substantially across individuals, and depends on both water THM levels and water use habits. Increased internal dose may affect fetal growth.

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Background

The association between exposure to disinfection by-products (DBPs), as measured by trihalomethanes (THMs), in drinking water and adverse reproductive/developmental effects has been extensively studied in recent epidemiological studies. Some epidemiological studies suggested that pregnant women exposed to water containing elevated THMs concentrations may be at greater risk for adverse pregnancy outcomes, including fetal growth, but findings of the studies to date have been inconsistent.[1-3] The relationship between DBP exposure and reproductive health outcomes remains unclear, mainly owing to limitations in the crude exposure assessment in most studies.[4-8] Epidemiological studies found mostly small increases in risk for low birth weight (LBW) at term or small for gestational age (SGA)[9-11] or yielded mixed results.[12,13] The epidemiological studies of reproductive outcomes have relied on different methods of assessing exposure, which presents difficulties in making comparisons between investigations and in generalizing results.[6] Recent studies have attempted to improve exposure assessment by using individual exposure measures combining routinely collected water system THM measurements with a measure of ingestion, such as number of glasses or water drank per day. However, only a few studies accounted for spatial and temporal fluctuations in THM levels across the distribution system over the time periods relevant to study pregnancy.[14,15] Furthermore, seeking to improve the exposure assessment, studies have begun to incorporate behavioral determinants of different routes of exposure to DBPs such as dermal absorption and inhalation during bathing and showering, and ingestion of drinking water but the contribution of these was unclear.[16-18] The recent epidemiological studies concluded that, while there appears to be suggestive evidence associating elevated total THM (TTHM) levels with some adverse reproductive outcomes, evidence for relationships with LBW and SGA are inconclusive and inconsistent, and further research is warranted, including on the importance of different exposure routes.

In the present study, we evaluated the effect of maternal THM dose on several indices of fetal development. Using prospective Kaunas cohort study with individual data, we were able to adjust for many important risk factors for BW and SGA. Through improvements in individual THM exposure and dose assessment and controlling for many possible confounding variables, our study aims to offer estimated total individual internal dose

assessment based on monitoring of tap water THM levels and detailed water use behaviors to examine dose-response relationships for THMs and fetal growth.

Methods

Participant recruitment and outcome assessment: We conducted a prospective cohort study of pregnant women in Kaunas city, Lithuania, as a part of the European Commission FP6 HiWATE Project Health impacts of long-term exposure to DBP in drinking water in Europe (HiWATE).[19]

On their first visit to a general practitioner, all pregnant women living in Kaunas city between 2007 and 2009 were invited to join the cohort. The women were enrolled in the study only if they consented to participate in the cohort. The study ethics complied with the Declaration of Helsinki.[20] The research protocol was approved by the Lithuanian Bioethics Committee and an oral informed consent was obtained from all subjects. In total 5,405 women were approached; 79% of them agreed to participate in the study. The first interview was completed during the first pregnancy trimester. The median gestational age at interview was 8 weeks. The interview queried women regarding demographics, residence and job characteristics, chronic diseases, reproductive history, including date of last menstrual period, previous preterm delivery. We also asked the women to report their age (less than 20 years, 20-29 years, 30 years, and more), educational level (primary, secondary, university), marital status (married not married), smoking (non-smoker, smoker at least one cigarette per day), alcohol consumption (0 drinks per week, at least one drink per week), blood pressure (<140/80 mm/Hg, ≥140 or ≥ 90 mm/Hg), body mass index (<25 kg/m2, 25-30 kg/m2, >30 kg/m2), and other potential risk factors for LBW. Adjustment for these variables was made for studies of various birth outcomes subgroups. The women also were examined by ultrasound to determine the gestational age of the fetus.

A special water consumption and water use habits questionnaire was used to interview the 4,260 women who agreed to participate in the study; 76.4% of them were interviewed during the third pregnancy trimester before delivery at the hospital and 23.6% by telephone within the first month after delivery. Consumption was ascertained for three types of water: cold tape water or dinks made from cold tap water; boiled tap water (tea, coffee, and other); and bottled water, used at home, at work, other. In addition, number of showers, baths, swimming pools weekly, and their average length was asked of all subjects. The interviews were conducted by trained nurses who did not know the THM exposure status and birth outcome.

Pregnancy outcomes were abstracted from the medical records. LBW were defined as infant's BW less than 2,500 g. Infants were considered SGA if they were in the lowest 10th centile of BW for each gestational week stratified by infant gender and maternal ethnic group. Gender-specific and ethnic group-specific deciles were determined from the 2004 data set of all births in Lithuania.[21] Women with multiple pregnancies (150), having inconsistent or invalid data for dating the pregnancy (5) or estimating THM exposure (mostly students moved out of the city during pregnancy, 839) or with newborn BW above 4,500 g (75) were excluded. We restricted our analyses to infants born with a BW below 4,500 g, leaving data for 3,341 women in the final analysis.

We also conducted analyses comparing questionnaire data and birth certificate data on various characteristics among participants and non-participants. The mean BW, gestational duration, prevalence of LBW and SGA were similar among the two groups. These two groups did not differed by ethnic group, consumption tap water, showering, and bathing, however, nonparticipating mothers were younger (<20 years, 3.9% vs 1.8%), less educated (did not graduate from university, 46.6% vs 54.3%), more often smokers (smokers, 9.6% vs 6.9%), and did have fewer prior births (no child, 64.1% vs 45.1%), than that of participants. In addition, to assess the level of accuracy in personal reporting that can bias the THM risk estimates, questionnaire information was collected repeatedly on 10% subjects. There were no

Table 1. THM levels (µg/L) by sampling site, water supply zone, year and season of sampling.

Tap water sampling	TTHMs[c]	$CHCl_3$	$CHBr_2Cl$	$CHBrCl_2$
	Mean (SD[d])	Mean (SD)	Mean (SD)	Mean (SD)
Sampling sites				
All sites	9.8 (12.4)	7.8 (10.2)	0.3 (0.5)	1.7 (2.2)
Low THM level[a]	1.3 (1.2)	0.9 (1.0)	0.1 (0.2)	0.3 (0.5)
High THM level[b]	21.9 (10.9)	17.7 (9.0)	0.5 (0.6)	3.6 (2.1)
Year of sampling				
2007 all sites	10.3 (13.5)	8.7 (12.0)	0 (0[e])	1.5 (1.6)
Low THM level[a]	0.9 (1.3)	0.39 (1.0)	0 (0)	0.6 (0.5)
High THM level[b]	24.2 (11.0)	21.3 (9.6)	0 (0)	2.9 (1.7)
2008 all sites	6.2 (10.2)	4.4 (7.5)	0.3 (0.5)	1.5 (2.4)
Low THM level[a]	1.5 (1.1)	0.9 (0.6)	0.2 (0.3)	0.5 (0.5)
High THM level[b]	12.7 (13.5)	9.3 (9.8)	0.6 (0.6)	2.8 (3.3)
2009 all sites	11.8 (12.8)	9.5 (10.0)	0.4 (0.5)	1.9 (2.3)
Low THM level[a]	1.3 (1.1)	1.3 (1.0)	0.1 (0.2)	0.1 (0.2)
High THM level[b]	26.5 (2.9)	21.0 (2.3)	0.9 (0.4)	4.6 (0.5)
Season of sampling				
Spring all sites	8.5 (12.1)	6.8 (9.7)	0.3 (0.4)	1.4 (2.1)
Low THM level[a]	1.4 (1.3)	1.2 (1.1)	0.1 (0.3)	0.2 (0.4)
High THM level[b]	18.3 (13.6)	14.7 (10.9)	0.5 (0.5)	3.1 (2.3)
Summer all sites	9.9 (12.7)	8.3 (11.3)	0 (0)	1.6 (1.7)
Low THM level[a]	1.0 (1.4)	0.4 (1.0)	0 (0)	0.7 (0.5)
High THM level[b]	24.1 (8.3)	21.0 (7.0)	0 (0)	3.1 (2.0)
Autumn all sites	11.1 (13.4)	8.8 (11.1)	0.2 (0.5)	2.0 (2.4)
Low THM level[a]	1.2 (1.1)	0.8 (0.9)	0 (0)	0.4 (0.5)
High THM level[b]	24.8 (9.7)	20.1 (8.6)	0.6 (0.6)	4.2 (2.4)
Winter all sites	10.9 (12.1)	8.4 (9.3)	0.5 (0.6)	1.9 (9.3)
Low THM level[a]	1.1 (1.0)	0.9 (0.6)	0.1 (0.3)	0.1 (0.3)
High THM level[b]	24.5 (1.4)	18.9 (1.2)	1.1 (0.1)	4.5 (0.2)

[a]Viciunai, Eiguliai, Kleboniskis.

[b]Petrasiunai.

[c]TTHMs = total trihalomethanes: the sum of CHCl3 (chloroform), $CHBr_2Cl$ (dibromochloromethane), and CHBrCl2 (bromodichloromethane).

[d]SD = standard deviation. [e]0 = below the limit of detection.

Table 2. Distribution of Kaunas cohort study subjects for various characteristic by exposure.

Risk factor/outcome	Low THM N (%)	Medium THM N (%)	High THM N (%)
Maternal age			
< 20 years	19 (1.8)	17 (1.5)	23 (2.1)
20–29 years	652 (60.1)	688 (59.7)	658 (59.6)
≥ 30 years	414 (39.2)	447 (38.8)	423 (38.3)
Marital status			
Married	876 (80.7)	958 (83.2)	910 (82.4)
Not married	209 (19.3)	194 (16.8)	194 (17.6)
Maternal education			
Primary school	59 (5.4)	50 (4.3)	57 (5.2)
Secondary school	454 (41.8)	465 (40.4)	442 (40.0)
University degree	572 (52.7)	637 (55.3)	605 (54.8)
Maternal smoking			
Nonsmoker	1003 (92.4)	1076 (93.4)	1031 (93.4)
Smoker	82 (7.6)	76 (6.6)	73 (6.6)
Paternal smoking[a]			
Nonsmoker	574 (53.4)	629 (55.4)	545 (49.8)
Smoker	501 (46.6)	507 (44.6)	550 (50.2)
Alcohol consumption[a]			
No	1000 (92.2)	1094 (95.0)	1048 (94.9)
Yes	85 (7.8)	58 (5.0)	56 (5.1)
Blood pressure			
<140/80 mm/Hg	969 (89.3)	1020 (88.5)	977 (88.5)
≥140 or ≥ 90 mm/Hg	116 (10.7)	132 (11.5)	127 (11.5)
Ethnic group			
Lithuanian	1054 (97.1)	1117 (97.0)	1082 (98.1)
Other	31 (2.9)	35 (3.0)	21 (1.9)
Parity			
No child	492 (45.3)	499 (43.3)	516 (46.7)
≥ 1 child	593 (54.7)	653 (56.7)	588 (53.3)
Infant gender			
Male	559 (51.5)	611 (53.0)	544 (49.3)
Female	526 (48.5)	541 (47.0)	560 (50.7)
Current residence			
1–4 years	437 (40.3)	492 (42.7)	472 (42.8)
5–9 years	257 (23.7)	288 (25.0)	296 (26.8)
≥ 10 years	391 (36.0)	372(32.3)	336 (30.4)
Work exposure			
No	996 (91.8)	1053 (91.4)	999 (90.5)
Yes	89 (8.2)	99 (8.6)	105 (9.5)
Chronic disease			
No	825 (76.0)	858 (74.5)	844 (76.4)
Yes	260 (24.0)	294 (25.5)	260 (23.6)
Previous preterm delivery			
No	1069 (98.5)	1123 (97.5)	1087 (98.5)
Yes	16 (1.5)	29 (2.5)	17 (1.5)
Socio economic status			
Low income	335 (30.9)	337 (29.3)	338 (30.6)
Medium income	582 (53.6)	642 (55.7)	600 (54.3)
High income	168 (15.5)	173 (15.0)	166 (15.0)
Body mass index (kg/m^2)			
<25 Normal	618 (57.0)	677 (58.8)	679 (61.5)
25–30 Overweight	329 (30.3)	334 (29.0)	284 (25.7)
30 Obesity	138 (12.7)	141 (12.2)	141 (12.8)
Water filter			
Yes	341 (31.4)	336 (29.2)	338 (30.6)
No	744 (68.6)	816 (70.8)	766 (69.4)
LBW[a]			
Yes	40 (3.7)	51 (4.4)	65 (5.9)
No	1045 (96.2)	1101 (95.7)	1039 (94.1)
SGA			
Yes	76 (7.0)	92 (8.0)	102 (9.2)
No	1009 (93.0)	1060 (92.0)	1002 (90.8)
Mean birth weight (SDs)	3449 (517)	3462 (524)	3430 (559)

› < 0.05.

significant differences in reporting water use habits and other covariates.

Exposure Assessment: The Kaunas city municipal drinking water is supplied by four water treatment plants system. The each treatment plant water supplied system is constituted of only one subsystem (ie, one chlorination, and branchy water supplied to the users). Groundwater sources are used for the whole water supply system.

Table 3. Summary of Kaunas cohort study subjects daily water intake for water users by THM exposure.

Mean daily ingestion (L/day)	Low THM		Medium THM		High THM	
	Mean	SD	Mean	SD	Mean	SD
Consumption tap water (52.1%)[a]						
At home	0.62	0.43	0.65	0.48	0.69	0.49
At work	0.10	0.23	0.10	0.24	0.11	0.25
Other	0.02	0.09	0.02	0.09	0.02	0.11
In total	0.74	0.52	0.77	0.11	0.82	0.60
Other tap–water beverages (12.2%)[a]						
At home	0.36	0.35	0.39	0.37	0.37	0.38
At work	0.09	0.18	0.07	0.17	0.07	0.15
Other	0.05	0.12	0.07	0.21	0.06	0.16
In total	0.50	0.37	0.53	0.42	0.50	0.41
Consumption bottled water (78.1%)[a]						
At home	0.61	0.51	0.70	0.54	0.61	0.56
At work	0.35	0.38	0.38	0.40	0.39	0.39
Other	0.06	0.16	0.06	0.20	0.06	0.17
In total	1.01	0.69	1.14	0.75	1.07	0.76
Boiled water (tea, coffee) (95%)[a]						
At home	0.51	0.30	0.53	0.30	0.51	0.32
At work	0.28	0.29	0.29	0.29	0.30	0.28
Other	0.05	0.13	0.05	0.14	0.05	0.13
In total	0.84	0.47	0.87	0.46	0.87	0.46

[a]% of individuals reporting daily water ingestion.

However, the four water treatment plants, which disinfected ground water with sodium hypochlorite (chlorine dose 0.26-0.91 mg/L, residual chlorine 0-0.22 mg/L), produced different concentrations of THMs in finished water. One treatment plant (Petrasiunai) supplied finished water with higher levels of THMs ("high level THM site," 54.9% subjects), and the three other plants supplied finished water with lower levels of all THMs ("low level THM site"). Water samples were collected four times per year over a 3-year study period (2007-2009) in the morning in three locations: close to the treatment plant, at 5 km, and at 10 km or more from every treatment plant. A total of 85 water samples were collected from 12 monitoring sites in four water supply zones for THM analysis. Samples were analyzed at the University of the Aegean, Greece, by using gas chromatography with electron capture detection.[22] Measurements included specific values for the four regulated THMs (chloroform, bromoform, bromodichloromethane, and dibromochloromethane) and nine haloacetic acids (HAAs). Selected samples were analyzed for five haloacetonitriles, two haloketones, chloropicrin, and chloral hydrate. In addition, selected samples were analyzed at the National Institute for Health and Welfare (THL), Finland, for the halogenated furanone MX. Only THMs data were evaluated in this study since the other halogenated DBPs were present only at low or sub µg/L levels, if detected at all.

We calculated the mean quarterly THM constituent concentrations for water zones and subsequently, depending on the TTHM levels within each zone, assigned "low level" and "high level" sites. We used tap water THM concentration, derived as the average of quarterly sample values over the time that the pregnancy occurred from all sampling sites located in the each

Table 4. LBW adjusted odds ratio and BW change for gestational exposure to internal dose THMs.

THM exposure	LBW	Non	Entire pregnancy	First trimester	Second trimester	Third trimester
Tertile limits (µg/d)	cases	LBW	OR[a] (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
TTHM[b]						
0.0025–0.0386	40	1046	Reference	Reference	Reference	Reference
0.0386–0.3545	51	1099	1.77 (0.95–3.30)	1.94 (1.04–3.62)	1.71 (0.92–3.18)	2.31 (1.22–4.35)
0.3545–2.4040	65	1040	2.13 (1.17–3.87)	2.29 (1.24–4.22)	2.06 (1.14–3.73)	2.12 (1.14–3.92)
Continuous (0.1µg/d)			1.08 (1.01–1.16)	1.08 (1.01–1.16)	1.07 (1.00–1.15)	1.07 (1.00–1.15)
Change in BW[c] g			-49.3[d]	-45.7[d]	-45.3	-47.2[d]
			(-146.3– -1.5)	(-91.4–0.0)	(-92.8–2.2)	(-92.7– -1.6)
Chloroform						
0.0013–0.0249	40	1050	Reference	Reference	Reference	Reference
0.0249–0.2868	52	1093	2.06 (1.10–3.85)	2.30 (1.21–4.36)	1.79 (0.95–3.36)	2.12 (1.11–4.02)
0.2868–2.1328	64	1042	2.17 (1.19–3.98)	2.41 (1.30–4.49)	2.13 (1.18–3.85)	2.13 (1.15–3.92)
Continuous (0.1µg/d)			1.10 (1.01–1.19)	1.10 (1.02–1.18)	1.10 (1.01–1.18)	1.09 (1.01–1.18)
Change in BW[c] g			-59.3[d]	-52.8[d]	-53.4	-57.8[d]
			(-114.8– -3.7)	(-104.4– -1.2)	(-108.2–1.3)	(-111.6– -4.0)
$CHBrCl_2$						
0.0001–0.0124	45	1046	Reference	Reference	Reference	Reference
0.0124–0.0501	53	1093	1.83 (1.01–3.34)	1.93 (1.05–3.55)	1.95 (1.07–3.58)	1.64 (0.89–3.02)
0.0501–0.3359	58	1046	1.64 (0.90–2.98)	2.06 (1.11–3.80)	1.82 (0.99–3.35)	1.80 (1.00–3.26)
Continuous (0.01µg/d)			1.05 (1.00–1.11)	1.05 (1.00–1.11)	1.05 (0.99–1.11)	1.04 (1.00–1.10)
Change in BW[c] g			-28.2 (-63.2–6.9)	-29.7 (-67.5–8.0)	-27.7 (-63.2–7.7)	-25.7 (-57.2–5.8)
$CHBr_2Cl$						
0.0000–0.0000	57	1058	Reference	Reference	Reference	Reference
0.0000–0.0039	49	1075	3.02 (1.23–7.40)	0.62 (0.28–1.37)	0.68 (0.31–1.46)	2.44 (1.05–5.70)
0.0039–0.0644	50	1052	2.52 (1.00–6.36)	0.74 (0.37–1.49)	0.78 (0.36–1.67)	2.42 (1.03–5.66)
Continuous (0.01µg/d)			1.18 (0.85–1.65)	1.06 (0.73–1.54)	1.16 (0.84–1.61)	1.23 (0.93–1.61)
Change in BW[c] g			-24.3	15.5	-18.8	-45.9
			(-215.7–167.2)	(-197.0–228.1)	(-203.3–165.7)	(-207.6–114.8)

[a]adjusted for squared gestational age, marital status, maternal education, chronic diseases, body mass index, blood pressure, smoking, alcohol consumption, previous preterm delivery, infant gender, and birth year.

[b]TTHM, total trihalomethane; CHBrCl2, bromodichloromethane; CHBr2Cl, dibromochloromethane.

[c]Change in birth weight in grams, of infants below 3,500 g, for every 1 µg/d increase in THMs internal dose.

[d]$p<0.05$.

[e]Change in birth weight in grams, of infants below 3,500 g, for every 0.1 µg/d increase in THMs internal dose.

distribution system, and geocoded maternal address at birth to assign the individual women residential exposure index. Estimates of exposure index to total and specific THMs from drinking water were tabulated first as an average level at the tap over the pregnancy period; this measure was then categorized at the tertiles of the distribution for birth outcomes. In addition, trimester-specific analyses were conducted.

We combined every subject's residential exposure index and water-use questionnaire data to assess individual exposure through ingestion of THMs. Women were asked to indicate the cup or glass size and number of cups or glasses of tap water consumed per day, including hot and cold beverages made from tap water. With this information, we calculated daily amounts of hot and cold tap water ingested. Integration of the information on residential THM levels (µg/L), ingested amounts (L/day), and modifications by heating using an estimated uptake factor of 0.00490 to derive an integrated index of blood concentration, expressed in micrograms per day (µg/d).[18,23]

The actual algorithms of internal dose from ingestion were chloroform level (µg/l) × water consumption (l/day) × 0.00490196 µg/µg/l; brominated THM level (µg/l) × water consumption (l/day) × 0.00111848 µg/µg/l. We assumed a null THM level for any bottled water consumption since in local bottled water production chlorination and ozonation is not used. Finally, we addressed dermal absorption and inhalation by considering showering and bathing alone and combined with ingestion. We multiplied residential THM levels (µg/L) by frequency and average duration of bathing or showering per day (min/day) and calculated each mother's trimester-specific and entire pregnancy average daily uptake of THM internal dose (µg/d). We derived indices of daily uptake by integrating THM concentrations, duration of bathing and showering reported in a questionnaire administered to study participants, and estimated uptake factors of 0.001536 and 0.001321 of THMs in blood per minute per microgram from showering and bathing, respectively.[24,25] The uptake factors of THMs individual constituents were assessed on the relative changes in blood levels after 10 minutes exposure (after versus before ingestion 1 L of tap water, 10 minutes showering, and 10 minutes bathing).

The actual algorithms of internal dose from showering and bathing were min/day showering × µg/l chloroform in water × 0.001536261 µg/min/µg/l, min/day showering × µg/l brominated THM in water × 0.001352065 µg/min/µg/l, min/day bathing × µg/l chloroform in water × 0.001320755 µg/min/µg/l, min/day bathing × µg/l brominated THM in water × 0.00129571 µg/min/µg/l. We then used average daily total uptakes in our analysis as continuous and categorized variables. We calculated tertiles of THM internal dose. This gave first (0.0025-0.0386 µg/d), second (0.0386-0.3496 µg/d), and third (0.3496-2.4040 µg/d) tertiles for average TTHM uptake. To reduce exposure misclassification errors in the subsequent analysis, we used a subset of women who through the entire pregnancy did not change their address.

Analysis: The data analysis compared the LBW, SGA, and BW of low, medium and high exposed women. We used logistic regression to estimate adjusted odds ratios (ORs) and 95-percent confidence intervals (CIs) for LBW, SGA, and the various exposure indices. We categorized TTHM internal dose in tertiles and evaluated the possible relationship between increases in adverse birth outcomes risk for an increase in estimated TTHM internal dose. We ran multivariate logistic regression models for the TTHMs, chloroform, dibromochloromethane, and bromodichloromethane for the total pregnancy and trimesterspecific periods. We also used multiple linear regressions for TTHM internal dose analysis as continuous variable to evaluate the relationship, if any between BW reductions and every 1 µg/d increase in TTHM internal dose.

Risk factors for LBW have been reported extensively elsewhere[26,27] and are not the subject of this article, except to allow for appropriate control of covariates in this analysis. In the logistic regression models for adverse birth outcomes, using personal data of the cohort sample, we assessed a variety of potential confounders identified by univariate analysis. Further, we examined the association of THM exposure and birth outcomes with a multivariable analysis controlling for effect of major covariates that changed the adjusted ORs for THM by 10% or more. The adjusted birth outcomes analyses included family status, maternal education, chronic diseases, body mass index, blood pressure, smoking, alcohol consumption, ethnicity,

previous preterm delivery, infant gender, and birth year. Two-tailed statistical significance was evaluated by using a p value of 0.05. All statistical analyses were carried out using the SPSS software for Windows version 12.0.1.

Results

The mean TTHM level in the low level site from three water treatment plants was 1.3 µg/L, and in the high level site (Petrasiunai) 21.9 µg/L (Table 1). The yearly and seasonal fluctuations in the levels of TTHMs were primarily the result of the lack of THM formation for Petrasiunai in March, 2008. There was little spatial and temporal variability within the high and low areas. Chloroform was the dominant THM species in this water, contributing approximately 80% of the mass of the TTHMs. The brominated THM species were significantly lower: dibromochloromethane ranged from 0.06 to 0.5 µg/L and bromodichloromethane ranged from 0.3 to 3.6 µg/L. Bromoform was below the limit of detection. The correlation between individual THM concentrations was high (r=0.91-0.99, p=0.000) and the correlations between each pregnancy trimester ranged from 0.62 to 0.96, (p=0.000). Although there was a difference in the concentrations of TTHMs between Petrasiunai and that of the other sites, there was no difference in the levels of the other halogenated DBPs, which were present at low or sub µg/L levels, if detected at all. The mean sum (and standard deviation) of the dihalogenated and trihalogenated HAAs for Petrasiunai was 0.5 (0.7) and 0.3 (0.7) µg/L, respectively; whereas they were 0.3 (0.8) and 0.1 (0.2) µg/L, respectively, for the other sites. The mean values of other individual halogenated DBPs (ie, haloacetonitriles, haloketones, chloropicrin, chloral hydrate, monohalogenated HAAs) were all less than 1.0 µg/L each for Petrasiunai and the other sites. MX was only measured once for Petrasiunai and it was not detected, whereas it was measured three times in the other sites and was 0.6-1.5 ng/L. Thus, only THM data were evaluated in this analysis, since there was a substantial difference in THM occurrence between Petrasiunai and the other sites.

The women recruited were predominantly Lithuanian in ethnic origin (97.4%) and did not smoke (93.1%). The mean age at enrolment was 28.4 years, and the women tended to be highly educated (54.3% with a university degree). The mean BW of the 3,341 singleton infants included in our analysis was 3,445 g. Among these, 156 (4.7%) were classified as LBW and 270 (8.1%) as SGA. The vast majority of SGA infants (93.0%) were term births (37 weeks or above). In general, mothers who smoked were single, less educated, had previous preterm delivery, or suffered from a disease during pregnancy delivered a higher proportion of LBW or SGA infants. We did not find a difference in fetal growth between water filter users and non-users. The analysis by TTHM internal dose tertiles showed, that most characteristics of the exposure groups were similar (Table 2). There were no differences in social and demographic characteristics, health behaviour, pregnancy history, and maternal diseases. However, paternal smoking and alcohol consumption differed between exposure groups. The proportion of LBW cases increased with increasing THM exposure (3.7, 4.4 and 5.9%, respectively, low, medium and high exposure). We also found an increase in the proportion of SGA cases (7.0, 8.0 and 9.2%, respectively).

Municipal water was the drinking water source of all study subjects. Fifty-two percent of the women consumed tap water and 12% of women reported consumption of other tap water beverages. Overall, women consumed an average of 0.79 L of cold tap water, 1.04 L of boiled water, and 1.09 L of bottled water per day. The cohort study subjects' daily water intake for water users of low, medium, and high THM exposure was similar (Table 3). The highest amount of tap water was consumed at home (0.62, 0.65, and 0.69 L, respectively, low, medium, and high exposure), while at work and in other places, tap water usage was low (mean 0.1 L).

Showering was common (96% of subjects) and 37% took either shower or a bath during the pregnancy. Mean frequency of showering was 6.5 times per week, with a mean duration of 15.2 minutes per shower. Average frequency of bathing was 1.8 times per week, with a mean duration of 33.5 minutes per bath. The percentage of participants who attended swimming pools was low (7%). The reporting of showering and bathing increased with increasing THM exposure. The mean time of showering was 69.73 minutes per week in the low-exposure group, 92.21 minutes per week in the medium exposure group, and 114.33 minutes per week in the high exposure group. Mean bathing time also increased with increasing exposure from 42.64 minutes per week to 63.53 minutes per week.

THM integrated uptake included ingestion, showering, and bathing. Uptake via ingestion contributed 8%; showering and bathing were the main contributors for TTHM and made up 92% of the total internal dose. The variability in frequency and duration of showering and bathing determined the TTHM internal dose variability. The individual total uptake of TTHMs ranged between 0.0025 and 2.40 µg/d. The total chloroform uptake ranged between 0.0013 and 2.13 µg/d. Mothers supplied with water who had a higher chloroform concentration generally also had a higher total internal dose, and mothers supplied with water that had a lower chloroform concentration generally also had a low total internal dose. Daily uptake of bromodichloromethane ranged between 0.0001 and 0.34 µg/d and dibromochloromethane ranged between 0 and 0.064 µg/d. We found a correlation between total pregnancy daily uptake tertile dose levels of TTHMs and trimester-specific levels. The correlation coefficient between TTHM uptake in the first and second trimester was 0.98, $p < 0.001$, and between the first and third trimester was 0.95, $p < 0.001$. A similar strong correlation was found for the uptake of THM constituents between the pregnancy trimesters (r = 0.99-0.81). The strong correlation is a result of limited variability in the amount of THMs produced from season to season at these groundwater treatment plants. Exposure to TTHMs was associated with an increased risk for LBW using tertiles and a reduction in BW using a continuous variable (Table 4). After adjustment for potential confounding factors, we observed a statistically significant increased risk with higher dose levels (second and third tertiles) of TTHMs during the three trimesters and entire pregnancy. During the entire pregnancy, the odds ratios for LBW were 1.77, 95% CI 0.95-3.30; and OR 2.13, 95% CI 1.17-3.87, respectively, for second and third tertiles compared to the first tertile. The LBW risk (OR) observed per 0.1µg/d increase in TTHMs was 1.08, 95% CI 1.01-1.16 and 1.07, 95% CI 1.00-1.15; and decrease in BW was 49.3 g (-146.3 to -1.5) and 47.2 g (-92.7 to -1.6) during the entire pregnancy and third trimester.

Similarly, first, second, and third trimesters chloroform dose categories were associated with a statistically significant increase in the risk for LBW. Chloroform analyzed as continuous variable (increase of 0.1 µg/d) was also associated with an

increase in risk for LBW (OR 1.10, 95% CI 1.01-1.19) for the entire pregnancy, as well as for trimester-specific time windows. In a linear regression we found a mean decrease in BW of 59.3 g (-114.8 to -3.7) for the entire pregnancy and 57.8 g (-111.6 to -4.0) for the third trimester, respectively, with increasing dose levels of chloroform. For bromodichloromethane, we observed statistically significant increases in LBW risk for the third tertile compared to the first tertile for the third trimester, OR 1.80, 95% CI 1.00-3.26. For bromodichloromethane internal dose as a continuous variable, we found an elevated risk in LBW for the entire pregnancy, first and third trimesters (ORs 1.04-1.05 for an increase of every 0.01 µg/d). The dibromochloromethane internal dose results were statistically significant for entire pregnancy and third trimester (OR 2.52, 95% CI 1.00-6.36 and OR 2.42, 95% CI 1.03-5.66, respectively). No significant reduction in BW as a continuous variable was found.

We found slight a increase in the risk of SGA related to elevated internal doses of THMs, however, the results were statistically non-significant (Table 5). We observed slight increases in the risk for SGA among TTHMs exposed women (ORs 1.13-1.34). Chloroform dose was also associated with a slight increases in the risk of SGA (OR 1.19, 95% CI 0.87-1.63 and OR 1.22, 95% CI 0.89-1.68, respectively, for second and third tertile of third trimester and OR 1.04, 95% CI 1.00-1.09 per every 0.1µg/d increase in the chloroform internal dose). Bromodichloromethane internal dose was associated with an increased risk but this was not monotonic (OR 1.37, 95% CI 1.00-1.88 and OR 1.25, 95% CI 0.91-1.73, respectively, for second and third tertile of third trimester), and it was not statistically significant as a continuous variable (OR 1.20, 95% CI 0.90-1.62).

Discussion

We conducted a prospective cohort study to examine the effects of internal dose of THM during the entire pregnancy and during three trimesters on LBW, BW, and SGA births. We observed a low spatial variation in THM levels measured in three locations: close to the treatment plant, at 5 km and at 10 km or more from every treatment plant in the each distribution system. The low spatial variability of TTHM present in Kaunas groundwater distribution systems could be explained by the relatively simple structure (ie one subsystem) and low presence of DBPs precursors at the groundwater sources.[4,28] Personal behavior was the main determinant of exposure variability of the study subjects. Uptake via showering and bathing provided a greater contribution to the uptake of the TTHM to the internal dose than did ingestion of tap water (92 and 8%, respectively). We demonstrated consistent, statistically significant effects of THM exposure on LBW and BW with an indication of dose-response relation. We found both excess risk of LBW during the entire pregnancy and during three trimesters as well. Specifically, there was a statistically significant excess risk of LBW for those exposed to higher internal doses of TTHM and chloroform in the three trimesters and a slight excess risk for those exposed to higher internal doses of bromodichloromethane and dibromochloromethane during the entire pregnancy and during third trimester. TTHM constituents (chloroform, bromodichloromethane and dibromochloromethane) analysed as categorical variables showed a slight excess risk of SGA during the entire pregnancy as well as trimesterspecific periods. The probability of delivering an SGA infant was elevated by 4% per every 0.1µg/d increase in the chloroform internal dose during the third trimester pregnancy. The lack of statistically significant effects for other TTHM constituents may be due to low exposure because of low levels, and lack of power in our study sample. Although the third trimester is the most important in terms of fetal body mass growth, it has been hypothesized that early-pregnancy exposure may hamper fetal growth.[15]

Therefore we conducted analyses exploring effects for three trimester-specific gestational exposures and entire pregnancy exposures. In our analyses it was more difficult to evaluate any independent effects of the trimesters because of the high correlation in exposure between them.

The epidemiological evidence for an association between exposure to THM and indicators of fetal growth is relatively inconsistent. A number of prior investigations have evaluated crude exposure during the third trimester of pregnancy, the time period of gestation when fetal growth may be most sensitive to environmental influences. No associations were reported between term LBW and trimester-specific exposures or entire pregnancy exposures to TTHM.[9,10] Investigators who were able to address variation in residential exposures observed a positive association between TTHM exposures and term LBW, decreased mean BW and increased risk of delivering a LBW infant despite low TTHM concentrations.[29,30] Others find a weak association of SGA with an exposure level of THM of 30 mg/L.[31] Some epidemiological studies reported a moderately increased risk of delivering a SGA infant among women exposed to high levels of TTHM, with relative risks ranging up to 1.5.[10-12,16]

An association between increased risk of intrauterine growth retardation and TTHM exposure was reported[10] and a dose-response trend was observed for exposure to chloroform.[32] Some authors did find a slightly elevated risk of intrauterine growth retardation during the second and third trimesters for TTHM[15] and others did not.[33] These studies differed in their exposure estimation because they mainly used the routinely measured DBPs levels in water and at times ingestion data. Lack of a consistent significant effect of the epidemiologic studies may be result of a study design, be a result of exposure misclassification or inadequate control for confounding variables, or a lack of power in studies sample, or actual lack of an effect of DBP on fetal growth. A recent meta-analysis of epidemiological studies data on the association of TTHM concentration in water and fetal growth, without taking into account showering, bathing, and other exposure routes, concluded that there was little or no evidence for associations between TTHM concentration and fetal growth and that the uncertainties-relating particularly to exposure may have affected the results. The authors concluded that there is need for a more accurate exposure assessment in the studies of the associations between TTHM and birth outcomes.[34,35]

Only few studies have incorporated information on individual water use to estimate personal DBP exposure.[16,19,36] However, personal exposure analyzed as categorical variable did not show a stronger association than residential concentration with respect to fetal growth and fetal survival outcomes. These studies did not explore the effect of THMs as continuous variables on LBW or SGA risk. Recently, findings of a case-control study suggested that exposure to THMs at the highest levels can affect fetal growth but only in genetically susceptible newborns.[37]

Our study offered advancement in individual internal dose assessment based on residential THM levels, detailed water

use behaviors and exposure during pregnancy. Every subject's exposure indices were estimated as daily internal dose of the THM constituents (µg/d) and birth outcome effects were assessed by using indices categorical variable and also as a continuous variable. An additional strength of our study is that pregnant women were prospectively followed, and did not move during pregnancy. This allowed collection of self-reported data on potential confounding covariates. However, there is a possibility of residential confounding in our study, because we did not adjusted for e.g. residential air pollution exposure that might have effect on adverse birth outcomes.[38] An additional limitation of our study is because of lack information on maternal. Nutrition and infection diseases. This study exposure assessment also could be improved by more frequent measurement of DBPs at the every home tap and including other water usage activities and validation of data on DBP blood concentration measurement, but this is prohibitively expensive. Furthermore, lack of information regarding the validity of the internal dose assessment models that we used is one of the limitations of this study, but again validity studies are difficult to conduct and are expensive. In this study, despite low concentrations of THM in drinking water, we found evidence of fetus growth restriction in mothers exposed to higher TTHM internal doses after controlling for family status, maternal education, chronic diseases, body mass index, blood pressure, smoking, alcohol consumption, previous preterm, infant gender, and year. However, the trihalomethanes are not the only byproducts of chlorine disinfection or other contaminants, although in this region the levels of other by-products appeared to be very low, we cannot exclude the potential effects of this low-dose mixture, or any other related exposure.

The health effects of LBW and SGA are important issue for public health since these infants are at an increased risk of significant morbidity and mortality during the early stages of life.

Conclusions

This study presented some epidemiological evidence for a dose-response relationship between THM internal dose exposure and LBW; a statistically significant association of THM with SGA was seen only for chloroform exposure. Our study used the questionnaire information to evaluate of pregnant women water usage habits and estimate integrated internal dose for THM exposure assessment. Our data showed that seeking to reduce exposure measurement errors in individual exposure determination, assigning exposure through dermal absorption, and inhalation should be considered combined with ingestion, since TTHM through ingestion composed less than 10% of integrated internal dose. This study finding suggest that internal dose in pregnancy vary substantially across individuals, depending on both water THM levels and water use habits and that internal dose may affect fetal growth. However, we do not feel this study provides strong support that any THM constituent is associated with fetal growth restriction. Futher research should focus on the use of integrated internal dose and individual susceptibility in the study of DBP effects on birth outcomes.

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Birth Weight in a Large Series of Triplets

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Abstract

Background: Triplets are often born premature and with a low birth weight. Because the incidence of triplet births is rare, there are relatively few studies describing triplet birth weight characteristics. Earlier studies are often characterized by small sample sizes and lack information on important background variables such as zygosity. The objective of this study is to examine factors associated with birth weight in a large, population-based sample of triplets registered with the Netherlands Twin Register (NTR).

Methods: In a sample of 1230 triplets from 410 families, the effects of assisted reproductive techniques, zygosity, birth order, gestational age, sex, maternal smoking and alcohol consumption during pregnancy on birth weight were assessed. The resemblance among triplets for birth weight was estimated as a function of zygosity. Birth weight discordance within families was studied by the pair-wise difference between triplets, expressed as a percentage of the birth weight of the heaviest child. We compare data from triplets registered with the NTR with data from population records, which include live births, stillbirths and children that have deceased within days after birth.

Results

There was no effect of assisted reproductive techniques on triplet birth weight. At gestational age 24 to 40 weeks triplets gained on average 130 grams per week; boys weighed 110 grams more than girls and triplets of smoking mothers weighted 104 grams less than children of non-smoking mothers. Monozygotic triplets had lower birth weights than di- and trizygotic triplets and birth weight discordance was smaller in monozygotic triplets than in di- and trizygotic triplets. The correlation in birth weight among monozygotic and dizygotic triplets was 0.42 and 0.32, respectively. In nearly two-thirds of the families, the heaviest and the lightest triplet had a birth weight discordance over 15%. The NTR sample is representative for the Dutch triplet population that is still alive 28 days after birth.

Conclusion: Birth weight is an important determinant of childhood development. Triplet status, gestational age, sex, zygosity and maternal smoking affect birth weight. The combined effects amount to a difference of 364 grams between monozygotic girl triplets of smoking mothers compared to dizygotic boy triplets of non-smoking mothers of the same gestational age. Birth weight in triplets is also influenced by genetic factors, as indicated by a larger correlation in monozygotic than in di- and trizygotic triplets.

Background

The incidence of triplet births is rare. In the Netherlands, up to 1980, a triplet birth occurred once per 10 thousand births. The number of triplet births increased after the introduction of assisted reproductive technologies (ART). In 1990, the number of triplet births had increased up to 6 per 10 thousand. From 2000 onwards, triplet birth rates decline again, mainly because of a change in policy of fertility clinics. The Central Bureau of Statistics of the Netherlands has monitored triplet birth rates at 2 per 10 thousand births since 2005.[1]

The prevalence of low birth weight (BW) and preterm deliveries is high in triplet births. Both low BW and prematurity are risk factors for adverse health, cognitive and behavioral outcomes later in life, e.g. see Arnoudse-Moens et al. (2009) and Bhutta et al (2002).[2,3] Among the factors that influence birth weight gestational age (GA) is the most important factor.[4-6] Alexander et al.[7]described how fetal growth in triplets does not follow the growth curves of singletons or twins. Triplet growth is characterized by different phases. In phase A, up to 26 weeks, triplet fetal growth is comparable to that of singletons. Phase B is roughly between 26 and 30 weeks. During phase B, there is a steady decrease in triplet growth relative to singletons, up to a difference of 20%. This is hypothesized to be due to the restricted intrauterine space. During phase C, 30 to 35 weeks, there is no further decrease relative to singletons. Triplet weight during that period is about 20% less than that of singletons. These three phases are also seen in twins, though later in time and to a lesser extent. Phase D is only seen in triplets and starts from a GA of about 35 weeks. In this phase, a marked decrease in triplet weight compared to that of singletons is seen. However only 10 - 13% of the triplets reach a GA of more than 35 weeks.[4,8]

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Other factors involved in triplet BW include sex, zygosity and birth order. As in singletons, boy triplets weigh more than girls.[9-10] In twins, dizygotic (DZ) twins weigh more than monozygotic (MZ) twins. This is mainly an effect of sharing a placenta. MZ twins are, compared to DZ twins, more in competition for nutrients.[11,12] In triplets a similar effect is found.[8,13] However, until now the effect of zygosity on BW in triplets has been based on small samples, and a distinction within DZ trios between the MZ pair and the DZ triplet has not always been made. Only a few studies specifically focused on birth order in twin and triplet pregnancies. These studies suggest that the first-born child is often the heaviest, followed by the second born child. In triplets, the third born child most often weighs the least[6,14]

Not all three children in triplet pregnancies are similarly affected with regard to BW. Inter-triplet BW discordance is thought to be a direct effect of physiological adaption to the limited uterine environment. One triplet grows at the expense of his brother or sister. Compared to twins, BW discordance in triplets is less well documented, although the phenomenon seems to be more common in triplets than in twins.[15] Especially severe discordance – defined as a difference in BW of over 35% – is higher in triplets than in twins: 9.5% in triplets compared to 3.1% in twins.[16,17]

Maternal smoking during pregnancy is a known predictor for low BW in children.[18,19] A study in twins found a negative effect of maternal smoking on the regression of BW on gestational age. Hence, the twins of non-smoking mothers had a more optimal development of BW.[20] The effect of maternal alcohol consumption during pregnancy is less clear. Some studies in singletons suggested that alcohol consumption is unrelated to BW when corrected for GA.[21,22] Other studies in singletons showed an effect in mothers who consume more than 100 grams or more than 5 drinks per week,[18,23] as well as an interaction between alcohol consumption and smoking during pregnancy. The effect of maternal smoking combined with maternal alcohol consumption on children's BW is larger than the summed effect of each separate causal agent.[18,19,24] As triplets are already more growth restricted compared to twins, the effects of maternal smoking and alcohol consumption could be even more detrimental. To our knowledge, no other studies have directly looked at the effect of maternal smoking and alcohol consumption during pregnancy on triplet BW.

In the past two decades, around 37% of the triplets born in the Netherlands have been registered with the Netherlands Twin Register (NTR). In this study we present descriptive statistics on triplet BW and analyses of the effect of sex, zygosity, birth order, GA, and maternal smoking and alcohol consumption during pregnancy. Correlations in triplet BW are calculated as a function of zygosity to investigate the role of genetic factors on BW. Lastly, BW discordance is described. We compare characteristics of triplets registered with the NTR with data from the Netherlands Perinatal Registry (NPR).[25] Data from the NPR consists of the total group of triplets born in the Netherlands, including the stillbirths and children that decease soon after birth.

Method

Subjects: We use the term "triplet" to denote one of three individuals born at the same birth, and refer to a 'trio' as three triplets born at the same birth. In total, 1966 triplets from 664 families were registered with the NTR. The sample includes 642 complete trios and 22 incomplete trios. The complete trios consisted of 125 trios comprising 3 females, 187 trios consisting of 1 male and 2 females, 207 trios consisting of 2 males en 1 female, and 123 trios comprising 3 males. The incomplete trios consisted of 18 males and 22 females. Trios were incomplete for various reasons (eg in young triplets: one of the triplets was deceased; in adult triplets: not all members of a trio participated).

The Adult NTR (ANTR) registers multiples who are recruited as adults and the Young NTR (YNTR) registers multiples at birth. In figure 1 the number of triplets per birth cohort is given. Note that birth cohort 1986 marks the division between the ANTR and YNTR, triplets born after 1986 are registered with the YNTR. The oldest trio registered with the NTR were born in 1939. Data on triplet BW came from triplets born between 1970 and 2006.

To investigate the representativeness of the NTR triplet sample, we compared our sample with the Dutch triplet population regarding parity, BW, GA and age of the triplet mother when giving birth. In addition, we investigated factors that could have influenced non-response by comparing the study sample with trios who were registered with the NTR but did not participate in our surveys. The responders and non-responders were compared on age of the mother when giving birth, maternal education and population density.

Data collection: Three questionnaires include items regarding pregnancy, delivery and BW. Questionnaire 1 (Q1) is completed by mothers of YNTR triplets just after registration. Q1 inquired about the pregnancy (ART, gestational age, smoking and alcohol consumption during pregnancy and mode of delivery) and characteristics of the triplet (birth date, sex, domicile and birth weight) and about characteristics of the parents. Over the years, Q1 has been collected in 323 trios. In 2008, Questionnaire 2 (Q2) was sent to mothers of all triplets born before 2006. In addition to the questions in Q1, Q2 inquired about the characteristics of the triplets up to age 2 (eg growth curves, health and temperament). Q2 was sent out to 535 mothers and was returned by 264 mothers. Since the data collection in 2008, all mothers of triplets who reach age 2 receive Q2.

In 2005, a questionnaire on familial twinning (Qft) was sent to all ANTR and YNTR mothers of multiples in the NTR.[26,27] This survey inquired about the occurrence of multiple births within a family, mode of conception, information on delivery and parental characteristics.

The Child Behavior Check List (CBCL[28]) was sent multiple times to parents of triplets between age 3 and age 12 of the children. In addition, a short general questionnaire on parental and triplet characteristics (eg parental employment and religion, triplet school achievements and health) was included.

The Youth Self Report (YSR[29,30]) was sent to YNTR triplets aged 14, 16 and 18. Triplets born between 1987 and 1992 were sent a paper and pencil version. Birth cohorts 1994 - 1995 received the YSR through the internet at ages 14 or 15. Birth cohort 1992 - 1993 completed the YSR via internet at age 16.

Starting in 2009, the Teacher Report Form (TRF[29]) is collected. In 2009 we asked parents of 170 trios for consent to approach the children's teachers. 106 parents returned the consent form and 80 gave permission. After the parental consent was obtained,

teachers of 240 triplets aged 6 to 12 received the TRF.

Triplets who agreed to participate in ANTR research have usually been included in the ANTR data collection. The procedure of data collection of the ANTR is described elsewhere.[31,32]

For the current study, we used the data on BW, smoking and alcohol consumption during pregnancy acquired from questionnaire Q1 and Q2, completed by the mother of the triplets. Data on ART came from Q1, Q2 or Qft. Data on BW and zygosity were available for 455 and 465 trios, respectively, out of the 642 complete trios. For 433 trios information on both was available. For 410 trios, data were available for all variables under study, ie BW, zygosity, GA, alcohol consumption and smoking. Information on ART was available for 329 out of these 410 trios.

Response consistency was investigated by correlating responses given at subsequent questionnaires. When comparing Q1 and Q2, correlation was 0.93 (N=521) for BW, 0.94 (N=182) for GA, 0.95 (N=182) for smoking, 0.57 (N=179) for alcohol consumption and 0.98 (N=100) for ART. Correlation for ART between Q1 and Qft was 0.95 (N=132), and for ART between Q2 and Qft it was 1.00 (N=132). Except for alcohol consumption, responses were highly consistent. For alcohol consumption, 14 mothers reported to have consumed alcohol on Q1 but not on Q2, and 7 mothers reported to have consumed alcohol on Q2, but not on Q1. In these cases, the response given at Q1 was used in the analysis.

Statistical analyses: Analyses were performed using the software package Mx, which allows modeling of the dependency that exists between measures of pairs of relatives.[33] We tested the effect of zygosity, birth order, sex, GA, smoking and alcohol consumption on mean BW, and the effect of zygosity on variance and covariance in triplet BW. The effect of ART was tested in a smaller sub set of triplets in which information on ART was available.

First a full model, in which all effects were estimated, was fitted to the data. Subsequently, nested sub models were tested. In the full model the following parameters were estimated: the grand mean BW as a function of birth order and zygosity, the variance and covariance in BW (as a function of zygosity), and the regression coefficients on BW of GA, GA^2, sex, alcohol consumption and smoking. In step 2, the means, variances and covariances of the MZ triplets from the MZ group were tested for equality with the MZ triplets from the DZ trio group. In step 3, the means, variances and covariances of the single remaining triplets in a DZ trio, not part of the MZ pair, and TZ triplets were constrained to be equal. In step 4, birth order effects on mean BW were tested within the zygosity groups. Finally, in step 5 it was tested whether the effects of GA, GA^2, sex, maternal smoking and alcohol consumption on mean BW significantly differed from zero.

Using the raw likelihood method as implemented in Mx, the different models were compared using the log-likelihood ratio test. The difference in -2 times the log-likelihood (-2LL) between two nested models has a χ^2 distribution with the degrees of freedom (df) equaling the difference in df between the two models. A p-value of 0.05 was used to determine statistical significance.

In the regression analysis, sex was coded 0 for boys and 1 for girls and GA was coded as actual GA minus 40, ranging from 0 (GA of 40 weeks) to -16 (GA of 24 weeks). A possible flattening of triplet BW at the highest GA's was modeled with GA^2. GA^2 was calculated by squaring the normalized score of the variable GA as described above (MeaN=0, SD=1). Smoking and alcohol consumption during pregnancy were analyzed as dichotomous traits: yes (1) or no (0).

The MZ and DZ correlations were used to infer the influence of genetic and/or environmental factors on triplet BW. MZ triplet pairs and trios are genetically identical, whereas DZ and TZ triplet pairs and trios share on average 50% of their genetic material. A MZ correlation that is higher than the DZ correlation implies the influence of genetic factors. A DZ correlation that is higher than half the MZ correlation implies that shared environmental factors influence BW.

Birth weight discordance: Three definitions are commonly used for BW discordance in twins. First, an absolute definition: the absolute difference in BW. Second, a percentage definition: BW disparity is calculated as a percentage of the largest child's BW. Third, a statistical definition: BW as percentile of one or two standard deviations from the mean.[34] Studies on trios often adopt the percentage definition. This means that the difference between the BW of the lightest and the heaviest triplet is calculated as an percentage of the BW of the heaviest.[35]

The third method, specific to trios, takes into account the BW of the triplet that falls in between the heaviest and lightest triplets. In this method, a relative BW ratio is calculated by taking the difference between the middle and lightest triplet as a percentage of the difference between the heaviest and lightest triplet.[16] An advantage of this method is that this ratio is representative for situations in which the trio consists of 2 heavy and 1 light triplet or trio of 1 heavy and 2 light weights. We used the percentage definition to estimate birth weight discordance, as this definition is most frequently used.

Results

Representativeness of the NTR triplet sample: The results show parity, BW, GA and age of mother for 1) the total group of Dutch triplets born in the Netherlands between 2000 and 2006 (the NPR gathered information on birth characteristics starting from birth cohort 2000), 2) the total group of triplets but without the trios in which one or more children were deceased before 28 days after birth, 3) the NTR sample. The NTR sample is highly comparable to the second group, but less to the first group, which contains more primiparous mothers. In the first group, GA is shorter and BW is lower. This indicates that the NTR sample is representative of trios with a favorable outcome, ie children that are still alive 28 days after birth.

Comparing the current study sample with trios registered in the NTR but not participating in this survey yielded no significant age difference between the two groups ($t(454)=1.90$, $p=0.06$). There was a difference in maternal education ($\chi^2(3)=8.69$, $p=0.03$). Maternal education in the responders group was lower than the educational level of mothers from the non-responders group (percentages of low, middle, middle high and high education: 12.4%, 36.0%, 29.4% and 22.2% for the responders versus 4.2%, 41.5%, 30.5% and 23.7% for the non-responders). There was also a difference in population density between the two groups ($\chi^2(3)=8.16$, $p=0.00$). Population density was categorized as more than or less than 1000 persons per square

meters. The distribution in the response group was 50.0% and 50.0% and in the non-response group 43.4% and 56.6%, for < 1000 and > 1000 persons per square meters, respectively.

Zygosity: Trio zygosity was determined by DNA, blood group assessments,[36] or survey questions. The survey questions pertained to resemblance in hair, eye, and face color, and facial appearance, of each triplet pair in a trio. Furthermore, items were included inquiring if the triplets were ever mistaken for each other by family members or strangers. When DNA, blood or survey questions were not available, self or parental report on zygosity was adopted. Self or parental report on zygosity was based on the answer to two survey questions "What do you think the zygosity of the trio is?" and "And if the trio is a DZ trio, which pair forms the MZ pair?"

DNA samples were available for 79 triplets from 31 families and blood samples for 65 triplets from 22 families. Both DNA and blood samples were available for 47 triplets from 16 families. Survey questions about resemblance and self or parental report on zygosity were available for 318 and 450 trios, respectively. Zygosity estimate was based on the trio. This signifies that if one pair wise comparison could be made but information on the third triplet was missing, trio zygosity could not be determined. There were 22 trios with zygosity based on DNA and/or blood information on all triplets. Seventeen trios had information on zygosity based on both DNA and survey questions regarding resemblance. This provided the opportunity to look at the reliability of the survey information. Pair wise comparisons were incorrect in 10% of the cases. This is comparable with zygosity determination based on survey questions on resemblance in twins.[37,38] However, zygosity determination in trios is based on three pair wise comparisons. DNA and survey questions on resemblance gave the same zygosity result for 12 of these 17 trios. For 5 trios, survey questions on resemblance suggested that the trio was dizygotic while DNA determined that the trios were trizygotic. In 4 of these last 5 cases, self and/or parental report also suggested that the trios were dizygotic. Pairs determined as MZ where checked on sex (an opposite-sex pair cannot be MZ). This resulted in a zygosity determination of 465 triplet trios.

ART: ART are more commonly seen in triplet pregnancies than in twin or singleton pregnancies. We asked the triplet mothers in 350 returned questionnaires about the possible use of ART. 127 answered that the pregnancy was spontaneous, 103 after in vitro fertilization, 17 after intracytoplasmic sperm injection, 25 after intrauterine insemination, and 63 after ovulation induction with hormone tablets or subcutaneous injections. The remaining 15 mothers gave an unclear or no answer to this question. The age of the triplet mothers who made use of ART ranged from 21 to 43 years (M=31, SD=3.5), the age of mothers who spontaneously conceived the trio ranged from 20 to 41 years (M=30, SD=3.8). ART was overrepresented in the TZ triplet group. 87% of the mothers of TZ triplets reported ART, compared to 19% of the mothers of DZ's and only 3% of the mothers of MZ triplets.

Within the subset of triplets with information on ART, we did not find a significant effect of ART on BW ($\chi^2_{(1)}$=0.23, p=0.63). ART was also tested in the TZ triplet group alone to correct for a possible confounding effect of zygosity, as TZ triplets are possibly heavier and overrepresented in the group of triplets born after ART. Still, no effect was found ($\chi^2_{(1)}$=1.23, p=0.27). All other analyses were therefore performed on the total set of triplets, including triplets without information on ART.

Birth weight: The total sample with complete data included 37 MZ trios, 102 DZ trios which consist of one MZ pair and one DZ triplet, and 271 TZ trios. Mean GA of the triplets was little above 33 weeks. 26% of the triplets was born after a cesarean section. Only 3% of the mothers of triplets both smoked and consumed alcohol, while 15% reported smoking and 11% reported consuming alcohol during the pregnancy.

The uncorrected data on BW are presented as a function of zygosity and birth order. For the DZ trios two columns are presented. One column gives mean BW for the MZ pairs within the trio. The other column gives mean BW for the single remaining DZ triplets that are not part of the MZ pair.

The 10th percentile of BW as a function of GA is often classified as SGA. However, this 10th percentile differs between singletons and triplets. For example, Alexander et al. (1998)[7] reported that for a GA of 33 weeks the singleton 10th percentile of BW is 1673 grams, but for triplets it is only 1418 grams. The discrepancy between singletons and triplets increases with increasing GA. As such data are not available for Dutch triplets, we present the percentages of triplets who are SGA based on singleton standards for the United States (US) and based on US triplet standards as reported by Alexander in addition to Swedish singleton standards which are comparable to Dutch singleton standards.[39,40]

We also noted the effects of GA, sex and smoking on mean BW as well as the variance, covariance and correlations of BW within MZ and DZ triplets. We found no difference between the mean, variance and covariance of triplets from the MZ group and MZ triplets from the DZ group (step 2). There were no significant differences in the variances and covariances of the DZ and TZ triplets, but there were differences between the means of the DZ triplets and the TZ triplets ($\chi^2_{(3)}$=16.57, p=0.00). A significant birth order effect was found within the TZ group ($\chi^2_{(2)}$=29.07, p=0.00), but not in the MZ and DZ group ($\chi^2_{(2)}$=5.61, p=0.06 and $\chi^2_{(2)}$=0.92, p=0.63, respectively).

The tests of the fixed effects showed that GA was the most important contributor to mean BW in triplets. Between a GA of 24 to 40 weeks, the triplets gained 130 grams per week. No significant flattening of the growth line (GA^2) was observed ($\chi^2_{(1)}$=2.49, p=0.11). An effect of sex was found with boys being 110 grams heavier than girls ($\chi^2_{(1)}$=36.69, p=0.00). Furthermore, triplets from mothers who smoked during pregnancy were 104 grams lighter than the triplets of mothers who did not smoke ($\chi^2_{(1)}$=10.9, p=0.00). We did not find a significant effect of alcohol consumption during the pregnancy on triplet BW ($\chi^2_{(1)}$=0.11, p=0.74).

Correlations in triplet BW as a function of zygosity were calculated before and after including the effects of GA, sex and smoking on mean BW in the model. Before correction, the MZ correlation was 0.70, and the DZ and TZ correlations were 0.64 and 0.67 respectively. Correlations in triplet BW were lower when the effects of GA, sex and smoking were included, indicating that these variables explain part of the resemblance in triplet BW. Furthermore, the MZ triplet correlation is higher than the DZ triplet correlation, 0.42 compared to 0.32, respectively. This indicates that in addition to common environmental effects, genetic factors also explain part of the variance in BW.

Finally, BW discordance was calculated. We compared the heaviest and the lightest triplet of a trio and found that in only 17.9% of the trios, BW discordance was less than 10%. In 60.6% of the trios BW discordance was between 10-30% and in 21.5% BW discordance was more than 30%. There are more MZ triplets in the low discordance categories compared to the DZ and TZ triplets, and less MZ triplets compared to DZ and TZ triplets in the high discordance categories. This is in line with the higher correlation in BW in MZ triplets as reported above.

Discussion

The present study describes the influence of genetic and environmental risk factors on BW in a large population based sample of Dutch triplets. BW is affected by zygosity and birth order. MZ triplets were lighter than DZ and TZ triplets, and BW decreased with decreasing birth order in TZ triplets. GA, sex and smoking during pregnancy also had an effect on BW. No effects of ART and alcohol consumption were seen. We did not observe a significant flattening of the BW curve in the last stage of mature triplet gestation. The resemblance for BW was higher in MZ triplets than in DZ triplets after correction for the other risk factors indicating that genetic factors are also of importance. BW discordance in triplets is common since in 21.5% of the trios the difference in BW between the heaviest and lightest triplet was more than 30%.

Factors affecting triplet BW: The most important factor in triplet BW is GA. As expected, in this sample a higher GA was associated with a higher BW in triplets. The literature describes the occurrence of a flattening of the growth curve during the last weeks of triplet pregnancies. This growth restriction period emerges round a GA of about 36 to 37 weeks.[17] In the NTR sample only 1.5% of triplet pregnancies reached a GA of 37 weeks or more and no flattening of the BW growth curve was seen.

The effects of alcohol consumption and smoking during pregnancy on BW were both examined. No effect of alcohol consumption on triplet BW was seen. We hypothesize that in this sample the absence of an effect was seen because of the low maternal alcohol consumption during pregnancy. In addition, mothers reported less consistent on alcohol consumption than on other variables.

Mothers of triplets who smoked had children who were on average around 100 grams lighter than non-smoking mothers, which is a decline in BW of 4%. This is the effect of smoking after correcting for the GA of the triplet. Studies in singletons report that children of smoking mothers are 119 to 241 grams lighter, which is 4 to 7% lighter than children of non-smoking mothers. The amount of loss in BW is dependent on the quantity the mother smoked during the pregnancy. Within the NTR group of smoking mothers around 70% smoked 0 to 5 cigarettes per day, 15% smoked 5 to 10, and about 15% smoked more than 10 cigarettes per day. In singletons an interaction between alcohol consumption and smoking has also been observed. We did not test for such an effect because only 3% of the triplet mothers both consumed alcohol and smoked.

First born TZ triplets were heavier than the second born TZ triplets, who were heavier than the third born children. No significant birth order effect was seen in the group of MZ and DZ triplets. As the MZ and DZ groups were small, this might reflect a lack of power to detect a difference. In twins, the first born (and heavier) twin, has an heavier placenta and a more optimal (a central instead of peripheral) cord insertion.[41] Possibly triplets higher in birth order are, on average, more optimally positioned with respect to nutrients intake.

BW discordance and SGA: The prevalence of BW discordance is comparable with a study of Jacobs et al. (2003)[42] and other studies (for a short review see Blickstein et al. (2002) or Blickstein & Kalish (2003).[15,34] Compared to singletons or twins, triplets are delayed in growth and cognitive development. There has been limited research on the effects of BW discordance, but it seems that triplets who are discordant in BW are at an even higher developmental risk than other triplets.[43,44] One study found that most triplets without BW discordance have caught up with singleton and twin standards on cognitive and executive functions at age 5. In contrast, BW discordant triplets still showed a lower performance on these functions at that age.[45] BW discordance in that study was defined as a difference in BW between the heaviest and lightest triplet of more than 15%. In the current sample, this includes 63.2% of the trios.

We also estimated the resemblance in BW of triplets. The resemblance for BW in MZ triplets was higher than in DZ triplets. Both were higher before correction for GA, sex and smoking than after adjusting for these factors. This suggests that genetic as well as common environmental factors influence birth weight and that GA, sex and smoking are some of the specific common environmental factors.

We observed that, when taking US singleton standards as a reference, 40-50% of the triplets were SGA. Children who are born SGA are at risk for asphyxia and intrauterine mortality.[46,47] As a consequence, children born SGA have to be monitored in neonatal intensive care units (NICU). In the Netherlands triplets are classified SGA based on singleton standards. As a result, at least half of all triplet births have to be born in tertiary referral centers with NICU facilities.

ART: Population based triplet zygosity distributions have changed over the years. Imaizumi[48] reported that in the Netherlands, the TZ rate increased from 1972-1973 to 1990-1991 and decreased thereafter. Imaizumi concluded that the temporary higher TZ ratio could be attributed to ART. This conclusion is confirmed by the present study in which ART was more common in TZ triplets than in the other zygosity groups.

Studies in singletons report that children born after ART are lower in BW than spontaneously conceived children. In twins the effect of ART is less clear, some studies find an effect, while others do not.[49,50] The reason for lower BW in children born after ART is not completely understood. Investigators suggest that the procedure of ART itself or maternal characteristics (eg age, weight, parity) may cause lower BW in children born after ART. In twins, the adverse effects on mean BW associated with ART are possibly balanced by the favorable effect of DZ zygosity as ART increases the prevalence of DZ twinning and DZ twins are heavier than MZ twins. In the present study we found no effect of ART. The effect was neither present in the entire triplet group, nor in the TZ triplet group. Therefore, in present study it can be concluded that the presumed lowering effect of ART on BW was not counterweighted by the higher prevalence of TZ triplets in the ART group.

Limitations and Strengths: The present sample consisted of

triplets who were registered at the NTR and whose parents were willing to participate in survey studies. This led to a small positive selection bias. Triplets from families in which all three children are alive 28 days after birth also have more favorable scores on BW and GA. Moreover, parents are possibly more willing to participate in research when the triplets are healthy compared to parents dealing with illnesses of one or more of their children. The NTR sample was more comparable with a selection of Dutch triplets that were still alive 28 after birth, than with a complete group of Dutch triplets including children who died soon after birth. A comparable positive selection bias was found in a study on secular trends in gestational age and birth weights in twins. In this study twins registered at the NTR were compared with a national reference set. The twins registered at the NTR were found to have a higher GA (36.5 (2.4) compared to 35.9 (3.0) weeks) and a higher BW (2498 (550) grams compared to 2459 (615) grams).[51] As a result of this positive selection bias, percentages of discordant triplets are probably underestimated compared to the total Dutch triplet population. The positive selection bias could also cause an underestimation of the percentage triplets that are classified as SGA. We also do not know whether the effects of the investigated risk factors might be more pronounced in this more vulnerable group.

We investigated whether zygosity influenced triplet BW. MZ triplets are more in competition for nutrients than DZ and TZ triplets. A more direct measure of triplets sharing placenta's and therefore triplet nutrients competition is chorionicity. Information on chorionicity would therefore have been a valuable addition to the information on zygosity. Currently, no reliable information on chorionicity was available.

Parity has been associated with BW but was not included in the analysis of present study, as information on parity was only available for about three-quarter of the mothers. Including parity would therefore have decreased sample size considerably. In an analysis within the reduced sample, there was no significant effect parity on BW.

Some strengths of this study are also noteworthy. The sample is relatively large. We do not know of another study that took so many risk factors into account analyzing their effect on triplet BW. This study is the first to describe triplet zygosity in the Netherlands based on individual zygosity measures instead of population based estimated zygosity distribution. We therefore could confirm the assumption that ART has inflated the Dutch TZ triplet population. Furthermore, this study is the first to investigate the effect of maternal smoking and alcohol consumption during pregnancy on triplet BW. In addition, although our sample is somewhat positively biased when comparing it to all triplets born in the Netherlands, it is a representative sample for the Dutch triplet population that is still alive one month after birth.

Conclusions

Longitudinal data collection on triplets is scarce. Data collection within the Netherlands Twin Register (NTR) is broad, including an important focus on behavior. The data collection in triplets that we are currently establishing is unique in its kind. With this dataset it is possible to study long term effects of low BW in triplets, both on physiologic and also on behavioral level. This study was limited to a description of the sex and zygosity distribution of the triplets and the effect of a number of BW characteristics. We found an effect of GA, sex, birth order, zygosity and maternal smoking on triplet birth weight, but found no effect of ART and maternal alcohol consumption. The combined effects implied that differences of 364 grams can be observed between MZ girl triplets of smoking mothers compared to TZ boy triplets of non-smoking mothers of the same GA. Furthermore, we found that MZ triplets resembled each other more than DZ triplets, indicating that, in addition to environmental factors, genetic factors contribute to triplet BW.

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