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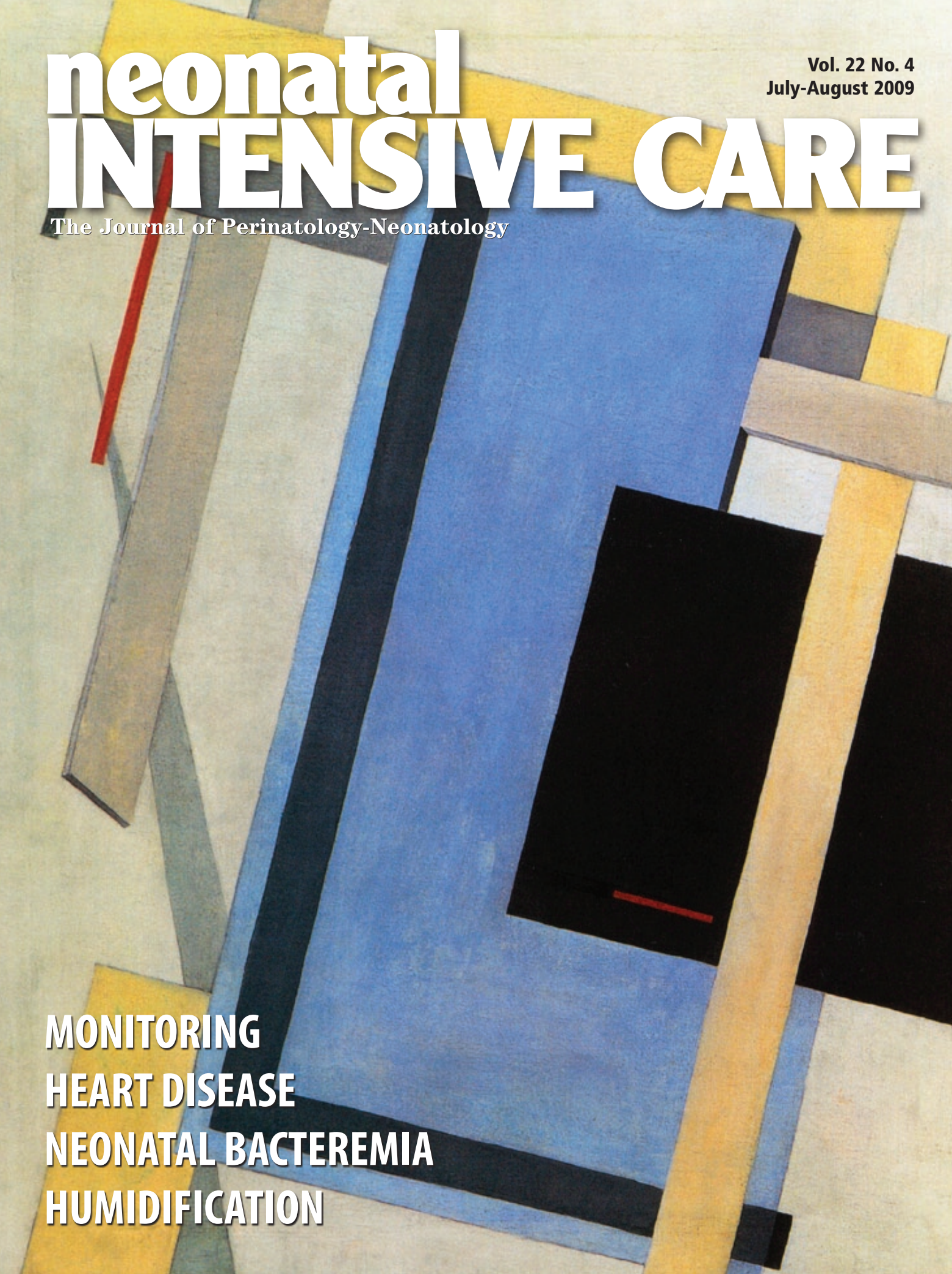
July-August 2009

neonatal INTENSIVE CARE

The Journal of Perinatology-Neonatology



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[1]MacLeod D, White W, Ikeda K, Newman M, Mathew J. Decreased Forebrain Cerebral Tissue Oxygen Saturation is Associated with Cognitive Decline after Cardiac Surgery. ANESTH ANALG 2009; 108(SCA Suppl); 1-104.
[2]Fischer G, Lin H, DiLuozzo G, Griepp R, Reich D. Decreased Cerebral Tissue Oxygen Saturation during Aortic Surgery Increases Risk of Post-Operative Complications. ANESTH ANALG 2009; 108(SCA Suppl); 1-104.
[3]MacLeod D, Ikeda K, Vacchiano C. Simultaneous Comparison of FORE-SIGHT and INVOS Cerebral Oximeters to Jugular Bulb and Arterial Co-Oximetry Measurements in Healthy Volunteers . ANESTH ANALG 2009; 108(SCA Suppl); 1-104.

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Editorial

Let's Think This Through

If the new administration has its way, information technology will soon put all medical records into an electronic database. Sounds like a swell idea, right? The government plans to spend $19 billion to accelerate the use of computerized medical records in doctors' offices. The New York Times recently noted, "Electronic patient records, when used wisely, can help curb costs and improve care… The administration has called for more than $40,000 spread over a few years for a physician who buys and uses electronic health records and puts them to "meaningful use." And that's the catch, that "meaningful use." Let's take a look at an alternate view. A letter writer to the Times noted: "I've been a physician for 11 years and worked in three healthcare systems. I've never worked in an office with paper charts, only electronic records. I've also been an administrator who has wrestled with how to share those records between offices. While the records may sound simple, they are preposterously complicated, with thousands of data points per chart… Before we embark on vastly expanding electronic records, let's decide how to use them well."

Anne Armstrong-Coben, writing in the NYT, says there's a whole other side to electronic records to be considered: She writes, "For 20 years, I practiced pediatric medicine with a 'paper chart.' I would sit with my young patients and their families, chart in my lap, making eye contact and listening to their stories. I could take patients' histories in the order they wanted to tell them or as I wanted to ask. I could draw pictures of birthmarks, rashes or injuries… We have all heard about the wonderful ways in which electronic medical records are supposed to transform our broken health care system. The benefits may be real, but we should not sacrifice too much for them. Doctors in every specialty struggle daily to figure out a way to keep the computer from interfering with what should be going on in the exam room — making that crucial connection between doctor and patient. I find myself apologizing often, as I stare at a series of questions and boxes to be clicked on the screen and try to adapt them to the patient sitting before me. I am forced to bring up questions in the order they appear, to ask the parents of a laughing 2-year-old if she is 'in pain.' The computer depersonalizes medicine. It ignores nuances that we do not measure but clearly influence care. In the past, I could pick up a chart and flip through it easily. Looking at a note, I could picture the visit and recall the story. Now a chart is a generic outline, screens filled with clicked boxes. Important points often get lost. I have half-joked with residents that they could type 'child has no head' in the middle of a computer record — and it might be missed. I have seen how choosing the wrong box can lead to the wrong drug being prescribed. So before we embrace the inevitable, there should be more discussion and study of electronic records, or at a minimum acknowledgment of the downside." It's been my own experience with electronic technology, that the law of unintended consequences is quickly made manifest. Let's be sure we know what we're getting into.

Les Plesko, Editor

For the full article from the New York Times, see the March 5 issue, "The Computer Will See You Now," by Anne Armstrong-Coben.

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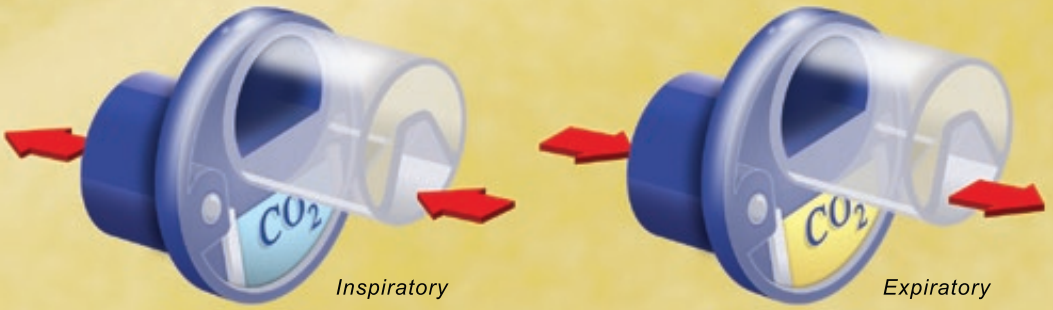

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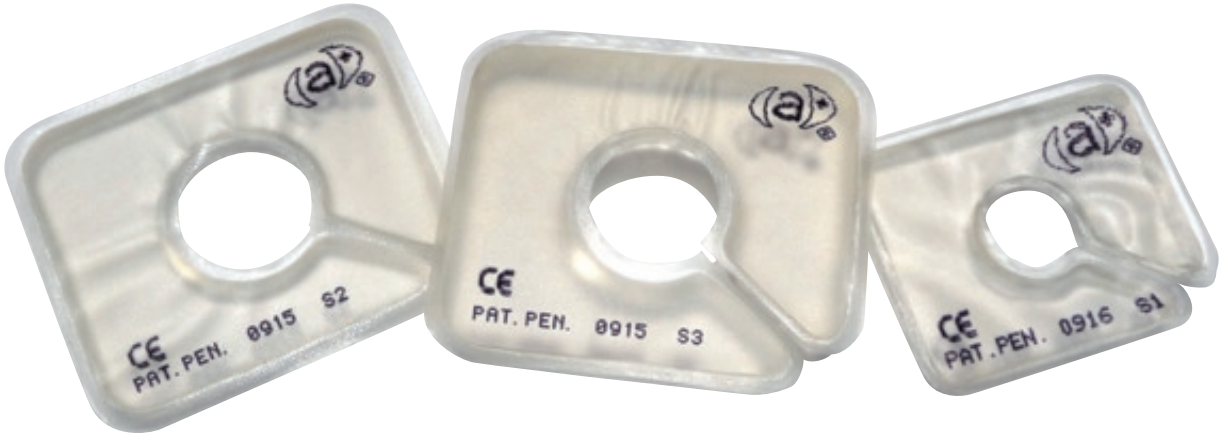

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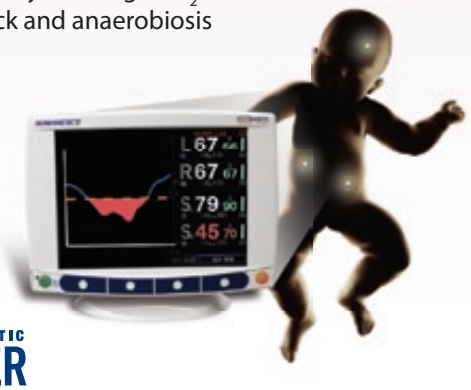

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News

☐ July-August 2009

UP AND DOWN

The National Vital Statistics Report Volume 57, Number 12, released recently, presented comprehensive data on US births in 2007. The report is based on 98.7% of 2007 births. The preliminary estimate of births in 2007 rose 1% to 4,317,119, the highest number ever registered for the US. The general fertility rate increased by 1% also, to 69.5 births per 1,000 women aged 15-44 years, the highest level since 1990. Increases occurred within all races and groups and for nearly all age groups. The birthrate for US teenagers aged 15-19 rose also by 1% to 42.5 births per 1,000. Birth rates increased for women in their 20s, 30s and 40s. All measures of childbearing by unmarried women rose to "historic levels" in 2007, with the number of births, birth rate and proportion of births to unmarried women increasing 3-5%. The c-section rate rose 2%, to 31.8%, marking the 11th year of increase and another record high for the US. The rate of preterm births (less than 37 weeks) decreased 1%, to 12.7%, with the decline predominately among infants born late preterm, at 34-36 weeks. The rate of low birthweight (less than 2,500 grams) also declined slightly, to 8.2%.

FRONT LINES

Nurses are the main source of support for NICU parents, according to a recent article in JOGNN, published by AWHONN. "Parenting in the Neonatal Intensive Care Unit," by Lisa M. Cleveland, RN, MN, CPNP, IBCLC, takes an in-depth look at 60 studies that focus on parents who have infants in the NICU, with the goal of uncovering the specific needs of these parents and what nurses can do to positively support them to establish their role as parents. According to the article, parents with an infant in the NICU have six main needs. These needs including: receiving accurate info and inclusion in their infant's care; the ability to watch over and protect their infants; the desire to be perceived positively by nursing staff, to receive specialized attention (especially dads), and to establish a therapeutic relationship with the nursing staff. To assist parents, the article says nurses can provide emotional support, empower parents, provide a welcoming environment, and give parents the opportunity to practice parenting skills. JOGNN, the Journal of Obstetric, Gynecologic and Neonatal Nursing, is a bimonthly peer-reviewed journal published by AWHONN, which has 23,000 members. Contact awhonn.org.

BALLOON RIDE

The Vancouver Sun recently reported that a team of doctors at two Toronto hospitals has completed Canada's first life-saving heart surgery on a fetus still inside its mother's womb. The experimental procedure was performed by doctors at Mount Sinai Hospital and the Hospital for Sick Children in an effort to widen the baby's aortic valve which had been severely narrowed. The fetus was 30 weeks old. The doctors, guided by ultrasound, inserted a needle through the mother's abdomen, into the uterus and precisely into its heart. The surgeons inflated a balloon into the heart valve and immediately saw the blood begin to flow. The heart was about the size of a grape. The surgery was also done with the mother wide-awake and the father by her side. Since the baby's birth, she has undergone two additional surgeries, from which doctors expect her to make a full recovery.

GO HOME

Research from the Netherlands, which has a high rate of home births, found no difference in death rates of either mothers or babies in 530,000 births. The research was carried out in the Netherlands after figures showed the country had one of the highest rates in Europe of babies dying during or just after birth, and it was suggested that home births could be a factor, as a third of Dutch women give birth at home. But a comparison of low-risk women who planned to give birth at home with those who planned to give birth in hospital with a midwife found no difference in death or serious illness among either baby or mother. A third of women who planned and started their labor at home ended up being transferred as complications arose, including for abnormal fetal heart rate, or if the mother required an epidural. The researchers noted the importance of both highly-trained midwives who knew when to refer a home birth to hospital as well as rapid transportation.

HAIR-RAISING

Half the baby shampoo tested by the Campaign for Safe Cosmetics contained formaldehyde and/or 1,4-dioxane. The chemicals, which are probable carcinogens, are byproducts of the manufacturing process and thus aren't listed on the label. Formaldehyde is a result of eventual chemical breakdown in the shampoo. The group tested 48 baby bath products, and 23 contained formaldehyde, 32 contained 1,4-dioxane; 17 had both. The Campaign said, "Our intention is not to alarm parents, but to inform parents that products that claim to be gentle and pure are contaminated with carcinogens, which is completely unnecessary."

STILL TOO POSHY?

Despite suggestions that the rising rate of c-sections for English moms is due to women being "too posh to push," a recent study of women's attitudes did not bear this out. Very few pregnant women opt for a planned cesarean section when thinking about how they wish to give birth, according to a study of 454 women in Liverpool, published this month in BJOG: An International Journal of Obstetrics and Gynaecology. Still, the c-section rate in England is rising. Times On Line reported that one in four babies in England are still being delivered by c-section. The rate of cesarean deliveries on the NHS increased slightly last year to 24.6% of deliveries, or 153,406. The WHO says that the rate should not exceed more than about one in eight births. The overall English birthrate is also continuing to rise, putting pressure on NHS services that midwives and doctors say are already overstretched, so to speak. There were nearly 650,000 deliveries in NHS hospitals in England in 2007-08, a rise of more than 20,000 births, 3.3% over the previous 12 months. The birthrate across Britain has risen by about 16% since 2001. Women are also leaving hospital more quickly after a cesarean, a trend blamed on a shortage of beds. The number of births that involved an instrumental delivery with forceps increased slightly

to 12.1%, or 75,253 of deliveries. More than a third of women had an epidural, up slightly from the previous year. The increasing number of hospital births may be a result of the rise in high-risk pregnancies because of rising levels of maternal obesity, teenage pregnancies and later maternal age, doctors said.

TELL US WHAT YOU *REALLY* THINK

Responding to a recent item on C-sections in the Times On Line, readers made the following comments: "It used to be that way in the USA, before women rebelled, because C-secs are very profitable. Doctors were shamed by the question: 'One in four by C-Sec? Is Mother Nature really that imperfect?' Before our first was born, we warned the docs: 'No rip-in! No rip-off!' Beautiful baby after 27 hrs!" Another mother wrote: "Another reason for the increase is lack of midwives on the wards. When you are short-staffed it is easier to strap a woman onto a monitor for hours and leave her laboring on her back than it is to help her labor actively (which helps avoid c-sections). More midwives are needed urgently." A contrarily-opinioned reader commented: "There should be no limit on C-sections. The reason why there is an increase is due to older mothers. I know of cases where hospitals put mother and baby at risk as they refused to give C-sections. After three days the baby's heart started to slow and suddenly it was an 'emergency' C-section."

TWICE OVER

Analysis of neonatal clinical trials with twin births by Shaffer et al, published on BioMed Central, reports on neonatal trial methodology for twin births. According to the abstract: In neonatal trials of pre-term or low-birth-weight infants, twins may represent 10-20% of the study sample. Mixed-effects models and generalized estimating equations are common approaches for handling correlated continuous or binary data. However, the operating characteristics of these methods for mixes of correlated and independent data are not well established. Simulation studies were conducted to compare mixed-effects models and generalized estimating equations to linear regression for continuous outcomes. Similarly, mixed-effects models and generalized estimating equations were compared to ordinary logistic regression for binary outcomes. The parameter of interest is the treatment effect in two-armed clinical trials. For continuous outcomes, while the coverage never fell below 0.93, and the type I error rate never exceeded 0.07 for any method, overall linear mixed-effects models performed well with respect to median bias, mean squared error, coverage, and median width. For binary outcomes, the coverage never fell below 0.90, and the type I error rate never exceeded 0.07 for any method. In these analyses, when randomization of twins was to the same treatment group or done independently, ordinary logistic regression performed best. When randomization of twins was to opposite treatment arms, a rare method of randomization in this setting, ordinary logistic regression still performed adequately. Overall, generalized linear mixed models showed the poorest coverage values. For continuous outcomes, using linear mixed-effects models for analysis is preferred. For binary outcomes, in this setting where the amount of related data is small, but non-negligible, ordinary logistic regression was recommended. To see the study, go to BioMed Central and type in the full title of the article ["Analysis of neonatal clinical trials with twin births." BMC Medical Research Methodology 2009.]

WORK IT OUT

A team from the Kansas City University of Medicine and Biosciences suggests exercise is linked to better fetal heart health and nervous system development. The study of 26 subjects used a non-invasive device to measure the magnetic fields produced by the electrical activity of maternal and fetal heart rates and fetal movements. The study showed that the babies of women who exercised had a more mature respiratory system, suggesting they would fare better after birth. There was no increased risk of miscarriage or premature labor linked to exercise.

DEFECTIVE?

Children born as a result of the fertility treatment may face a higher risk of birth defects. Scientists in Atlanta found IVF babies could be up to 30% more likely to suffer from certain health problems and genetic flaws. The study from the Centers for Disease Control and Prevention found IVF babies suffered from higher rates of conditions such as heart valve defects, cleft lip and palate, and digestive system abnormalities. According to a recent article by Gina Kolata in the New York Times, studies indicate that there may be some abnormal patterns of gene expression associated with IVF and a possible increase in rare genetic disorders that appear to be directly linked to those unusual gene expression patterns. The CDC has published a paper reporting that babies conceived with IVF have a slightly increased risk of the conditions noted above. The agency based its findings on a study that involved about 9,600 babies with birth defects and 4,800 babies without. Among the mothers of babies without birth defects, 1.1% had used IVF or related methods, compared with 2.4% of mothers of babies with birth defects. (There is a 3% percent chance that any given baby will have a birth defect.) Kolata noted, "Even though the risks appear to be small, researchers who are studying the molecular biology of embryos say they would like a better understanding of what happens, so they can improve the procedure and allow couples to make more informed decisions." In another study, which is now eight years old, researchers focused on Beckwith-Wiedemann syndrome, characterized by a 15% risk of childhood cancers of the kidney, liver or muscle. The syndrome was often caused by changes in the expression of a cluster of genes, and these changes were also found in colon and lung cancers. Children with the same gene alterations had a 50% risk of the childhood cancers. The researchers investigated the prevalence of IVF and related methods in the pregnancies that resulted in children with the syndrome. Their conclusion, and the conclusion from at least half a dozen other large studies, was that there were about 10 times more parents who had used IVF or related methods than would be expected. But why would growing embryos in petri dishes elicit changes in gene expression? Says Kolata, IVF scientists know that the composition of the broth affects how quickly embryos grow, and that embryos grow more slowly in the lab than in the body. The culture medium provides chemicals that can be used to add methyl groups to genes, and the presence, or absence, of the methyl groups can control whether genes are active or not. Such epigenetic changes not only cause rare disorders like Beckwith-Wiedemann syndrome but also are associated with low-birth-weight babies and an increased risk of a variety of cancers. This does not mean that growing embryos in petri dishes has such effects, but it does raise questions about what is known about the procedure. Researchers have also seen epigenetic changes in stem cells but aren't sure what they mean. The Society for Assisted Reproductive Technology discussed whether to ask IVF centers to report what media they were using to grow their embryos, but programs use multiple media, and often switch from one to another. Also, Kolata notes, following babies born

after IVF or intracytoplasmic sperm injection is not easy, and if problems emerge from epigenetic changes, they may not be apparent until adulthood or middle or old age. Reported by the BBC and the New York Times.

MAKE NO BONES

Enobia Pharma, an emerging biotech company focused on developing therapeutics for serious bone disorders, announced that the FDA granted Fast Track status to ENB-0040 for the treatment of hypophosphatasia (HPP). ENB-0040 is Enobia's enzyme replacement therapy (ERT) for HPP. The FDA noted, "preliminary clinical data have suggested that ENB-0040 has potential as a specific treatment for hypophosphatasia." HPP is severe in perinatal or infantile forms, with profound skeletal hypomineralization and respiratory compromise. ENB-0040 is a subcutaneous enzyme replacement therapy of tissue non-specific alkaline phosphatase fused to a patented bone targeting peptide.

DON'T BREATHE

Exposure to air pollution during early and late pregnancy may curb the normal growth of the developing fetus. Researchers based their findings on singleton births between 1999 and 2003 in New Jersey. During this period, 492,678 singleton babies were born in the state. Almost 336,000 births were included in the analysis. The researchers used information from birth certificates and hospital discharge records, including the mother's ethnicity, marital status, educational attainment, tobacco use during pregnancy, start of prenatal care, and residence at the time of the birth. Daily readings of air pollution from monitoring points around the state of New Jersey were retrieved from the EPA. Data from the monitoring point within 6 miles of the mothers' homes were used to calculate levels of exposure to average air pollution during each of the three trimesters of the pregnancy, to estimate the associated risk of fetal growth restriction. Researchers also looked at whether mothers with certain complications of pregnancy were more likely to have a restricted growth baby following increases in air pollution late in pregnancy, compared to mothers without these complications. Mothers of small and very small birth weight babies were more likely to be younger, less well educated, of African-American ethnicity, smokers, poorer, and single than mothers with normal birth weight babies, but levels of ambient air pollutants were linked to restricted fetal growth, even after taking account of these risk factors. The risk of a small birth weight baby rose significantly with each increase in particulate matter of 4 ug/m3 during the first and third trimesters of pregnancy. Similarly, the risk of a very small birth weight baby rose significantly with each 10 parts per billion increase in nitrogen dioxide, suggesting that restricted fetal growth may be linked to traffic pollution or living close to a major road. Exposure to particulate matter in late pregnancy was also associated with a two to fivefold greater risk of restricted fetal growth among mothers with separation of the placenta before birth and premature rupture of the membrane than in mothers without these complications.

BROKEN HEARTS

Reported in the New York Times, by Tara Parker: "Screening Babies for Broken Hearts." NYT guest columnist Darshak Sanghavi, MD of UMass wrote how researchers studying infant deaths over the past 16 years in California reported that hundreds of American infants die each year due to missed but treatable congenital heart defects. The quality of prenatal sonograms varies widely, he wrote, depending on the skill of the technician and the supervising doctor. Current guidelines supported by ACOG mandate only a limited four-chamber view of the heart. A Southwestern Medical School study reported that only a quarter of major heart defects are identified prenatally. As a result, pediatricians have a hard time telling if critical cardiac problems are present. Normally, doctors examining newborns suspect heart defects if they hear a murmur with a stethoscope, notice the child has a bluish color, or lacks a pulse in the lower extremities. But in 1999, British researchers found that half of serious heart defects were missed by routine exams after birth. If sent home, these newborns become seriously ill. Folic acid can prevent up to 50% of many heart defects, but only if taken for about two months prior to conception. Because most pregnancies are unplanned, the CDC recommends that all menstruating women should take a daily multivitamin.What's needed is a large-scale formal screening program, similar to mammography or colonoscopy to identify at-risk individuals. We already do this to identify newborns with certain hidden but deadly conditions like PKU and galactosemia. Recently, pulse oximetry has been indicated. Last year, Norwegian doctors published one of the largest clinical trials of this strategy, and checked half of all babies born in the country. Within a few hours of birth, pulse oximetry detected three-quarters of critical heart defects that had been previously missed. For every 2,000 newborns screened, roughly one with a critical heart defect might have been prevented from going home. The cost-benefit ratio compares favorably to current practices of newborn screening for PKU and hypothyroidism. In January, a Swedish study of 40,000 newborns showed that oximetry entirely eliminated death from missed critical cardiac defects. Of course, as with any screening, the technique may miss some defects and also involves some unnecessary, though benign, testing of normal children. But these false positive rates were low (only about one in 1,000 in the Swedish study) and triggered only about two instances of extra, noninvasive testing for every serious heart defect that was picked up. While the screening test is not done routinely in the United States, some hospitals have adopted it, mostly in Texas and Florida, where some small trials have been conducted.

WHAT'S A HUMAN?

The North Dakota Senate voted 29-16 recently to reject a bill that would have defined a human being as "any organism with the genome of homo sapiens," including a fertilized egg from the moment of conception, whether inside or outside the womb. The Associated Press reported that the measure created an intense lobbying campaign among abortion-rights supporters and opponents. Reproductive endocrinologists testified that it would create complications in the in vitro fertilization field. An opponent of the bill said the legislation would make it difficult for doctors to address medical complications if a pregnancy threatened a woman's life, since the fetus would have the same equal rights as the woman. The above is edited from a report published by nationalpartnership.org,

EYES AND WEIGHT

A simple way of establishing which preterm infants are at risk of developing the eye disease ROP is to follow their weight gain, according to a study from the Sahlgrenska Academy, University of Gothenburg, Sweden, which suggests that following weekly weight development might replace the need for considerably more expensive ophthalmological examinations. The researchers had previously identified another important link between preterm birth and vascular disease in the eye, the

protein IGF-1, which is strongly linked to the infant's weight gain. The researchers developed an assessment model known as WINROP (Weight IGF-1 Neonatal ROP), which is based on weekly measurements of the infant's weight and analyses of the serum levels of IGF-1. However, researchers decided to use only the surveillance model, and skipped the bloodwork. In a review of medical records, information on the weekly weights of 350 infants was entered into the model, and the outcome was compared with the ophthalmological examinations performed on them. All infants at risk were identified a few months before the ophthalmologist had seen signs of ROP requiring treatment. The method could therefore not just save money but also make it possible for infants with eye problems to be identified earlier.

HERE IT COMES!

The relationship between two different types of estrogen, estradiol (E2) and estriol (E3) and corticotrophin-releasing hormone may serve as the mechanism for signaling labor, according to a new study by researchers at John Hunter Hospital in Newcastle, Australia. When E2 and E3 are in roughly equal amounts there is no drive to labor, but the opposite holds true once one is in greater excess than the other. This study evaluated the ratio of E3 to E2 in 500 pregnant women and found that it went up rapidly as labor approached indicating that E3 could stimulate the onset of labor. A previous study showed that CRH in the placenta rises rapidly through pregnancy, peaking at the time of labor. CRH levels rise earlier in women who deliver prematurely and later in women who deliver late, forming a biological clock that regulates the length of pregnancy. Researchers also showed that CRH can act on the adrenal glands of the fetus to stimulate the production of a steroid hormone which the placenta uses to make E3. This study showed a strong relationship between CRH levels in the mother's blood in the weeks before birth and the levels of E3 supporting the view that CRH increases E3. As such, CRH was posited as the catalyst for the onset of labor, by driving steroid hormone production in the fetus, which then leads to an increase in E3 so that it exceeds E2. Researchers said it may be possible to delay or advance labor by varying the ratio of E3 to E2 by giving either E2 or E3 to the pregnant woman

SLOW LEARNERS

Infants born at 34 to 36 weeks' gestation were 36% more likely than full-term infants to have developmental delays in kindergarten, according to researchers at the University of Florida. About 70% of preterm births are considered to be in the late-preterm category. As such, researchers noted that doctors shouldn't push early deliveries and c-sections. For more, see the New York Times of March 30.

SIDS AND SMOKE

A recent study revealed that maternal smoking is associated with an impaired infant arousal process that may increase the risk for SIDS. The authors suggested that maternal smoking has replaced stomach sleeping as the greatest modifiable risk factor for SIDS. Researchers from the Ritchie Centre for Baby Health Research at Monash University in Melbourne, Australia showed that the progression from sub-cortical activation to cortical arousal was depressed in smoke-exposed infants, who had lower proportions of full cortical arousals from sleep and higher proportions of sub-cortical activations than infants born to non-smoking mothers. The study also indicated that there's a dose-dependent relationship between cortical activation proportions and levels of infant urinary cotinine, a nicotine metabolite. Cortical arousals were lowest in babies with higher levels of smoke exposure. The study involved 12 healthy, full-term infants born to mothers who smoked an average of 15 cigarettes per day. Their arousal responses during daytime sleep were monitored and compared with that of 13 healthy infants who were born to nonsmoking mothers.

THE WEAKER SEX

A Tel Aviv University study provided proof that a male baby comes with a bigger package of associated risks than his female counterparts. In a study of 66,000 births, researchers at the Sackler School of Medicine found that while girls were at a higher risk for restricted growth in utero and for breech presentation at birth, risks associated with boy fetuses were more abundant. Pregnancies with a male fetus were found to be more often complicated and to result in a premature rupture of the embryonic sac. Male fetuses which make it to term are more likely to suffer from excessive growth in the uterus, making delivery more difficult and leading to more cesarian sections. Researchers reiterated that boys are more vulnerable in utero, and that this vulnerability continues to exist throughout their lives. Men are known to have a shorter lifespan, are more susceptible to infections, and have less chance of withstanding disease than women. In short, men are the weaker sex.

INFLAMED

Low birth weight may increase inflammatory processes. If the source of infection or injury is not repressed, low-grade inflammation can persist and may promote the development of heart disease or diabetes. Babies born small for gestational age have weak immune systems, but at six years old have more white blood cells than babies born at a normal weight. White blood cells are cells of the immune system that defend the body against both infectious disease and foreign materials. These findings suggest that age might amplify the association between early growth and inflammatory processes. Researchers followed 5,619 children born in 1966 until they reached adulthood. As compared to children with normal weight in the first year of life, researchers observed that babies born relatively smaller and gained the least weight during infancy had a higher number of white blood cells, an indicator of inflammation, in adulthood.

BUMMED

Mothers of multiple births have 43% increased odds of having moderate to severe depressive symptoms nine months after giving birth compared to mothers of single-born children, according to researchers at the Johns Hopkins Bloomberg School of Public Health. Researchers examined the relationship between multiple births and maternal depressive symptoms and found that multiple births increased the odds of maternal depression, and that few mothers with depressive symptoms, regardless of the multiple births status, reported talking to a mental health specialist or a general medical provider. The findings revealed that 19% of mothers of multiples had moderate to severe depressive symptoms nine months after delivery, compared to 16% among mothers of singletons.

LESS WORK

According to the paper "Work of Breathing Using High-Flow Nasal Cannula in Preterm Infants, by Saslow, et al, which evaluated the use of HFT with a Vapotherm 2000i, HFT up to 5 lpm does not produce more airway pressure than CPAP set to 6 cm H_2O. In fact, these authors demonstrate that at 5 lpm, airway pressure was significantly less than with a CPAP of 6. The

study's objective was to compare WOB in premature neonates supported with HFNC and NCPAP. Eighteen preterm neonates <2.0 kg on HFNC or NCPAP support were studied in a random order. A ventilator was used to deliver 6 cm H_2O of NCPAP with nasal prongs. High-flow nasal cannula delivered with Vapotherm (VAPO) at 3, 4 and 5 l/min was used. Tidal ventilation was obtained using respiratory inductance plethysmography calibrated with face-mask pneumotachography. An esophageal balloon estimated pleural pressure from which changes in end distending pressure were calculated. Inspiratory, elastic and resistive WOB and respiratory parameters were calculated. No differences were found in the WOB for all settings. Changes in end distending pressure did not vary significantly over all device settings except VAPO at 5 l/min. In these preterm infants with mild respiratory illness, HFNC provided support comparable to NCPAP. [J Perinatol. 2006 Aug;26(8):476-80. Work of breathing using high-flow nasal cannula in preterm infants.]

WINNERS

BioMed Central recently announced its Research Awards for 2008. The biology award went to Basil Honegger, University of Zürich, who is studying Imp-L2 as it counteracts insulin. The medicine award went to Weiqi Yan and Guomin Xiao, Zhejiang University, who studied improved outcomes from the administration of progesterone for patients with acute severe traumatic brain injury. The case report of the year award went to Derek Rajakumar, University of Saskatchewan, who studied mycobacterium tuberculosis monoarthritis in a child. The editor of the year award went to Chris Arme, with the open access journal Parasites & Vectors. The Open Access Institute of the Year was The University of Nottingham, ranked in the UK's Top 10 and the World's Top 100 universities by the Shanghai Jiao Tong (SJTU) and Times Higher (THE) World University Rankings.

HYPO & HYPER

The New York Times reports: Thyroid problems can easily go undiagnosed, and their hazards have set off a debate over whether every woman who is pregnant or planning to be should have a blood test to check her thyroid. That test measures for TSH, which spurs the gland's hormone production. Most doctors' groups have not endorsed universal prenatal thyroid screening, citing uncertainties over whether it would yield health benefits justifying the expense of testing in roughly 6.4 million pregnancies each year and educating doctors to read results that are tricky to interpret. But the big unanswered question—and crux of the debate—is whether treatment would help women with subclinical hypothyroidism. For now, medical societies advise testing only high-risk women. The American Association of Clinical Endocrinologists endorsed routine TSH testing in all women considering pregnancy. But other organizations, including the American College of Obstetricians and Gynecologists, have said wide-scale screening is premature until more data prove that treating subclinical hypothyroidism would prevent adverse effects in women and their offspring. Studies suggest that T4-replacement therapy is protective. But few large clinical trials have rigorously tested this intervention in mildly thyroid-deficient women. So far, promising results have come from one major, well-designed Italian study that showed miscarriage and preterm delivery rates dropped sharply when thyroid hormone pills were given to pregnant women who tested positive for thyroid antibodies. Experts are now looking to the outcomes of two major clinical trials under way in Wales and the United States. Both aim to confirm the IQ effects and the ability to avert them by studying pregnant women with underactive thyroids who receive hormone therapy or no treatment. A study will track 1,170 expecting mothers, including women with subclinical hypothyroidism, and their children will undergo IQ testing at age 5. Results are expected in 2015. Two years ago, the Endocrine Society released recommendations for testing TSH in women at high risk for thyroid disorders, including anyone with symptoms of a goiter or sluggish thyroid, or a family history of thyroid problems, as well as those with Type 1 diabetes or autoimmune disease or previous miscarriage or premature delivery. But research since then has revealed flaws in that strategy. A British study found that such testing missed 30% of those with hypothyroidism and 69% with hyperthyroidism. Reported by Ingfei Chen, in the New York Times.

NEWS FEATURES

Ventilator Care Takes 2 Safety Hits

Paul Garbarini, MS, RRT, is Clinical Operations Manager, Hamilton Medical. This article is from Hamilton Medical's newsletter.

The ECRI Institute, which independently tests and studies medical devices, published their 2008 Top 10 Health Technology Hazards in a December 2008 news release. (The complete list of 10 is available for a limited time through ECRI at ECRI.org.) Considering the thousands of medical devices in various categories, it's revealing that ventilators are associated with two of the top ten device hazards. The #1 ranked device hazard was related to alarm hazards (ventilators were specifically cited). Some of the hazards were related to issues such as clinicians disabling or dialing out low minute volume or high pressure alarms; using systems with too many nuisance alarms and using alarms that are not easily positioned for viewing. Due to the wide variations in patients' underlying lung disease, breathing pattern, settings and/or modes, policies and let's say, human nature, alarms often are dialed out or simply standardized across all patients.

One of the solutions ventilator manufacturers have started to implement is various levels of alarms such as alerts, cautions, and warning alarms which are differentiated by both color and sound patterns.

I believe the next generation of alarms should include smart alarms such as those recently introduced for pulse oximeters. These systems provide alarms based on the degree of desaturation and the duration of the desaturation. The ventilator analogy might be to not sound a high level warning (eg high pressure alarm) for a patient coughing for only a few breaths, whereas a progressive rise in pressure over a longer period of time would warrant a high level warning.

While alarms for obvious hazards like patient disconnects and obstructed exhalation tubings will always be required, the need for alarms such as respiratory rate, high pressure, low minute volume, etc may have already been reduced with the introduction of closed loop ventilation systems. The purpose of traditional respiratory monitoring alarms is to alert the clinician of changes in patient status such as failing a wean trial due to tachypnea.

A high pressure alarm should alert the clinician to assess whether the alarm is a transient event versus, for example, the development of ARDS, which would warrant implementing a protective ventilatory pattern. Similarly, a patient that develops severe bronchospasm might develop tachypnea, elevated pressures and/or erratic exhaled volumes due to autopeep/air trapping and set off associated pressure, rate and/or volume alarms. The problem of course is that the alarm is occurring after the adverse event (hazard) has already occurred! Then again, this assumes that the alarm settings have been appropriately set for particular patient.

Perhaps the best solution would be to prevent the underlying reason for the alarm from occurring in the first place. A closed loop ventilation system will prevent some of these deteriorations in patient status. For example, a knowledge based closed loop system such as SmartCare follows a set of rules to wean pressure support during a wean trial. So if the tidal volume is too small, pressure support will titrate up to prevent tachypnea. Hamilton's Adaptive Support Ventilation (ASV) is a closed loop system that targets the optimal breathing pattern for a given patient's lung mechanics and size. If pressures start increasing due to development of ARDS, ASV automatically decreases tidal volume and increases rate to protect the patient from Ventilator Induced Lung Injury as the clinician would do by manually titrating settings as in ARDSnetwork protocol. ASV creates a safety window such that the system cannot target too high a volume or pressure to prevent volutrauma, too low a tidal volume to avoid deadspace and/or too high a rate to prevent autopeep.

I'd call these systems pre-emptive and pro-active in that they intervene in real time to prevent the hazard from occurring in the first place. (Addressing the issue of alarm visibility, the Hamilton G5 ventilator features a large alarm light bar that is visible from 360 degrees.)

The #7 ranked health device hazard was displays that are misleading, such as infusion pump displays that are misinterpreted and led the user to program the wrong medication dose. Here again ventilators are culpable. Typical ventilator displays show a gaggle of numeric monitoring data. The problem is that it's difficult for the clinician to easily be aware of what monitored data is out of range or abnormal. For example, how many clinicians know what the normal airway resistance range should be for a 55kg ideal body weight female on a ventilator or what a red flag value should be? Yet this awareness may be critical to know as it may be the cause of weaning failure. Monitored data is not presented in a such a way as to allow the clinician to discern the degree of abnormality or with any point of reference. Certainly the display of waveforms is useful but an even higher skill level is required to interpret pressure, volume and flow waveforms.

IT Marches On

Business Week recently reported on Kaiser Permanente's paperless medical record-keeping system. The excerpt below is from Business Week, April 7, "How Kaiser Permanente Went Paperless," by Rachel King, a San Francisco-based writer for BusinessWeek.com.

President Barack Obama plans to spend $17.2 billion to induce care providers to maintain patient records electronically, scrapping the current paper-based system. The Obama Administration wants electronic health records for every American by 2014.

Kaiser Permanente's medical clinics and two-thirds of its hospitals operate in a paperless environment and the rest are scheduled to be completely digitized by next year. Across the system, about 14,000 physicians access electronic medical records for 8.7 million patients in nine states and the District of Columbia.

Early efforts began more than 40 years ago. Kaiser has spent $4 billion and encountered disgruntled doctors, system outages, and a temporary decrease in productivity as physicians got accustomed to the new system. Industry experts say the upgrade has resulted in a higher quality of care in some cases. A 2002 report indicated that in Northern California, Kaiser Permanente had reduced death from heart disease so significantly among the region's then-3 million members that it no longer was the leading cause of death in that population. The report gave partial credit to Kaiser's databases, reports, and tracking and reminder systems.

As much as 30% of healthcare spending goes to ineffective or redundant care, according to studies that say digital health records can improve care by reducing the incidence of medical errors and eliminating duplicative procedures. For instance, electronically stored results of an MRI or CT scan can be more readily accessible to a wider range of care providers. As records are integrated with a pharmacy, a doctor or nurse can tell whether a patient hasn't filled a prescription. How much these efforts reduce overall costs is another matter. Electronic medical records reduce waste, but patients who live longer may ultimately end up consuming greater healthcare resources. "We like what we get for the money but we're not going to save any money," a Kaiser physician has noted. "There is no hard evidence that if you invest $20 billion, you'll get back $200 billion."

As a so-called integrated health system, Kaiser Permanente is different from other providers not only because it owns the hospitals, pharmacies, and labs but also because the physicians in the Permanente Medical Groups only see patients insured by Kaiser. Unlike most physicians, who are paid by the office visit or procedure, Kaiser doctors are paid salaries. This is an important distinction because Kaiser Permanente as an organization bore the costs of implementing the system and has the power to mandate that doctors use it.

At NorthShore University Health System, near Chicago, the situation is more typical of hospitals that work with independent doctors. In 2003 and 2004, NorthShore implemented electronic medical records at three hospitals and 65 medical group offices. Over the past five years, the organization has tried to encourage independent physicians to adopt it, offering 50% discounts on the Epic software. Still, industry experts say it can easily cost $50,000 or more to get a small office up and running. So far, 15 independent offices have installed the software. Today about 60% of the patients who come into the emergency department at NorthShore have a full electronic record, with medications and allergies listed, all of which helps increase patient safety. The first-year cost of installing e-health records for a three-doctor practice is somewhere around $70,000 to $80,000 per doctor. The benefits of digitizing health records are largely realized by entities other than the doctor, including the patient, the hospital,

the health plan, and the pharmacy. In fact, if waste does come out of the system, physicians can expect fewer patient visits in the near term. "Explain to me again why the doctor down the street wants to spend $80,000 to put in a system so that Walgreens can save money," one source said.

CIOs at a number of hospitals say that getting doctors to change how they work is one of the biggest hurdles. When this software is first introduced at a location, Kaiser typically cuts doctor patient loads by 50%. Most doctors bounce back to full volume in about two weeks. Inconveniences aside, most doctors don't want to go back to a paper-based system once the new approach is in place, Kaiser says.

PRODUCTS

NICU SUCCESS

Vapotherm's hospital newsletter recently spotlighted the UMASS Memorial Medical Center's Newborn Intensive Care Unit. Located in Worcester, MA, it is the region's only Level III NICU for high-risk neonatal care. The department has earned benchmark status for its encouragement of family participation in newborn care, making it a model for other hospital NICUs throughout the world. The NICU has 43 beds, including 27 intensive care beds in three pods designed for maximum privacy and 16 beds in a Continuing Care Nursery which eases the transition to home as the baby's health improves. The NICU initially purchased four Vapotherm units, which quickly became so popular, according to hospital staff, that nurses were constantly searching for available units for their patients. The NICU respiratory therapists and nurses quickly experienced excellent clinical outcomes as well as strong support from staff members and families. Recently, the NICU migrated to Vapotherm's new device, Precision Flow. It currently has 10 units and has treated 270 babies, totaling 2,300 days of care with Vapotherm technology. When the first Vapotherm device was nearing the end of its evaluation period, it was still supporting a patient, who was recovering and doing well. The company's clinical products division had expected to retrieve the device, but the patient was recovering and the company simply didn't want to put him back on mechanical ventilation. When the mother of the patient heard the conversation between them about the status of the device, she said, "I overheard your conversation and I am here to write a check to purchase the unit and donate it to the NICU." Contact vtherm.com.

LITTLE HELPER

Mercury Medical's new Neo-StatCO_2<Kg is the first CO_2 detector for babies below 1 kg. While Mercury's Mini StatCO_2 detector reliably performs on patients between 1-15 kgs, the new Neo-StatCO_2<Kg is the only CO_2 detector indicated for infants below 1 kg. Neo-StatCO_2<Kg is designed for use on infants between 0.25 – 2 kgs. The new Neo-StatCO_2<Kg detects CO_2 at 1 ml tidal volume and up to 100 breaths per minute. It offers reliable 24 hour continuous performance in up to 100% humidity. and detects CO_2 with a vivid breath-to-breath color change from blue to yellow. Small and compact, it weighs only 5 grams nominal, readily available for added efficiency. Contact (800) 237-6418, mercurymed.com.

RAPID READ

Darren Braude, MD, a noted airway expert and educator and co-director of the Airway911 program at the University of New Mexico, has recently released the second edition of Rapid Sequence Intubation and Rapid Sequence Airway, An Airway911 Guide. This remains the only book focused exclusively on RSI. All aspects of RSI are covered in an evidence-based fashion including: Basic Principles, Pharmacology, The Difficult and Missed Airway, The Multiple Attempts Algorithm, Pediatric Considerations, The 10 Ps, Legal Issues, Documentation and Quality Assurance. The book is written in a unique, easy-to-read conversational style. The 192 page text is supplemented with over 100 color photos and illustrations, tables and case scenarios, as well as color-coding to highlight key points, pitfalls and evidence-based material. This is a great introduction to RSI for RT students and a great review of the latest thinking and evidence for the experienced practitioner. The book may be purchased on Amazon or through www.airway911.com for $50.

TUBULAR

Discovery Labs presented a pharmacoeconomic analysis from its SELECT and STAR Phase 3 clinical trials for Surfaxin in preemies at the 2009 International Congress on Clinical Pharmacy. The analysis showed that in-hospital costs are higher for infants who require reintubation after surfactant administration and successful extubation when compared with infants who don't require reintubation. The presentation reaffirmed data demonstrating that infants treated with Surfaxin in the above trials required less reintubation compared with infants treated with animal-derived surfactants. The analysis was conducted on 1,546 infants treated with Surfaxin, Exosurf, Survanta, or Curosurf. After surfactant treatment, the infants either remained extubated through 36 weeks or required reintubation. Infants who were reintubated required significantly more days on mechanical ventilation and experienced longer NICU stays than un-reintubated infants. Infants who required reintubation were estimated to increase hospital costs by more than $33,000 per child. Previously presented results showed that successfully extubated patients who didn't require reintubation experienced low mortality rates across all treatment groups, while reintubated babies showed higher rates. Infants treated with Surfaxin had significantly lower reintubation rates compared with animal-derived surfactants. At the current time, Surfaxin is an investigational product. Contact discoverylabs.com.

LABELED

Somanetics Corporation announced a new 510(k) clearance from the FDA to expand the labeling for its INVOS Cerebral/Somatic Oximeter. The new labeling allows a claim of improved patient outcomes after surgery when the INVOS System is used to manage therapies in patients above 2.5 kilograms at risk for reduced or absent blood flow. Additionally, its indications for use now reflect the INVOS System's ability to generate accurate real-time measurements of blood oxygen saturation (sometimes referred to as "absolute") in this same patient population, in addition to its previous clearance as a trend monitor in any individual. These changes make the INVOS System the only commercially-available cerebral/somatic oximeter backed by an improved patient outcomes claim, and the only cerebral/somatic system cleared for use on neonates less than 2.5 kg. The INVOS (In Vivo Optical Spectroscopy) Cerebral/Somatic Oximeter noninvasively monitors site-specific blood oxygen levels. The system uses near-infrared light to noninvasively provide site-specific perfusion data on tissues beneath the sensors. The labeling also removed "not demonstrated in disease states" from the indication for patients weighing greater than 2.5 kg, and

includes additional 510(k) language that states: "In neonates, infants and children, cerebral and somatic rSO_2 provide noninvasive indications of oxygen changes in the cerebral and peripheral circulatory systems and may provide an early indication of oxygen deficits associated with impending shock states and anaerobiosis." Contact somanetics.com.

OUTSOURCING

Australia-based clinical research company Novotech announced it had entered into a strategic venture with ETI Klinical Pvt Ltd, part of the Karle Group of companies, a $600 million Indian multinational. The joint venture designed to service the growing demand for global clinical research in the region will operate across India and offer full clinical and data management services. The two companies have extensive experience managing FDA clinical research and will collaborate to service both regional and international pharma and biotech firms. Therapeutic areas include oncology, gastroenterology, urology, nephrology, ophthalmology, cardiology, diabetology, dermatology, orthopedics, postoperative pain, neurology, otorhinolaryngology, infectious diseases, respiratory diseases, endocrinology, psychiatry, geriatrics, hematology, metabolic disorders devices and vaccines. The joint venture data management services include Oracle Clinical and SAS, and Novotech's Clintrial. Contact novotech-cro.com

HEY BABY

Parents can have a tremendous impact on their baby's ability to reach its full learning potential by using techniques that stimulate the brain through everyday interactions and strategic play. With this in mind, respected occupational therapist Judy Kang announces the launch of Spotlight Baby. Kang is currently working on a book that will provide parents with strategies to bring out their babies' full potentials. The book will be supplemented by workshops and an interactive DVD that promotes gross motor skills and cognitive skills. Spotlight Baby offers parents eco-friendly products made from naturally soft, organic, hypoallergenic, sustainable and non-toxic bamboo fibers. The products include Bamboo Buddy ultra-soft plush toys and the Squeez-Ease, an alternative to no-scratch mitts that also helps promote sensory development. Contact spotlight-baby.com.

NEW DIMENSIONS

Siemens Healthcare showcased its latest ultrasound solutions at the recent ACOG conference, featuring knowledge-based workflow and 4D applications that increase diagnostic confidence and improve clinical workflow. One of the highlights includes syngo Auto OB measurements, which are an advanced clinical tool that automates routine biometry measurements of the fetus. Measurements include BPD, HC, AC, FL, HL, and CRL. The application also addresses the challenges related to user-dependence and variability, as well as consistency and reproducibility in fetal biometry. syngo Auto OB measurements are available exclusively on Siemens' premium performance ACUSON S2000 and the ACUSON X300 PE ultrasound systems. The Siemens workflow solutions for ob/gyn encompass sophisticated applications that were migrated from the high-end performance S Class into the X Class product series. To complete the solution it offers Advanced fourSight volume imaging technology, providing complete 3D/4D capabilities. Specially dedicated for use on the ACUSON S2000 system, Siemens will also offer Fetal Heart STIC (Spatio-Temporal Image Correlation). This application captures data over multiple heart cycles to create a 3D fetal heart volume. Contact siemens.com/healthcare.

GIVE 'EM A HAND

The PresHand System is a bereavement tool for presenting the deceased baby to the mom and family, and a manner of handling an infant after it has died. The baby is brought in to the family in a rattan baby basket, instead of an isolette. The body lies on a soft coverlet that lines the PresHand Insert. Once in the staff work area, after the family has finished visiting with the infant, the baby is enfolded and secured. The discreet transporting of the baby throughout the facility, even through public areas, can be accomplished without stress and anxiety for the staff person, and the baby is still being treated with dignity and respect. The inserts will store (and retain fluids) for up to about three months. They are constructed of eco-friendly paper and are stackable and disposable. An ID label identifies each infant. Contact Memories Unlimited, memoriesunlimited.com.

SPOTLIGHT ON MONITORING

NUMBER ONE

Cardinal Health NeuroCare's NicoletOne Monitor, the ICU Brain Monitor for Neonates, provides neonatal brain monitoring capabilities in a form and format that fits the unique challenges of the NICU. Traditionally difficult to monitor, brain injury is a serious and constant threat to the newborn. Neonatologists now require more knowledge about the newborn's brain function to achieve early diagnosis and a greater understanding of required neonatal care. Neurodevelopmental disabilities and clinically silent seizures are estimated to affect more than 16% of the NICU patient population. This is a higher rate than in any other age group – a majority occurring in the first week. EEG is the only way to confirm seizure activity. The challenging clinical conditions the NicoletOne Monitor enables NICU staff to address include: preterm babies and/or low Apgar score and treatment; asphyxia; intubated infants; rhythmic movements, pedaling, chewing or ocular movements that might indicate subtle seizures; epileptic diagnosis; sepsis; and hypothermia. The NicoletOne Monitor allows for better evaluation of cerebral function, faster time to treatment and better prognostic information which results in quality care for the NICU patient. Visit cardinalhealth.com/viasys.

SOMANETICS STUDIES

Somanetics Corporation announced that its INVOS System was featured in 25 posters and presentations at the recent Pediatric Academic Societies (PAS) annual conference held in Baltimore.The studies focused on early applications of the technology in the NICU, including investigations of how cerebral/somatic blood oxygen data may correlate to severe conditions that are traditionally difficult to diagnose, such as necrotizing enterocolitis and patent ductus arteriosis, as well as to the need for blood transfusions. One disease elusive to detect is necrotizing enterocolitis (NEC). When NEC is suspected, one standard response is to stop feedings so that the affected gut is not taxed. To better confirm which patients should not be fed, investigators are studying whether cerebral/somatic oximetry values have a correlation to feeding intolerance and the eventual development of NEC. Six PAS studies explored the technology's role in caring for neonates with patent ductus arteriosus (PDA). Studies are exploring how cerebral/somatic oximetry via the INVOS System may potentially be used to help detect oxygen deficits indicative of PDAs and to help determine whether surgical or drug intervention is required. Another study examined four drugs, commonly used in the NICU to manage

a range of severe conditions, and their effect on cerebral and somatic (eg, abdomen, kidney area, muscle) regional oxygen saturation (rSO_2). The INVOS System showed that each drug produced distinct medication-specific changes to rSO_2, and that this pattern was also tied to dosage.The INVOS (In Vivo Optical Spectroscopy) Cerebral/Somatic Oximeter noninvasively monitors site-specific blood oxygen levels in patients at risk for restricted or no blood flow. It helps hospital critical care teams detect and correct blood oxygen deficiencies that can cause brain and vital organ area damage. Sensors simply adhere to the skin like a Band Aid. In infants and neonates the most commonly monitored areas are the brain, abdomen and kidney area. Contact somanetics.com.

A REAL GEM

GEM Premier 4000 from Instrumentation Laboratory is the revolutionary analyzer (BG, Electrolytes, Metabolites, Glu, Lac, Hct, tHb, O2Hb, COHb, HHb, MetHb, sO_2, BUN*, Creat*, Total Bili*, HCO3* [*in development]) with integrated CO-Oximetry that quickly provides consistent, accurate, lab-quality results throughout the hospital. Easy-to-use touch-screen displays make it simple to select and customize parameters. Self-contained cartridges incorporate all components for patient testing and are maintenance-free. iQM automates quality control and continuously detects, corrects and documents to assure quality results and compliance, 24/7, regardless of operator or testing location. GEMweb Plus software enables remote access to any networked analyzer for real-time status updates and supervision of remote locations. Contact ilww.com.

FAMILY-CENTERED

As the NICU continues to focus on ways to promote family-centered care, you want technology that gives vital information where and when you need it. GE Healthcare monitoring products offer the following features: Access to accurate, reliable patient data virtually anywhere, anytime; Remote viewing and near-instantaneous alarm management; Seamless interface to communication devices; Advanced data analyses and information management. Whether you have a traditional pod configuration, an all single-family room design, or are somewhere in between, GE Healthcare has neonatal monitoring solutions to help simplify and improve workflow. Contact gehealthcare.com.

MULTI-LEVEL

Spacelabs Healthcare is committed to providing monitoring and measurement of neonates, allowing clinicians to concentrate on managing vulnerable patients, not monitors. Spacelabs monitors address every level of neonatal care, with sophisticated alarm management and remote viewing/controlling between monitors. The outside is specifically designed to support a comforting environment for baby and family. ICS G2 brings almost real-time surveillance of patient data and advanced review options to any PC on the hospital network. USCOM, a totally non-invasive cardiac output monitor, measures the hemodynamic condition of neonates as small as 500 grams, presenting vital information toward treatment of sepsis and other critical conditions. Contact spacelabs.com.

NO TRAUMA

Covidien offers prevention of adhesive-related skin trauma in micro-preemies and neonates with its Nellcor OxiMax SoftCare nonadhesive pulse oximetry sensors. Sterile, single-patient-use SoftCare sensors are made of a soft, pliable foam material that wraps around the infant's foot and fastens with Velcro instead of adhesive tape. Unlike many reusable sensors, SoftCare nonadhesive sensors provide a secure, comfortable "second-skin" fit suitable for long-term monitoring. Brighter, high-efficiency optics enhance signal quality, promoting accurate, reliable SpO_2 readings even with weak pulses or darkly pigmented skin. SoftCare nonadhesive sensors work exclusively with Nellcor OxiMax pulse oximeters and OxiMax-enabled patient monitors. Covidien offers SoftCare sensors for preterm, neonate and adult patients. Contact covidien.com.

TRY A LITTLE TENDERNESS

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Epidemiology of Neonatal Bacteremia in a South Bronx Hospital

Deepthi Alapati, MD; Dinabel Peralta-Reich, MD; Ginaida Cirilo, MD; Benamanahalli K. Rajegowda, MD; Robert J. Leggiadro, MD

Abstract

Background: Bacteremia in neonates increases risk for morbidity and mortality. The objective of this study was to evaluate the incidence of neonatal bacteremia and identify any trends in an inner-city teaching hospital in the South Bronx.

Methods: Medical records of neonates age <28 days with positive blood and/or cerebrospinal fluid cultures admitted to nurseries (normal newborn and intensive care), pediatric inpatient and intensive care units between Jan 2000 and Dec 2006 were reviewed retrospectively using data obtained from logbooks and medical record charts.

Results: 136 (0.75%) positive blood cultures were identified, out of 18,307 births. 72 (53%) of 136 were considered contaminants and the remaining 64 (47%) represented true bacteremia. The combined incidence of early and late bacteremia was 3.4 per 1000 live births. Our study showed an early onset group B streptococcus bacteremia incidence of 0.76 per 1000 live births. Nearly half (46%) of early onset bacteremia was due to non-GBS organisms. 84% of late onset bacteremia occurred in low birth weight premature infants who required invasive procedures and prolonged hospital stay. These infections were caused by commensal species.

Conclusions: Bacteremia due to GBS in our population is 2-3 times higher than nationally reported rates. Racial differences continue to exist. The population served by our hospital is primarily Hispanic and Black of low socioeconomic status. Close monitoring of maternal infection and treatment, strict hand washing, aseptic precautions for all invasive procedures and avoidance of overcrowding are essential preventive measures. Continued surveillance is warranted to assist in strategy formulation to decrease morbidity and mortality.

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Introduction

Newborns have increased risk of bacteremia, which varies with weight and gestational age. Important risk factors include: maternal infections, prematurity, Black or Hispanic race, invasive procedures, indwelling lines, prolonged hospital stay, inappropriate antibiotic use, improper hand washing, and overcrowding. Bacteremia in newborns is associated with signs and symptoms of clinical sepsis and/or meningitis. However, symptomatology can be subtle and laboratory tests are required for diagnosis. Blood culture remains the gold standard test for diagnosis. Neonatal bacteremia is divided into two distinct groups based on presentation. Early-onset sepsis (EOS) is described as infection occurring within the first seventy two hours of life as per the NICHD network [11,12] and less than seven days of life as per CDC and AAP.[1,2,4] In our study we have used the definition of less than seventy-two hours. These are perinatally acquired infections from mother-fetus-infant through vertical transmission. Most of the organisms implicated in early-onset infection are due to group B streptococcal infections (GBS). The majority manifest with symptoms within 24 hours.[1,2] Late-onset sepsis (LOS) is horizontally transmitted and manifest as focal infections, including meningitis. Such infection may occur during hospitalization or may be acquired from the community after the infant is discharged home.

Trends are changing in the epidemiology of neonatal bacteremia. Studies have shown a decline in bacteremia caused by group B streptococcus following the implementation of intrapartum chemoprophylaxis guidelines.[5,8] Additionally, other microorganisms have been responsible for this type of infection and its consequences.[11] In addition, with increasing survival of extremely low birth weight preterm infants, late-onset infection is a challenging complication with some studies showing that the incidence of late-onset bacteremia is increasing.[3,12] Racial differences have been identified in the incidence as well as mortality caused by certain bacteria in neonates.[5] The objective of this study was to evaluate the incidence of bacteremia and identify any trends in an urban hospital in the South Bronx.

Materials and Methods

This is a retrospective, epidemiological and descriptive study. We reviewed medical records of neonates with positive blood and/or cerebrospinal fluid cultures, admitted to the normal newborn

nursery and NICU during the seven-year period from January 2000 to December 2006 to Lincoln Medical and Mental Health Center, a 347 bed community teaching municipal hospital serving the South Bronx. Our patient population is approximately 70% Hispanic, 20% Black and 10% others. We examined and abstracted data reflecting maternal risk of infection, delivery characteristics, gestational age, birth weight, time of onset of infection and its clinical features, blood culture reports, procedures and management performed during inpatient stay and the outcome. The data was obtained from nursery logbooks, medical record charts, and infection control and bacteriology lab. Only neonates who were born and admitted in our hospital were included. Those neonates who were discharged home and later readmitted for possible sepsis were not included.

Positive blood cultures were considered contaminants if they fulfilled the following criteria 1. infant's clinical status as documented in the medical record, 2. negative repeat cultures within 24 hrs, 3. normal complete blood counts, 4. type of microorganism and 5. no antibiotics were given. Contaminants will be discussed in detail under the discussion section.

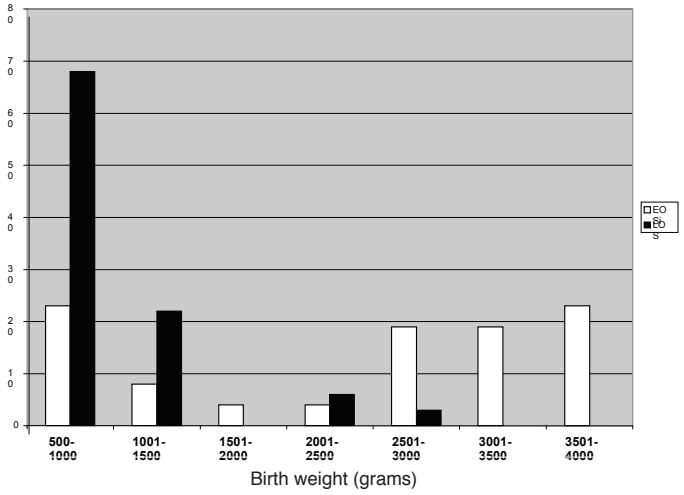
Results

18,307 neonates were born during the study period. A total of 79 positive blood cultures were identified. Of these, 20 (25%) were considered as contaminants. Of the remaining 59 cases of bacteremia, 24 (41%) were early onset and 35 (59%) were late onset. The overall incidence of bacteremia in our population was 3.2 per 1000 live births: early onset was 1.3 per 1000 live births and late onset 1.9 per 1000 live births.

The total hospital neonatal unit mortality rate during the study period was 3.9 per 1000 live births. Neonatal mortality due to sepsis was 0.5 per 1000 live births. Early onset bacteremia related mortality was 0.27 per 1000 live births and late onset bacteremia related mortality was 0.27 per 1000 live births. The cause of death was multifactorial as shown in table 2.

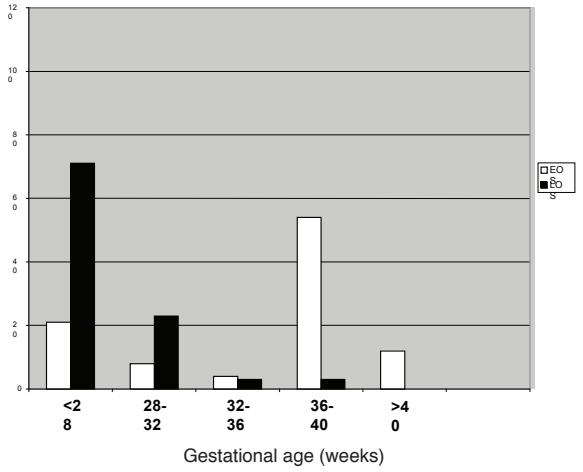
Our study showed an early onset GBS-bacteremia incidence of 0.76 per 1000 live births. Nearly half (42%) of early onset bacteremia was due to non-GBS organisms, predominantly E coli. Late onset bacteremia was observed particularly in very low birth weight premature babies (94%) who required invasive procedures and prolonged hospital stay (figure 1 and 2). Commensal organisms were responsible for 62% of the hospital acquired late-onset disease as shown in table 1, predominantly coagulase negative staphylococcus and candida.

Figure 1. Correlation of early-onset vs late-onset neonatal bacteremia with birth weight



EOS: percentage of early onset bacteremia
LOS: percentage of late onset bacteremia

Figure 2. Correlation of early-onset vs late-onset neonatal bacteremia with gestational age



EOS: percentage of early onset bacteremia
LOS: percentage of late onset bacteremia

Table 1. Microbiology of non-GBS organisms causing early-onset vs late-onset bacteremia.

NON GBS ORGANISMS	EOS N=10	LOS N=35	TOTAL N=45
E.coli	5	3	8
C.albicans		8	8
S.epidermidis		8	8
K.pneumoniae	1	4	5
E.faecalis		6	6
S.aureus	1	4	5
S.marcescens		1	1
S.pneumoniae	1		1
H.influenzae	1		1
E.cloacae	1		1
P.aeruginosa		1	1

Discussion

The maternal genital tract is a common source of bacterial pathogens that cause EOS. For many years, group B streptococcus (GBS) was the leading organism in early-onset sepsis.[3,4] In 1996, after several clinical trials and intensive research, the American College of Obstetricians and Gynecologists (ACOG), the Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics (AAP) issued guidelines for risk-based approach or culture-based screening and intrapartum antibiotic prophylaxis as prevention of perinatal GBS invasive infection.[4,5] As a result of the implementation of chemoprophylaxis guidelines, a significant decrease of over 70% was observed in the incidence of EOS due to GBS infection, thus reducing GBS sepsis-related mortality rates.[7] In 2002, these strategies were modified to broaden culture-based screening methods and management algorithms, emphasizing chemoprophylaxis regimens.[4]

Table 2. Neonatal Bacteremia and Mortality

S.No	Gestational age (weeks)	Birth weight (g)	Problems	Organism	Day of onset of infection	Day of death
1.	23	526	Severe RDS	Candida albicans	16	21
2.	23	554	Severe RDS	Candida albicans	11	15
3.	24	550	RDS	Candida albicans	13	24
4.	24	627	NEC	Enterobacter cloacae	1	9
5.	24	643	RDS, Severe hypovolemia due to placental abruption	E.coli	1	1
6.	24	774	Staphylococcal scalded skin syndrome, septic shock	MSSA	13	17
7.	25	680	RDS	Pseudomonas	6	8
8.	27	1210	RDS vs pneumonia	GBS	1	10
9.	32	14480	RDS vs pneumonia	GBS	1	1
10.	40	3175	Pneumonia	GBS	1	2

In our study, the combined incidence of early and late onset bacteremia was 3.2 per 1000 live births of which the incidence of early onset GBS disease was 0.76 per 1000 live births. Though this seems to be greater than that determined by the Active Bacterial Core (ABC) Surveillance system, United States, 2004 (0.34 per 1000 live births),[5] it is noteworthy to add that in the same study significant racial differences were identified.

The rates per 1000 live births for early onset GBS disease were 0.73 for black infants and non-white infants and 0.2 for white infants. Between 2003 and 2005, a steady decrease in the incidence of early-onset GBS disease among white infants was reported, but there was a 70% increase among the black infants. This disparity in the incidence of early onset sepsis between black and white races is thought to be due to high maternal colonization among blacks, higher incidence of preterm births, a risk factor for infection and poor prenatal care that decreases the opportunity for universal GBS screening between 35-37 weeks.[15] Moreover, nearly a third of the patients who deliver in our hospital have their prenatal care in other prenatal clinics where documentation of adequate GBS screening is not available. Our higher incidence can be explained by predominance of blacks and Hispanics in our population. In our study, 57% of early onset GBS bacteremia occurred among Hispanics, 35% among blacks and 7% Asian population. Although Healthy People 2010 objectives have been achieved for early-onset infection, the fact that racial differences exist is disturbing.[5] In a population like ours, one should look into measures for overcoming the barriers of missed opportunities for GBS screening. Under such conditions, risk assessment, culturing and prophylaxis during the intrapartum period must be strictly adhered to.

There was no significant annual difference in the incidence of early-onset GBS bacteremia during the study period between the years 2000 and 2006. However, there was significant decrease in GBS related mortality. There were three neonatal deaths (of which one occurred in a full term infant) due to early onset GBS before 2003 and none after 2003, also seen nationally. This is due to improved perinatal surveillance and management because until 2003, universal maternal GBS screening was not instituted.

Of the total neonatal deaths during the study period, 10 had positive blood cultures. The incidence of neonatal deaths associated with bacteremia was 0.5 per 1000 live births, whereas the incidence of neonatal death due to any cause was 3.9 per 1000 live births. As shown in table 2, the cause of death was attributable to various factors such as extreme prematurity, less than 27 weeks gestational age and less than 750g birth weight with related complications, high-risk pregnancy and prolonged hospital stay in extremely low birth weight babies. There was one full term baby who died of fulminant GBS pneumonia.

Some studies have shown an association of intrapartum antibiotic exposure and increased EOS caused by non-GBS species, including E coli, other Gram-negative organisms or ampicillin-resistant pathogens,[11] and others have not.[6,10] In our study, the incidence of EOS caused by non-GBS organisms was nearly 42%. The non-GBS organisms causing early onset bacteremia are summarized in table 1. E coli was the most common non-GBS etiologic agent of early onset bacteremia.

Despite a decline in the early onset sepsis, similar studies have reported that late onset sepsis rates remain constant or increased.[3,4,5,12] This trend might be a result of extensive use of antibiotics or prolonged hospital stay with invasive procedures among infants that require NICU admission, especially preterm, very low birth weight infants. Prolonged intravascular access, parenteral nutrition, mechanical ventilation and the effects of prematurity contribute to infection onset, complications of the disease and fatal outcome.[5,11,14] The same was reflected in our study. All with late onset disease had undergone invasive procedures and 71% were < 28 weeks gestation and 68% weighed less than 1000g as shown in figure 2a and 2b. As also observed in table 1, 62% of outcomes were caused by nosocomial commensal organisms, including, Candida albicans and Staphyloccus epidermidis being the most common. We do not give antifungal prophylaxis in our hospital.

A large number of contaminants was identified in our study. This was a function of procedural and technical issues. These blood cultures were drawn from asymptomatic babies whose mothers had a risk factor for infection and were not adequately treated. Most were pregnant women who had prenatal care in other clinics without documentation of adequate GBS screening. There is no single definition for a contaminant and the criteria for considering a positive blood culture as a contaminant varies

from institution to institution. In our study, we used the criteria mentioned above under the materials and methods section.

Limitations of this study include the retrospective nature of the study. We also do not have data about babies who were born and discharged healthy from our nursery, and who might have been admitted in other hospitals. As a result, late onset community acquired infections are not completely represented in our study.

Conclusions

Bacteremia continues to be a major determinant of neonatal morbidity and mortality when it is associated with sepsis with or without meningitis. Racial differences in the incidence of early onset disease continue to exist.[5] More studies are needed to clearly understand the reasons for the racial differences. At present, universal culture-based GBS screening between 35 and 37 weeks and intrapartum antibiotic prophylaxis for high risk as well as mothers with unknown GBS status is the most effective method for prevention of early onset GBS disease in neonates. The incidence of late onset disease is related to infants with prematurity and very low birth weight who require invasive procedures and it continues to increase.

We recommend close monitoring of maternal cultures and prophylaxis, strict hand washing and aseptic precautions for all invasive procedures, avoiding overcrowding in the nursery, adequate staffing, close monitoring for signs and symptoms of clinical sepsis, early discharge of stable infants home and appropriate use of antibiotics. Careful attention to technique in obtaining cultures is indicated in order to decrease the rate of contamination. Continued surveillance is needed to identify the changing trends in the epidemiology of neonatal bacteremia to assist in strategy formulation to decrease the morbidity and mortality.

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NAVA in the Post-Operative Treatment of Congenital Heart Disease Infants

The Shanghai Children's Medical Center, affiliated with Shanghai Jiao Tong University School of Medicine, was jointly constructed and established ten years ago by the US based Project Hope, the Shanghai Municipal People's Government and the Xin Hua Hospital. Ever since the inauguration ceremony with Hillary Clinton in June, 1998, the Shanghai Children's Medical Center has made rapid progress in the areas of pediatric cardiology and surgery, improving the lives of Chinese children with congenital heart disease, as well as establishing comprehensive cooperation and training collaboration with over ten well-known medical institutions around the world.

The Department of Cardiovascular Thoracic Surgery of Shanghai Children's Medical Center is the key program of the Shanghai Bureau of Higher Learning, and the first clinical medical center for pediatric cardiology and cardio-thoracic surgery. In addition to becoming a clinical educational and research center, it is the national top-ranking diagnostic and treatment center for congenital heart disease.

The latest advancement within the Department of Cardiovascular Thoracic Surgery is the implementation of NAVA—Neurally Adjusted Ventilatory Assist in the post-operative treatment of infants undergoing congenital heart surgery. Critical Care News met with the staff of the CICU, who shared their recent and expanding experience of Edi monitoring and NAVA as a treatment modality.

Can you give us a description of the operations of the Department of Cardiovascular Thoracic Surgery and the CICU?
ICU Chief Dr Shi Zhenying: Our department, cardiovascular thoracic surgery and the CICU here at Shanghai Children's Medical Center have been in existence for 10 years, ever since the hospital was constructed. We have 9 physicians on staff in the CICU. I have been chief of this unit for the past 10 years, ever since the beginning. Prior to that I was surgeon at the Xin Hua hospital, and thereafter I was an intensive care physician for 10 years, before my current position as chief of this unit.

How many children are treated in the department on an annual basis?
Dr Shi Zhenying: At the present time, we conduct surgeries for nearly 3,000 infant cases on an annual basis. We receive patients from Shanghai, as well as other cities and the countryside.

Respiratory therapist Ji Gang and Dr Zhu Limin with infant cardiac surgery patient, post-op on ventilation with NAVA.

They are born with congenital heart defects and sent here for surgery.

Diagnosis and treatment of congenital heart disease is one of the primary specialization areas at this center. How many patients in this category do you treat on an annual basis, and what other types of patients do you treat in addition to these?
Dr Shi Zhenying: We treat infant patients with acute and complex congenital heart disease, pulmonary artery atresia and infants with single ventricles. About 90% of our caseload consists of babies born with congenital heart disease. The other 10% of patient categories are here due to many different factors, such as lung disease and various types of congenital tumors. We have achieved an overall success rate of 97%.

Which ventilation therapies do you most frequently use in these patient categories?
Dr Shi Zhenying: Primarily we use synchronized intermittent mandatory ventilation - SIMV. We also use PRVC—Pressure Regulated Volume Control as well as Pressure Support ventilation. The mode of mechanical ventilation we choose is always dependent upon the patient condition and sedation levels.

Can you describe the primary factors and process leading to the decision to implement NAVA in this CICU?
Dr Zhu Limin: The first time we heard about NAVA was two years ago, when our chief Dr Shi Zhenying attended a symposium at

Intensive care physician Dr Zhu Limin, ICU Chief Dr Shi Zhenying and respiratory therapist Ji Gang.

Dr Zhu Limin and colleagues with patient on Edi monitoring, post-extubation after NAVA ventilation.

the ESICM meeting in Barcelona, and she heard the lecture by Dr Christer Sinderby. She informed us of this new technology, and I received much information about NAVA, and I became very interested.

When did you have your first patient experience with NAVA, and how many infants have been treated with NAVA so far?

Dr Zhu Limin: We had our first patient experience with NAVA only two months ago. We have placed the Edi catheter in about 16 patients, and treated about twelve patients with NAVA. The other four cases were babies with diaphragmatic paralysis, and since the babies were not spontaneously breathing, we could not use NAVA in those patients. However, in using the Edi catheter, we were able to monitor the Edi and detect the paralysis in these four cases. Some patients develop a bilateral diaphragmatic paralysis after surgery, so the Edi monitoring will confirm this by indicating no Edi signal.

How routinely is NAVA used in the ICU?

Dr Zhu Limin: We have been gaining a lot of experience since we just started using NAVA only two months ago, so now we are selecting more difficult cases to gain even more experience with Edi monitoring and with NAVA. For the patients we have treated with NAVA, they have been on NAVA for a range of times, between a few hours up to three days, depending on their condition.

Is monitoring of the Edi signal used in conventional ventilatory modes, or in stand-by post-op after extubation?

Dr Zhu Limin: For patients that have had diaphragmatic paralysis, we want to leave the Edi catheter in for 2-3 days to monitor the status of the diaphragm. Our surgeons need verification; so now we can give all this information to them, ultrasounds, Edi signals and X-rays, so that they see the actual condition of the diaphragm. It is very interesting and very useful for the surgeons. For our NAVA patients at post extubation, we leave the Edi catheter in for another 24 hours just to monitor the Edi, if we suspect the patient may re-develop something, or just to confirm that their spontaneous breathing is doing well on their own. We have been doing this as a routine for our NAVA patients. We have also monitored the Edi signals in other modes, such as Pressure Support, to monitor diaphragmatic status.

What in your opinion is the advantage or benefit of Edi monitoring as a bedside parameter?

Dr Zhu Limin: I think it is very useful. For example, just in the past two days, right after surgery we had a patient with a low Edi signal and very labored breathing, but after 12 hours the Edi signal became much stronger. We switched the patient to NAVA and the next day we successfully extubated him, and now we are just monitoring the Edi signal. I think the Edi signal is very helpful and useful; you can get answers to all kinds of questions during the treatment process. It is a new bedside parameter for us. I think that maybe the Edi signal can tell us about sedation levels and the wash-out process and behavior patterns of the patient coming out of sedation that we were not able to see before.

How do you perceive NAVA from a therapeutic perspective?

Dr Zhu Limin: From our CICU department, I think we have two patient perspectives. On the one hand, for the simple cases after cardiac surgery, you want to extubate them as safely and as quickly as possible. If you place the Edi catheter and use NAVA, and find the Edi signal returning after surgery, the patient can be extubated as early as possible. On the other hand, in complex cases, the patient needs mechanical ventilation for some longer lengths of time. If we use NAVA, the patient and ventilator are in synchrony, which means that the baby is more comfortable, and the dosage of sedation can be reduced. The Edi monitoring gives the opportunity to extubate earlier as well as monitor the sedation process.

Do you think esophageal ECG is valuable as a diagnostic tool in this patient category?

Dr Zhu Limin: Esophageal ECG is very important for us, as our open heart surgery patients sometimes have post-operative arrhythmia. From the normal ECG, we cannot always see a clear diagnosis, such as SVT, or sometimes atrial tachycardia. If we have an esophageal ECG, we can see the correct diagnosis of the arrhythmia, which is very useful for our treatment.

Have you had any infant patient cases with NAVA of particular interest you would like to share?

Dr Zhu Limin: We had a baby which came to the hospital at two months of age, who was suffering from transposition of the great arteries. An emergency operation was necessary, and it was very difficult to extubate him. We had three failed extubation attempts, with breathing difficulties and bronchospasm. We performed a bronchoscopy contrast CT, which revealed another problem, a vascular ring that compromised the trachea. Another surgery was performed after he had been in the CICU for about one month. After the second surgery, we placed the Edi catheter and treated the child with NAVA. He was spontaneously breathing with NAVA for about three days, followed by a successful extubation. One week later, we were able to finally

Respiratory therapist Liu Liping and Dr Zhu Limin.

The Shanghai Children's Medical Center was established 10 years ago, and has become an internationally known center for treatment and research.

ICU Chief Dr Shi Zhenying surrounded by her staff members Bian Jun, Ji Gang, Zhu Limin and Liu Liping.

discharge him. (Editors note: details of this patient case report may be found at criticalcarenews.com).

Are there specific staff members using NAVA, or has the general ICU staff received training?

Dr Zhu Limin: All of the CICU staff has received training, doctors and nurses. We have also trained our RT group for special cases, so everyone has been educated. Our respiratory therapists place the Edi catheter and verify the positioning.

How do the respiratory therapists experience the Edi catheter placement and positioning process?

Ji Gang, RT: It is not very difficult to place and position the Edi catheter, and we just monitor placement by means of the ECG signals. We use the Edi catheter as a normal feeding tube as well. As a team, we have a follow-up after each NAVA treatment for every case, so that we can all continue to learn about NAVA together.

What role do you think NAVA will have in the future in this patient population of congenital heart defects and disease?

Dr Zhu Limin: I think that NAVA will be used increasingly in cardiac surgery, especially for pediatric patients, because of the opportunity of earlier extubation for simple cases post-op, and for complex cases, the opportunity to monitor Edi and diaphragmatic status, in order to monitor and decrease dosage of sedation. Also, I think that the NAVA technique is easy to learn for any ICU staff member.

Do you think that your institution will be researching and expanding the use of NAVA in future?

Dr Zhu Limin: I think that the research is very important, and we are planning to do some research in three areas. First, we would like to compare NAVA with traditional Pressure Support ventilation in terms of patient-ventilator synchrony as well as if we determine reduction of sedation dosages. Secondly, we are interested in research with NAVA to confirm the safety of hemodynamics in cardiac surgery patients. One other area of research we are interested in is to measure the Edi signal after extubation and chart and track to establish the normal range for children.

Biography

Dr Shi Zhenying, MD, received her medical degree in 1975. She worked in Xinhua Hospital from 1975 to 1999, and was employed as physician of the cardiac intensive care unit there from 1989.

Dr Shi Zhenying has been the chief of the cardiac intensive care unit of Shanghai Children's Medical Center, China since 2000. She was versed in the clinical and research work in perioperative treatment for congenital heart disease in children, especially in the prevention of low cardiac output syndrome and the treatment of multiple organ dysfunction syndrome. Dr Zhu Limin, MD, obtained her medical degree in 1999. Thereafter she was employed as a physician of the cardiac intensive care unit at Shanghai Children's Medical Center, China. She received the fellowship of respiratory therapy and pediatric intensive care in Schneider Children's Medical Center of Israel in 2006. She has been the manager of the team for respiratory management in the Cardiac Intensive Care Unit since 2006. She specializes in treatment of pulmonary hypertension and post-operative lung protective mechanical ventilation. From 2008, she has conducted clinical research of NAVA in neonates and pediatrics following cardiac surgery.

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How Effective is Your HME?

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A Heat Moisture Exchanger (HME), sometimes referred to as an "artificial nose," is a passive humidification device designed to heat and humidify inspired gases. If inspired gases are not adequately humidified, a host of respiratory system compromises can follow, such as thick retained secretions, increased resistance, increased work of breathing, the destruction of cilia and mucus membranes, increased incidence of pneumonia, etc.[1-3]

For mechanically ventilated patients, HMEs can be used to heat and humidify inspired gases rather than an active humidification system. HMEs are placed between the patient Y and the connection to the endotracheal tube, allowing a transfer of moisture from the patient's exhaled air to the HME and then back to the patient on the next inspiration.

HMEs are the most commonly used humidification device in Europe[4] and have become increasingly more popular in North America. Some of the reasons for their popularity may be due to the fact that they have no moving parts, they do not require electricity, and depending upon a number of factors such as how frequently they are changed, they can be a less expensive method for providing an acceptable level of humidity to mechanically ventilated patients.[5] However, HMEs may not be indicated for all patients such as those with a low core temperature, those suffering from dehydration, or those with an increased flow demand or minute ventilation requirement as the moisture returned to the patient will be diminished or mechanical deadspace increase may be adverse to the patient.

Many basic HMEs consist of a paper medium or sponge filament inside a low compliance case. Some newer versions of HMEs have an interior surface that is treated with a hygroscopic salt (lithium chloride or calcium chloride), which increases its ability to extract moisture. Either type of HME is available with or without a viral/bacterial filter. Numerous HME devices are now available commercially from a wide variety of manufacturers and distributors. Because of the multitude of devices available on the market, it is important for the clinician to be aware that characteristics of the devices such as size, weight, deadspace, amount of moisture return, and resistance to flow can vary greatly from one device to another. Some studies have shown significant differences in the effectiveness of different HME devices in how much humidity is returned to the patient.[6-7] Basic HMEs may return 10mg to 14mg H20/L, while others have been shown to return 22mg to 34mg H20/L.[7] However, few large scale independent studies have been conducted to assess humidification performance of HMEs.[6-7]

A recent study published by Lellouche et al in Chest online, the official publication of the American College of Chest Physicians, did exactly that, assessing humidification performance of a large number of adult HMEs. According to the researchers, this is the largest evaluation of its type for HMEs and antibacterial filters ever conducted. The researchers assessed 48 devices using a bench test apparatus that reproduced real-life saturated expired gas conditions in order to assess the hygrometric performance of the devices. Thirty-two devices were described by manufacturers as HMEs and 16 were described as antibacterial filters. The bench test apparatus provided expiratory gases with an absolute humidity (AH) of 35mg H2O/L. A Servo 900C ventilator was used in assist-control mode, a respiratory rate of 20, 500cc tidal volume, positive end expiratory pressure of 5cm H2O, and a fraction of inspired oxygen of 21%. Room temperature was held constant. The AH of inspired gases was measured after steady state using the psychrometric method. They performed three hygrometric measurements for each device. The devices were classified into different categories: HMEs with an antibacterial filter (HMEF) or without an antibacterial filter (HME) and those described as antibacterial filters. The measurements obtained with the bench test apparatus were then compared to manufacturer data.[8]*

Of the 32 HMEs (HME and HMEF) tested, only 37.5% (12) performed well (> 30mg H2O/L), 12 were intermediate (< 30 to ≥ 25mg H2O/L), and 8 performed poorly (< 25mg H2O/L). The average AH of these devices was 17.3 ± 3.6 mg H2O/L. Humidity efficiency of the devices ranged from 91.1% to 37.8%.[8]

Manufacturer data was available for 29 devices (25 HMEs and 4 antibacterial filters), and the researchers then compared their results to the manufacturer data. Of the 29 devices that could be compared, manufacturer data were higher than the value determined using the test apparatus for 23 of the devices (79%).[8]

Resistance measurements were not the primary objective of the study, but they were performed on 34 of the 48 devices tested for humidification properties. The average resistance of these devices was 2.17 ± 0.70 cm H2O/L/s at 1 Ls. In contrast to hygrometric comparisons, there was no significant difference in resistance measurements compared to manufacturer data.[8] The deadspace of the HMEs ranged from 22 to 95 mL, and deadspace of the antibacterial filters ranged from 24 to 101 mL.[8]

Lellouche et al concluded that several HMEs performed poorly and should not be used as HMEs. The values determined by independent assessments may be lower than what the manufacturer data claim. Describing a device as an HME does not guarantee that it provides adequate humidification. In fact, some should only be used for short term ventilation, such as during anesthesia, as they are mainly antibacterial filters with poor humidification performance.[8]

Standards for HMEs have been developed by organizations such as the American Association for Respiratory Care (AARC),
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Herpes Simplex Virus Infection in Pregnancy and in Neonate: status of art of epidemiology, diagnosis, therapy and prevention

Elena Anzivino, Daniela Fioriti, Monica Mischitelli, Anna Bellizzi, Valentina Barucca, Fernanda Chiarini, Valeria Pietropaolo

Abstract

Herpes simplex virus (HSV) infection is one of the most common viral sexually transmitted diseases worldwide. The first time infection of the mother may lead to severe illness in pregnancy and may be associated with virus transmission from mother to foetus/newborn. Since the incidence of this sexually transmitted infection continues to rise and because the greatest incidence of herpes simplex virus infections occur in women of reproductive age, the risk of maternal transmission of the virus to the foetus or neonate has become a major health concern. On these purposes the Authors of this review looked for the medical literature and pertinent publications to define the status of art regarding the epidemiology, the diagnosis, the therapy and the prevention of HSV in pregnant women and neonate. Special emphasis is placed upon the importance of genital herpes simplex virus infection in pregnancy and on the its prevention to avoid neonatal HSV infections.

Introduction

Herpes simplex virus (HSV) infection is one of the most common viral sexually transmitted diseases (STD) worldwide. Herpes simplex virus type 2 (HSV-2) is the cause of most genital herpes and is almost always sexually transmitted. Herpes simplex virus type 1 (HSV-1) is usually transmitted during childhood via non-sexual contacts. However, HSV-1 has emerged as a principle causative agent of genital herpes in some developed countries. In the United States (US), HSV-1 is an important cause of genital herpes and its importance is increasing in college students.

The greatest incidence of HSV infections occurs in women of reproductive age, the risk of maternal transmission of the virus to the foetus or neonate has become a major health concern. Recent findings reveal that first-time infection of the mother is the most important factor for the transmission of genital herpes from mother to foetus/newborn. In fact, the pregnant woman who acquires genital herpes as a primary infection in the latter half of pregnancy, rather than prior to pregnancy, is at greatest risk of transmitting these viruses to her newborn. Additional risk factors for neonatal HSV infection include the use of a foetal-scalp electrode and the age of the mother less than 21 years. Interventions based on these findings led to new management of the pregnant patient with genital herpes prior to pregnancy and to prevention measures to avoid the acquisition of herpes during pregnancy.

The authors of this review looked for the medical literature and pertinent publications to appreciate the importance of genital HSV infection in pregnancy and in neonate. They focused their research on the epidemiology of genital HSV infection, the risks of transmission, the diagnosis, the current therapy and the prevention strategies. For reviewing they used Medline and recent bibliographies.

HSV-1 and HSV-2 are DNA viruses that belong to Alphaherpesvirinae, a subfamily of the Herpesviridae family. Both viruses, transmitted across epithelial mucosal cells, as well as through skin interruptions, migrate to nerve tissues, where they persist in a latent state. HSV-1 predominates in orofacial lesions and it is typically found in the trigeminal ganglia, whereas HSV-2 is most commonly found in the lumbosacral ganglia. Nevertheless these viruses can infect both orofacial areas and the genital tract. In recent years, genital herpes has become an increasing common sexually transmitted infection. From the late 1970s, HSV-2 seroprevalence in the US has increased by 30%, resulting that one out of five adults is infected.

Comparing the developing countries, substantially higher rates of HSV2 have been observed in sub-Saharan Africa, where prevalence in adults ranges from 30% to 80% in women and from 10% to 50% in men, finally more than 80% of female commercial sex workers are infected. In South America, available data are mainly for women, in whom HSV2 prevalence ranges from 20% to 40%. Prevalence in the general population of Asian countries shows lower values, from 10% to 30%.

HSV seroprevalence in patients attending STD clinics varies from 17% in Italy (6% in the general population) to 40% in Australia (14% in pregnant women). Age and sex are important risk factors associated with the acquisition of genital HSV-2 infection. In fact, the prevalence of HSV infection is very low in childhood and early adolescence but it rises with age, reaching the maximum around 40 years.

Regarding sex, serological surgery have confirmed that infection is more frequent in women than in men in the general population of US (23.1% in women versus 112% in men) and other countries,

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Table 1. Direct methods for HSV diagnosis.

Method	Tissue sampled	Sensitivity	Specificity	Advantages	Disadvantages
Virus isolation by cell culture[1]	Skin/mucosal lesions (stage): -vesicular content -ulcers -scabs -mucosa without lesions Biopsies Conjunctival smear/corneal Neonates	>90% 95% 70% 30% unknown	~100%	Gold standard Simplicity of sampling Virus typing Resistance phenotype determination	Specialized laboratories Virus transport medium Transport rapid, cooled, protected from light Results in 2/7 days Not suitable for CFS Arrangement with laboratory necessary
Cytologic diagnosis (Tzanck's smear)[35]	Skin/mucosal lesions Biopsies Conjunctival smear/corneal	73-100%	100%	Easy, quick, reproducible and inexpensive	Optimal lesions are fresh, intact bisters of 1/3 days' duration
IF (detection of infected cells)[30]	Smears, tissue sections, smears from base of vesicle	41-70%	>95%	Rapid (<4 h possible) Typing possible	Fresh vesicles Specialised laboratories Technically demanding Not standardized
Virus antigen detection by EIA o ELISA[30]	Smears from lesions, vesicular content with base of vesicle	41-80%	80%	Simplicity of sampling Does not require the integrity of the specimen Rapid (<4 h possible) Typing possible	Suitable only for fresh vesicles
Virus DNA detection by PCR[30] or Real-time PCR[31]	CSF Aqueous or vitreous humour Skin lesions, vesicular content or mucosa without lesions	97-98%	~100%	PCR: Most sensitive method Result within 24-48 h Virus typing and resistance genotyping Method of choice for CSF Real-time PCR: Rapid amplification Quantitative analysis Reduced risk of contamination Method of choice for skin lesions	Only in specialised laboratories Not standardised Not validated for all samples Risk of contamination (PCR) High costs (real-time PCR)

Table 2. Indirect methods for HSV diagnosis.

Method	Tissue sampled	Sensitivity	Specificity	Advantages	Disadvantages
Western Blot[2]	Serum	~100%	~100%	Distinguish between HSV-1 and 2 Detect early seroconversion to HSV-2 in patient with prior HSV-1 infection.	Not commercially available Expensive 2-3 days for results
EIA[2]	Serum	93-98%	93-98%	Commercially available Distinguish between HSV-1 and HSV-2	Lack of sensitivity (compared to amplified tests)[2]
Point of care tests[2]	Serum Capillary blood[37]	96%	87-98%	Less expensive than western blot2 Accurate results rapidly (6 min.)[37] Easily performer[37] Detects seroconversion within 4 weeks of presentation of 80% of patients with HSV-2 episodes[37]	Commercially available only for HSV-22 Expensive[36] Not for large volume screening[36] Complexity nonwaived (moderate)[36]

although in Italy, the seroprevalence is slightly higher in men (6.7%) than in women (4.9%). It is probably due to the younger age of the female group, as well as to the low number of sexual partners for these women, may explain the results. In fact the strongest association with HSV-2 infection appears related to the number of sexual partners.

The specific geographic distribution can also influence the difference in HSV-2 prevalence. In fact, the seroprevalence found in a STD clinic in Northern Italy is lower than that found among STD clinic attendees in US, Australia and in a previous Italian study, but it is comparable with that found in similar populations within United Kingdom and New Zealand. In addition, ethnicity, poverty, cocaine abuse, earlier onset of sexual activity, sexual behaviour and bacterial vaginosis can facilitate a woman's risk of infection before pregnancy.

Regarding pregnant population, there is a high prevalence of genital herpes. Among Italian pregnant women, the 7.6% seroprevalence observed in Rome is consistent respect to the 8.4% seroprevalence found in Northern Italy in a similar setting. Nevertheless it is lower than that reported among pregnant women in other countries. For example, in US, approximately 22% of pregnant women are infected with HSV-2, 10% are at risk of acquisition of genital HSV from their infected partners (during periods of asymptomatic viral shedding) and 2% of women acquire genital herpes during pregnancy, placing their newborn at risk for herpes infection. In Italy, the number of women who acquire HSV infection during pregnancy is about 3%. The acquisition of genital herpes during pregnancy has been associated with spontaneous abortion, intrauterine growth retardation, preterm labour, congenital and neonatal herpes infections. The risk of neonatal infection varies from 30% to 50% for HSV infections that onset in late pregnancy (last trimester), whereas early pregnancy infection carries a risk of about 1%. When primary HSV infection occurs during late pregnancy, there is not adequate time to develop antibodies needed to suppress viral replication before labour. Transmission of HSV from mother to foetus during pregnancy is uncommon; about 85% of perinatal transmission occurs during the intrapartum period. Moreover, studies in HIV-infected pregnant women show that co-infection with HSV increases significantly the risk of perinatal HIV transmission above all in women who had a clinical diagnosis of genital herpes during pregnancy.

Table 3. Antiviral treatment of genital herpes in pregnancy.

Pregnancy	First episode			Recurrent episodes		
	Antiviral drug	Recommended daily dosage	Length of therapy	Antiviral drug	Recommended daily dosage	Length of therapy
Episodic treatment	Acyclovir Valacyclovir	Orally: 5 x 200 mg Orally: 2 x 500 mg	10 days 10 days	Acyclovir Valacyclovir	Orally: 5 x 200 mg Orally: 2 x 500 mg	5 days 5 days
Suppressive treatment	Acyclovir Valacyclovir	Orally: 3 x 400 mg Orally: 2 x 250 mg	From week 36 until delivery	Acyclovir Valacyclovir	Orally: 3 x 400 mg Orally: 2 x 250 mg	From week 36 until delivery

The newborn could be also infected by HSV-1, that may represent almost one-third of all new genital HSV diagnoses. An increasing proportion of genital herpes infections due to HSV-1 is particularly evident among college-age populations (16-21 years) of the Midwest (US), where it reached about 78% in 2001 (31% a decade earlier). This result suggested that there is a risk of HSV-1 transmission to newborn when these young women become pregnant and that oral–genital contact is a risk factor for HSV-1. HSV-1 infection during childhood has declined so that more adolescents and young adults are HSV seronegative when becoming sexually active. This would explain the observed increase in HSV-1 first time infection of the genital tract in this age group.

Genital herpes: clinical features : Genital HSV infection may be symptomatic or asymptomatic. Symptomatic infection is generally described as genital herpes and include primary, first-episode and recurrent herpes outbreaks. Primary genital herpes is usually the most serious event for the individual, especially in pregnancy, since it can cause the most severe neonatal disease. Moreover, it is defined as first-episode of genital herpes where the patient has no antibody against HSV-1 and HSV-2.

Primary symptomatic genital herpes, that occurs after an incubation of a period of 2-20 days, is usually important and prolonged (up to 21 days). Within women it causes blistering and ulceration of the external genitalia and cervix leading to vulval pain, dysuria, vaginal discharge and local lymphadenopathy. Vesicular and ulcerative lesions of the internal thigh, buttocks, perineum or in perianal skin are also been observed. In men the lesions typically develop on the glans, but also on the penis, internal thigh, buttocks or in perianal skin. Both in man and in woman primary infection may be complicated by systemic symptoms such as fever, headache and myalgia (38% in men, 68% in women) and occasionally meningitis and by autonomic neuropathy resulting in urinary retention, mainly in women. Meningitis has been found in 42% of primary HSV-2, 12% of primary HSV-1 infections and 1% of recurrent infections. Nevertheless, pre-existing HSV-1 antibodies can alleviate clinical manifestations of subsequently acquired HSV-2. In some cases, systemic clinical findings may be the only presenting symptoms of infection and in more than half of patients, primary infection goes unnoticed.

The most important HSV infection during pregnancy is the primary genital HSV infection, although, in the majority of pregnant women, the first manifestation of genital herpes is not a primary infection.

Primary HSV infections in pregnant women can result in more severe diseases than that in nonpregnant ones. In particular, gingivostomatitis and vulvovaginitis herpetica tend towards dissemination. As a result, women can develop disseminated skin lesions associated with visceral involvement such as hepatitis, encephalitis, thrombocytopenia, leucopoenia and coagulopathy. Although disseminated HSV infection is uncommon in pregnancy, the mortality is about 50%. In particular, pregnant women with primary mucous membrane infection during the third trimester, have an increased risk for dissemination and they could transmit HSV to their babies during vaginal delivery.

Recurrent episodes of HSV infection are characterized by the presence of antibody against the same HSV type and the herpes outbreaks are usually mild (7-10 days) with less severe symptoms than the first episode. Prodromal symptoms (itching, tingling, neuralgia) may occur hours or days before a recurrent herpes episode. The great majority of recurrent genital herpes is due to HSV-2 because this virus reactivates more frequently than HSV-1.

The apparently asymptomatic phases between clinical outbreaks of genital herpes are important, since HSV can reactivate periodically in latently infected cells of sensory ganglia travelling via the neuronal axons back to the genital mucosa, without clinical signs or symptoms. This mechanism is known as asymptomatic virus shedding. The majority of sexual HSV transmission occurs during asymptomatic periods because the patients are unaware of asymptomatic virus shedding. Moreover, asymptomatic shedding has been shown to be higher in women with HSV-2 infection compared with those with HSV-1 (7% versus 2% respectively).

Although there is a small risk of vertical transmission, recurrent genital herpes must be regarded as the most common cause of neonatal infections and the passage through an infected birth canal is the most probable route of transmission. In recurrent infections associated with clinical symptoms, the risk of neonatal disease is reduced dramatically by caesarean section. Transmission of HSV by women with asymptomatic viral shedding is of greater significance, since neonates mostly acquire infection without being recognized.

Management of pregnant women with a first or recurrent episode of genital herpes: Diagnosis of genital HSV infections is often complicated because non-classical presentations are common or clinical signs are mild and non-specific. Moreover, HSV infection is characterized by clinical outbreaks followed by asymptomatic periods within HSV transmission is possible. Therefore, it is necessary to improve the recognition and hence diagnosis of genital herpes, because a correct laboratory diagnosis is important for clinical management, counselling, treatment, management of pregnancy and assessment of the risk of transmission.

The HSV infection may be identified directly by detection of the virus or one of its components (Table 1), or indirectly by assaying for specific serum antibodies of the viruses (Table 2). Direct site-specific methods, such as virus or antigen detection,

Table 4. Antiviral treatment of neonatal HSV infection

Infants	Antiviral drug	Recommended daily dosage	Length of therapy
Treatment of neonatal hsv infection	Acyclovir	Intravenously: 3 x 10-20 mg/kg	Localised infections: 14 days CNS or disseminated infections: 21 days
Suppressive treatment of cutaneous recurrences after neonatal herpes	Acyclovir	Orally: 2-3 x 300 mg/m^2	For weeks to months

Source: Swiss Herpes Management Forum, 2004.

are the most relevant in patients with active, vesicular lesions at or near a genital site. When lesions have scabbed or are not evident, HSV-1 or HSV-2 infection can be diagnosed indirectly by detection of type-specific IgG against the glycoprotein G of HSV-1 (gG-1) or the glycoprotein G of HSV-2 (gG-2). Indirect (serological) testing can provide useful information in symptomatic patients when direct methods have yielded negative results. Although serological testing cannot reveal the onset of HSV infection or identify the locus of shedding, it allows identification of HSV infection when direct virus detection methods are not viable or when evidence of seroconversion is required. Moreover, indirect approaches are useful to determine the type of recurrence. In general, genital HSV-1 causes a severe initial outbreak but fewer recurrences than HSV-2. However, type-specific testing is useful but not essential, because treatment regimens do not vary by virus type.

Therapeutic measures: Pregnant women with a first clinical episode or a recurrence may be treated with acyclovir or valacyclovir at the recommended dosages (Table 3). Since acyclovir and valacyclovir are not officially approved for treatment of pregnant women, patients should be informed to give consent before the administration. However, no increase of foetal abnormalities was ascribed to these treatments, although long-term outcomes were not evaluated. Randomized studies have shown that suppressive treatments with acyclovir and valacyclovir from 36th week of pregnancy until delivery, significantly reduces the frequency of clinical manifestations and the virus shedding at the time of delivery decreasing the need for caesarean delivery and probably the risk of vertical transmission (Table 3).

Mode of delivery: When primary infection is acquired during the first two trimesters of pregnancy, it is advisable to carry out sequential viral cultures on genital secretions from 32th week of gestation. If two consecutive cultures result negative and there are no active herpetic genital lesions at the time of delivery, it is possible to perform a vaginal delivery (Fig 1, section A1). If seroconversion is completed at the time of delivery, caesarean section is not required since the risk of HSV transmission to the foetus is low and the neonate should be protected by maternal antibodies. If primary genital infection is acquired during the third trimester of pregnancy, the optimal way of proceeding is not well defined. Most guidelines propose caesarean section for women developing a primary clinical infection within the last 4-6 weeks of gestation, because they can not complete their seroconversion prior to the time of delivery and therefore they could infect the neonates. When vaginal delivery is irreversible, since the risk of vertical transmission is high (41%), a maternal and neonatal intravenous acyclovir therapy is recommended (Fig 1, section A2).

For women who present an episode of recurrent genital herpes several weeks before the expected delivery date, a suppressive therapy with acyclovir or valacyclovir is recommended during the last 4 weeks of pregnancy and viral cultures on cervical-vaginal secretions from 36th week of gestation are required. Furthermore, when there are no clinical herpes lesions but virus detection tests result positive at the time of delivery, an elective caesarean section is indicated. On the contrary, if all viral cultures are negative and there are no genital herpetic lesions at the time of delivery, it is possible to perform a vaginal delivery (Fig 1, section B1).

Finally, since active genital HSV lesions are present or prodromal symptoms occur at the onset of delivery and consequently the risk of viral exposure to the infant is high, a caesarean section should be performed as quickly as possible within 4-6 hours after membranes rupture if foetal lungs are mature. When foetal lungs are immature, there are no established guidelines. A cesarean delivery before ruptured membranes virtually eliminates the risk of intrapartum transmission to the infant, although it does not completely remove the risk of HSV transmission. An antiviral treatment with acyclovir is recommended to the mother and eventually to the newborn (Fig 1, section B2).

Neonatal HSV infections: Mode of acquisition and clinical manifestations: HSV infection of the newborn can be acquired in utero, intrapartum and postnatally. The mother is the most common source of infection for the first two routes of viral transmission. Intrauterine HSV infection is a rare disorder and accounts for 5% of HSV infections in neonates. The highest risk of intrauterine infection has been observed in pregnants (about 50%) who develop disseminated HSV infections and 90% of those are related to HSV-2. Both primary and recurrent maternal infection can result in congenital disease, even if the risk after recurrent infection is small. Intrauterine viral transmission is highest during the first 20 weeks of gestation leading to abortion, stillbirth and congenital anomalies in infants who survive. The perinatal mortality is 50%. In 85–90% of neonatal HSV infections, HSV is acquired at the time of delivery and 5-10% are caused by early postnatal viral acquisition. 70-85% of neonatal HSV infections are caused by HSV-2, whereas the remaining cases are due to HSV–1. Usually, an infection with HSV-2 carries a graver prognosis than that caused by HSV-1. The estimate rate of occurrence ranges widely from 1/3200 to 1/20000 of life births.

The disease transmission to the newborn is dependent on the type of maternal genital infection at the time of delivery. In fact, neonatal herpes is much more frequent (50%) in babies from mothers with a primary HSV infection respect to babies from mothers with recurrent HSV infection (<3%). However, most neonatal HSV infections (about 70%) result from exposure to asymptomatic genital HSV infection in the mother near delivery

The prolonged rupture of membranes is a risk marker for acquisition of neonatal infection. Women with active genital lesion at the time of labor usually have their infants delivered by caesarean section. Nevertheless, it is not clear whether this procedure reduces HSV transmission to the newborn.

Finally, invasive obstetric procedures and the use of foetal scalp monitors appear to have a great effect on neonatal herpes transmission because they can create a site of inoculation of the virus. The clinical presentation of infants with neonatal HSV infection, that is almost invariably symptomatic and frequently lethal, is a direct reflection of the site and extent of viral replication. Congenital intrauterine infection, that usually is identified within the first 48 hours following birth, is characterized by skin vesicles or scarring, eye lesions (chorioretinitis, microphthalmia, cataract), neurologic damage (intracranial calcifications, microcephaly, seizures, encephalomacia), growth retardation and psychomotor development. Infants infected intrapartum or postnatally by HSV can be divided into three major categories: 1) HSV disease localized to the skin, eye, and/or mouth; this syndrome is associated with a low mortality but it has a significant morbidity and it may progress to encephalitis or disseminated disease if left untreated; 2) HSV encephalitis with or without skin, eye, and/or mouth involvement which causes neurologic morbidity among the majority of survivors; 3) disseminated HSV which manifests as severe multi-organ dysfunction (including central nervous system, liver, lung, brain, adrenals, skin, eye and/or mouth) and has a mortality risk that exceeds 80% in absence of therapy. At diagnosis, symptoms are found with the following frequency: skin vesicles 68%, fever 39%, lethargy 38%, seizures 27%, conjunctivitis 19%, pneumonia 13%, disseminated intravascular coagulation 11%. Symptoms may occasionally be present at birth, but occur in 60% later than 5 days after birth and sometimes are present after 4–6 weeks of life.

Localized infections have been found in 50% of the affected neonates, involvement of the central nervous system (CNS) in 33% and disseminated infections in 17% of the cases. Several studies have demonstrated that disseminated HSV infections are characterized mainly by liver and adrenals failure associated with shock symptoms and disseminated intravascular coagulopathy. Other symptoms of HSV disseminated infection include irritability, seizures, respiratory distress, jaundice and frequently the characteristic vesicular exanthem that is often considered pathognomonic for infection. However, over 20% of infants with disseminated infection do not develop skin vesicles during the course of their illness. Encephalitis appears to be a common component of this infection form, occurring in about 60-75% of infants with disseminated HSV infection. Mortality in the absence of therapy exceeds 80%.

Despite the availability of antiviral drugs for treatment of neonatal HSV infections, the outcome remains poor, particularly for babies with disseminated multi-organ infections or manifestations of CNS. Infection of the CNS, alone or in combination with disseminated disease, is characterized by neonatal hemorrhagic-necrotizing encephalitis that manifests as lethargy, seizures (both focal and generalized), irritability, tremors, poor feeding, temperature instability, bulding fontanelle and pyramidal tract signs. Although the mortality rate is only 5% for neonates with encephalitis, over 50% of survivors are left with significant neurological impairment, whereas for children with disseminated multi-organ disease, the mortality rate approaches 30% and nearly 20% of survivors have neurological impairment. After a neonatal herpes infection, cutaneous recurrences may occur. Moreover, the outcome is correlated with the virus type and disease classification. In particular, for treated babies with skin, eye and mouth involvement attributed to HSV-1, there are no consequences, whereas 3% of those with skin disease caused by HSV-2 subsequently develop neurological complications. Regarding infants with encephalitis, the neurological outcome is significantly better for HSV-1 respect to HSV-2 infection. In fact 25% of babies with HSV-1 infection show severe impairment, compared with 55% with HSV-2 infection. The outcome is reversed for babies with disseminated disease. In this circumstance, 70% of babies with HSV-1 infection die or have severe neurological impairment compared with 50% of babies infected by HSV-2.

Diagnostic procedures: When perinatal HSV exposure is known, it is advisable to collect and to analyze swabs from neonate's conjunctiva, oropharynx and rectum within 24-48 hours after delivery. Moreover, these neonates must be monitored closely up to 4–6 weeks of age. If the neonate exhibits suspicious symptoms of infection, cultures of vesicular, conjunctival, oropharyngeal, stool/rectal swabs, urine and blood must be performed. In addition, HSV-PCR analysis on cerebrospinal fluid (CSF) and routine laboratory tests should be carried out (Table 1). Cerebral imaging and/or ophthalmological examination should be performed.

Antiviral therapy and prognosis: All infants with a suspected or diagnosed HSV infection must be treated with an intravenous therapy with acyclovir (60 mg/kg/day). The starting time of treatment is crucial for prognosis, especially in case of disseminated infections. HSV infections localized to skin, eyes and mucous membranes are treated for 14 days, whereas CNS or disseminated infections required 21 days of therapy (Table 4). Suppressive antiviral treatment with acyclovir is indicated when cutaneous recurrences are observed after neonatal HSV infection (Table 4). In case of ophthalmic herpes, infection monitoring should be carried out in order to rule out keratitis. Although high-dose of intravenous acyclovir for a sufficient period has been proven to be effective, neonatal HSV infection is still associated with high residual lethality and morbidity because acyclovir administration may suppress but not eradicate the virus in exposed infants. Localised form heals without sequelae whereas the CNS form is lethal in 6% of cases leaving 69% of permanent late sequelae. The disseminated infection takes a lethal course in 31% and has late sequelae in 17% of cases.

Prevention of neonatal infections: The high rate of undiagnosed or asymptomatic HSV infections complicate the prevention. In order to avoid the majority of neonatal herpes cases, identification of the at-risk mother is the goal. The first and most important step is the determination of the pregnant women serostatus to establish their susceptibility to the infection during early pregnancy. However, current recommendations of ACOG do not include universal testing because at the present time, type-specific serologic tests are not widely available and their reliability is questionable. The most effective measure to prevent perinatal herpes infections is to avoid viral exposure to the neonate when primary genital herpes develops in late pregnancy whereas the risk of severe neonatal infection is small in recurrent episodes. A history of HSV infection in all pregnant women and their partner should be obtained at the first prenatal visit. Women with a negative personal history of HSV and especially those with a positive history in the male partner, should be strongly advised to have no oral and sexual intercourse at the time of recurrence in order to avoid infection (in particular during the third trimester of gestation). Moreover, use of condoms throughout pregnancy should be recommended to minimize the risk of viral acquisition, although

Figure 1. The figure resumes in a schematic diagram the mode of delivery in HSV primary infection (A) and in recurrent genital herpes infections (B).

the male partner has no active lesions. However, condoms are not a complete barrier for the genital region. Prophylactic administration of acyclovir or valacyclovir in the third trimester of pregnancy should be provided to all pregnants with frequent genital herpes outbreaks and with active genital HSV infection near term or at the time of delivery. A careful examination of the vulva, vagina and cervix should be performed on any woman who presents signs or symptoms of HSV infection at the onset of labor. Artificial rupture of membranes should be avoided. All pregnants who have a suspected active genital HSV infection or prodromal symptoms of HSV infection should undergo caesarean section, although membranes are intact. On the contrary, when genital herpes lesions are not present, caesarean delivery is not required but lesions should be covered with an occlusive dressing before vaginal delivery. It is important to remember that fetal scalp electrodes monitoring during labour and vacuum or forceps delivery should be used only if necessary, since these practices appear to increase the risk of HSV transmission.

Neonates, born to women with active genital lesions, with a confirmed or suspected HSV infection should be isolated, managed with contact precautions to avoid direct contact with skin and mucosal lesions, excretions, body fluids and immediately treated with intravenous acyclovir. Since neonatal herpes can also be acquired postnatally, postpartum women, family members and nursery personnel with active herpetic lesions of the mouth, skin or breast should take necessary precautionary measures to prevent direct contact with the neonate and/or should be excluded from the neonatal unit until the lesions are fully healed.

HSV vaccine studies: The development of vaccines against herpesviruses has major public health importance in both immunocompetent and immunocompromised populations. Because these viruses establish latent infections capable of subsequent reactivation, both immunotherapeutic and prophylactic vaccine strategies are needed.

About prophylactic vaccines, partially effective prophylactic vaccines may still be useful if they shift the threshold of infection, or if they prevent or improve disease. They could reduce HSV-2 incidence by preventing infection or by reducing the shedding or clinical recurrences in a HSV-2- infected individual. On the other hand, these vaccines could increase HSV2 incidence reducing symptomatic signs of disease without effect on viral shedding. In particular, the Chiron-gD2gB2- MF59 vaccine provided only temporary protection lasting a few months, whereas the GlaxoSmithKline (GSK)-gD2-alum-MPL prophylactic vaccine had no effect in men or HSV-1 positive women although in HSV-1 seronegative women the risk of HSV-2 infection and disease was reduced. A further trial of the GSK vaccine in HSV1 negative women is ongoing.

Numerous approaches including subunit vaccines, peptide vaccines, live virus vectors and DNA vaccine technology have been used in developing both prophylactic and therapeutic vaccines, since several antiviral therapies are available to control disease and spread, but these are not completely effective and do not affect latent virus. A range of vaccine formulations has been devised, largely as a result of the rapid growth in knowledge in molecular microbiology and genetic engineering, including live and inactivated whole virus vaccines and subunit vaccines consisting of recombinant viral glycoproteins in various adjuvants. Although animal studies on vaccination strategies to prevent genital and neonatal herpes may be promising, clinical trials of HSV-2 vaccines in humans have failed to prove efficacy. In a previous study, an HSV-2 glycoprotein D vaccine using alummorpholine (MPL) as adjuvant, induced protection from clinical disease (73%) and overall HSV-2 transmission (about 40%). Nevertheless, the protective effect of the MPL vaccine was seen only in women who were HSV-1 and SV-2 seronegative and there was no protection among men or among HSV-1 seropositive women. In conclusion, many prophylactic and therapeutic vaccination approaches have been explored but no effective vaccine is presently available.

Conclusion

A large body of information on the transmission of herpes from male to pregnant partner, on the mode of transmission from mother to newborn, mainly by maternal first-time infection in the third trimester of pregnancy, have been published in literature. Since the increasing prevalence of genital HSV infection and apparent increase in the incidence of neonatal herpes, we have focused our attention on prevention of maternal–foetal transmission as well as on the management of infected pregnant women and neonate. Further studies are needed to monitor the changing HSV-1 and HSV-2 trends and to develop effective strategies to prevent HSV infection. Finally, the major vaccine strategies under development should take in an account the three important features of herpesviruses: the viral latency, the herpes immune escape and the high seroprevalence.

Cup Versus Bottle Feeding for Hospitalized Late Preterm Infants in Egypt: A Quasi-Experimental Study

Amel M. Abouelfettoh, Donna A. Dowling, Soheir A. Dabash, Shadia R. Elguindy, Iman A. Seoud

Abstract

Background: Although previous studies have demonstrated beneficial breastfeeding outcomes when cup feeding rather than bottle feeding was used for feeding preterm infants, cup feeding has not been implemented in Egypt. The aim of the current study was to examine the effect of using cup feeding as an exclusive method of feeding preterm infants during hospitalization on breastfeeding outcomes after discharge.

Methods: A quasi-experimental design, with the control group studied first, was used to examine the effect of cup feeding for preterm infants on breastfeeding outcomes after discharge. Sixty preterm infants (mean gestational age was 35.13 weeks and mean birth weight was 2150 grams) were recruited during Neonatal Intensive Care Unit (NICU) stay. Control group infants (n = 30) received only bottle feedings during hospitalization and the experimental group (n = 30) received only cup feedings during hospitalization. Both groups were followed up after discharge for six weeks to evaluate infant's breastfeeding behavior and mother's breastfeeding practices. Data were analyzed using descriptive statistics and repeated measures ANOVA for testing the differences between the cup feeding and bottle feeding groups over six weeks after discharge.

Results: Cup fed infants demonstrated significantly more mature breastfeeding behaviors when compared to bottle fed infants ($p < 0.01$) over six weeks, and had a significantly higher proportion of breast feedings one week after discharge ($p = 0.03$).

Conclusion: Cup fed infants were more exclusively breast fed one week after discharge, supporting the Baby Friendly Hospital Initiative recommendations for using cup feeding and avoiding bottle feeding when providing supplementation for preterm infants. The current study provides initial evidence for the implementation of cup feeding as a method of supplementation for late preterm infants during hospitalization.

Background

The provision of breast milk is essential for preterm infants as it provides unique health benefits that are unmatched by other types of feeding. However, breastfeeding presents unique challenges for preterm infants that include establishing and maintaining the mothers' milk supply and transitioning the infant from gavage feeding to breastfeeding. One of the issues that presents during the transition to breastfeeding is that mothers of preterm infants are rarely available for all oral feedings during hospitalization; making it necessary for infants to receive oral feedings by other methods, usually bottle feeding.

However, exposure of newborn infants to artificial nipples has been strongly associated with breastfeeding problems. Frequently these problems have been explained by a phenomenon called nipple confusion. Nipple confusion occurs when infants are exposed to two different feeding methods, bottle and breast, resulting in the infant refusing to breastfeed. Consequently, it has been recommended that bottle feeding be avoided and that cup feeding be used for the supplementation of term as well as preterm infants.

Cup feeding is known as an alternative method of feeding breast milk to an infant using a small cup without a lip. Cup feeding is also recommended by the Baby Friendly Hospital Initiative. The use of the cup for feeding newborn infants was originally based on the goal of avoiding propping up of bottles and also to increase bodily contact with the mother during feeding. Although cup feeding receives little mention in medical literature, and may seem to be a new technique for some, cup feeding has been used in several developing and developed countries. Lang, who observed cup feeding in South Nepal, implemented cup feeding in England and the practice expanded to other developed countries. Consequently cup feeding was established as a method for feeding infants who could not be breastfed from birth.

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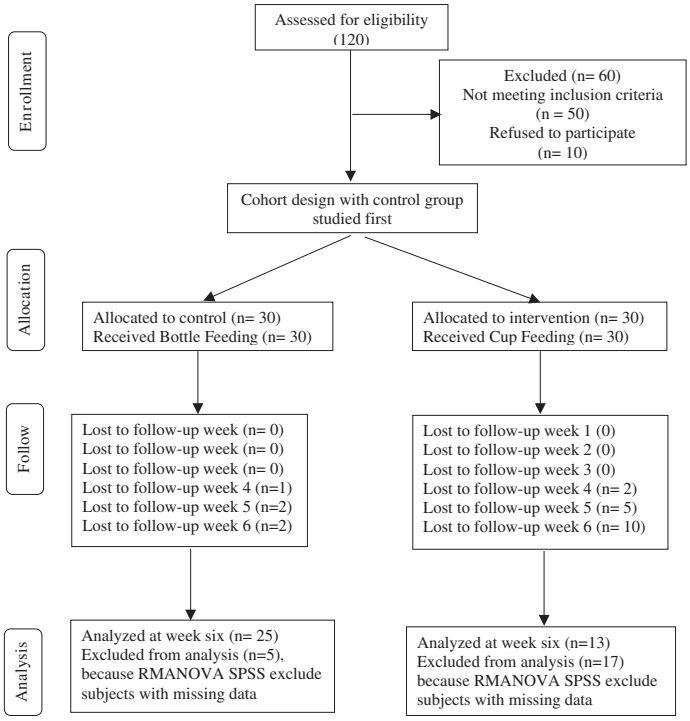

Figure 1. Sampling Flow Chart.

The findings of studies concerning breastfeeding outcomes of cup fed infants have been inconsistent. A Cochrane review concluded that cup feeding cannot be recommended over bottle feeding as a supplement to breastfeeding because cup feeding had no significant benefit in maintaining breastfeeding beyond hospital discharge. Also, the review suggested that cup feeding had the potential for the unacceptable consequence of a longer hospital stay. A randomized controlled trial compared the impact of cup or bottle supplementation for preterm infants on subsequent breastfeeding at discharge from the hospital. No significant differences were found between the bottle and cup feeding infants in terms of whether they were breastfeeding or not at discharge from the hospital. However, the small sample size (n = 12) may have contributed to the lack of differences. In contrast, another report suggested that infants in special care units who are supplemented by cup are more likely to breastfeed longer than those supplemented by bottle.

Cup feeding has not been implemented in Egypt, making evaluation of its use essential. Additionally, given the absence of definitive evidence as to the most effective method of supplementation for preterm infants during hospitalization and the effects of cup feeding on breastfeeding patterns after hospital discharge, the purpose of the current study was to examine the effect of cup feeding on breastfeeding in late preterm infants after discharge. The following research questions were addressed: (1) Are premature infants supplemented by cup during hospitalization more likely to be fully breastfed six weeks after discharge when compared to premature infants supplemented by bottle during hospitalization?, and (2) Do preterm infants supplemented by cup during hospitalization demonstrate more mature breastfeeding behavior at 1, 2, 3, 4, 5, and 6 weeks after discharge when compared to preterm infants supplemented by bottle?

Methods

A quasi-experimental cohort design was employed using two groups. The first group, the control (bottle) group, received all oral feedings by bottle during hospitalization as that was the standard practice in the Neonatal Intensive Care Units (NICUs) where the study was conducted. The control group was studied first to avoid the exposure of the control group to the intervention, cup feeding. The second group, the intervention (cup) group, received all oral feedings by cup during hospitalization. Infants in both groups were studied weekly for six weeks after discharge.

The convenience sample consisted of 60 late preterm infants admitted to the NICU. Thirty infants were assigned to the control group and the next 30 to the intervention group. To calculate the sample size, statistical power analysis was performed using a

Table 1. Comparison of demographic characteristics of infants and mothers.

Characteristic	Bottle group N = 30 mean (SD)	Cup group N = 30 mean (SD)	t	p
Gestational age at birth (wks)	35.3 (1.1)	34.9 (0.9)	1.27	0.23
Gestational age at discharge (wks)	38.1 (1.2)	37.2 (0.9)	3.16	< 0.01
Birth weight (grams)	2033 (329)	2267 (319)	2.78	< 0.01
Days in hospital	19.4 (9.8)	15.5 (8.1)	1.69	0.09
Days using cup or bottle	12.5 (8.2)	9.1 (5.6)	1.85	0.06
Mothers' age	26.5 (5.2)	27.3 (6.1)	0.55	0.58
Numbers of breastfeeds in hospital	2.4 (2.9)	3.2 (3.3)	0.99	0.33
	Bottle group N = 30 n (%)	**Cup group N = 30 n (%)**	x^2	p
Mothers' education			0.38	0.83
No education	8 (27)	8 (27)		
Some education	8 (27)	10(33)		
Educated	14 (46)	12 (40)		
Mothers' occupation			0.07	0.57
Not working	20 (67)	23 (77)		
Working	10 (33)	7 (23)		
Delivery			0.07	0.39
Vaginal	13 (43)	12 (40)		
Caesarian section	17 (57)	18 (60)		
Previous breastfeeding	16 (53)	15 (50)	0.07	0.79
Previous bottle feeding	11 (37)	12 (40)	0.07	0.79

Table 2. Feeding practices one week post discharge.

Feeding practices	Bottle group N = 30 n (%)	Cup group N = 30 n (%)	t	p
Proportion of breastfeeding	64.4 (29.5)	80.2 (25.7)	2.22	0.03
No. of breastfeeds/day	6.8 (3.4)	8.5 (3.1)	2.07	0.04
No. of bottle feeds/day	3.6 (3.0)	1.8 (1.9)	2.79	< 0.01
Bottle feeding	20 (56)	16 (44)	1.11	0.22
Formula	15 (75)	7 (44)		
Expressed breast milk	1 (5)	0 (0)		
Ritualistic feeds	3 (15)	9 (56)		

medium effect size and a power of 80%. Breastfeeding prevalence at discharge from a previous study was used to conduct the power calculation. Infants met the following inclusion criteria: (a) singleton birth, (b) 34 to 37 weeks of gestation at birth, (c) maternal intention to breastfeed, (d) no supplemental oxygen required, and (e) being fed only by intermittent gavage feeding at the time of recruitment. Infants could be in open cribs, radiant warmers, or incubators. Infants who had any condition interfering with oral feeding, including an oral congenital anomaly, intracranial hemorrhage, and/or craniofacial anomalies, were excluded. All potentially eligible infants and mothers were approached sequentially until the required sample was completed for each group, with the intervention group being recruited after completion of the control group. Total attrition for the study was 22 mothers, with one mother not returning for the fourth week visit, nine more mothers not returning at week five and an additional 12 mothers were lost at week six. At week six, 25 mothers in the control group and 13 mothers in the intervention group remained in the study (Figure 1).

The study was conducted in two transitional nurseries in neonatal intensive care units at Pediatric University Hospital, Cairo, Egypt. Mothers in the current study setting were not instructed on how to express breast milk.

Two study instruments were used for data collection. The first was The Maternal Breastfeeding Practice Questionnaire (MBP), developed for use in this study to assess daily infant feeding practices during the past week. The MBP included demographic questions as well as questions that assessed breastfeeding frequency and the number of bottle feedings, and whether artificial formula or any other type of feedings had been given to the infant. The proportion of feedings that were breastfeeding (direct breastfeeding or any expressed breast milk) was classified according to the Labbok and Krasovec schema for the definition of breastfeeding. The schema divides the act of breastfeeding into three major categories: full breastfeeding (exclusive and almost exclusive), partial breastfeeding, and token breastfeeding. Exclusive breastfeeding means that nothing other than breast milk enters the infant's mouth. Almost exclusive breastfeeding means that water, vitamins or ritualistic feedings like herbal drinks are given infrequently but not for nutritional purposes. Partial breastfeeding means supplementing the infant's feedings with other foods or liquids, and includes three levels: High, Medium, and Low. Partial breastfeeding levels represent the proportion of breastfeedings per day, or the relative amount of breast milk consumed to any other feeds (> 80%, 20 – 80%, < 20%). Token breastfeeding reflects minimal and irregular breastfeeding that constitute less than 15% of the total daily feedings, and using the breast primarily for infant comfort and consoling, not for nutrition.

The Premature Infant Breastfeeding Behavior Scale (PIBBS) was the second instrument. The PIBBS was used to measure the infant's breastfeeding behaviors at one to six weeks after discharge. The PIBBS consists of 11 items; six of these items measure the development of preterm infant's breastfeeding behavior, while the other five items measure factors related to the breastfeeding session, such as the infant's general behavior, presence of letdown reflex, how long the infant was held, presence of any breast problem, and influence of the environment. Consequently, only the six items used for the scoring of the infant's breastfeeding behavior were used in the current study. The items were rooting, areola grasp, longest duration of latching, amount of sucking, longest sucking burst, and swallowing. Face validity of the PIBBS was determined by three experts working in a WHO project on breastfeeding.

Infants were fed either by bottle (control group) or by cup (intervention group) from the time oral feeding was started until discharge. Bottle feedings were given either by the assigned nursing staff or by the PI. All cup feedings were given by the PI or by one of two research assistants who are staff nurses at the NICU and who had been trained in the cup feeding technique by the PI. Lang's cup feeding technique was used.

After infants were discharged from the NICU, mothers were interviewed at the first outpatient visit (one week post discharge) in a private room adjacent to the NICU to recall their breastfeeding practices during the previous week. Additionally, mothers and infants were observed by the PI during one breastfeeding session weekly for six weeks for assessment of infants' breastfeeding behaviors. The observation unit was a breastfeeding session defined as beginning when the mother initiated skin-to-skin contact with her infant and ending when

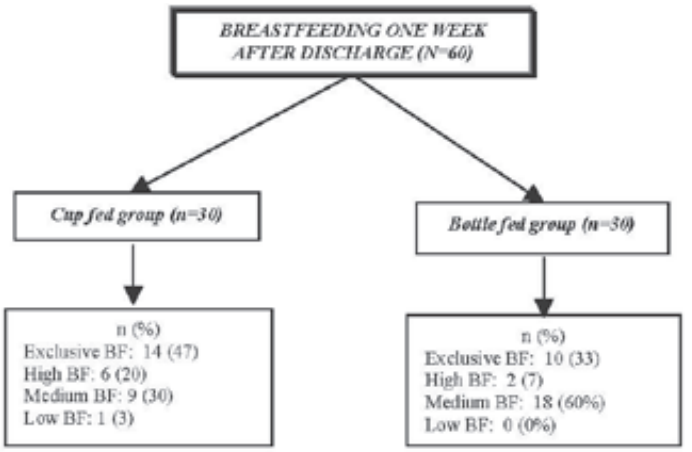

Figure 2. Daily feeding type one week post-discharge.

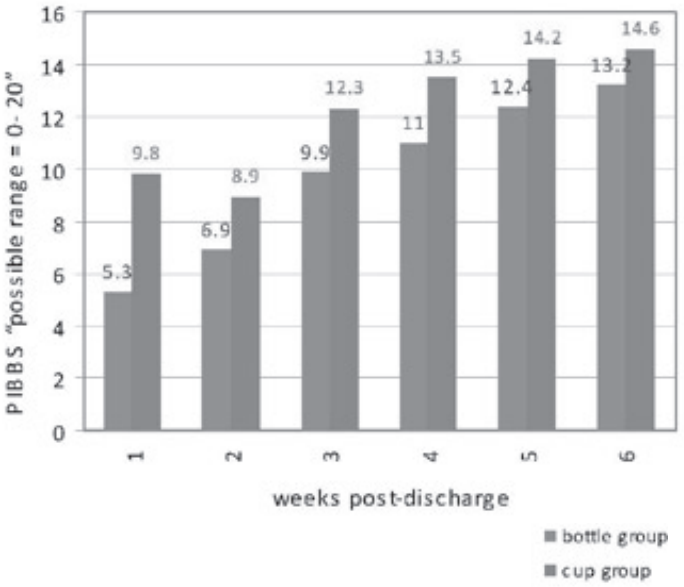

Figure 3. PIBBS mean scores over six weeks post-discharge.

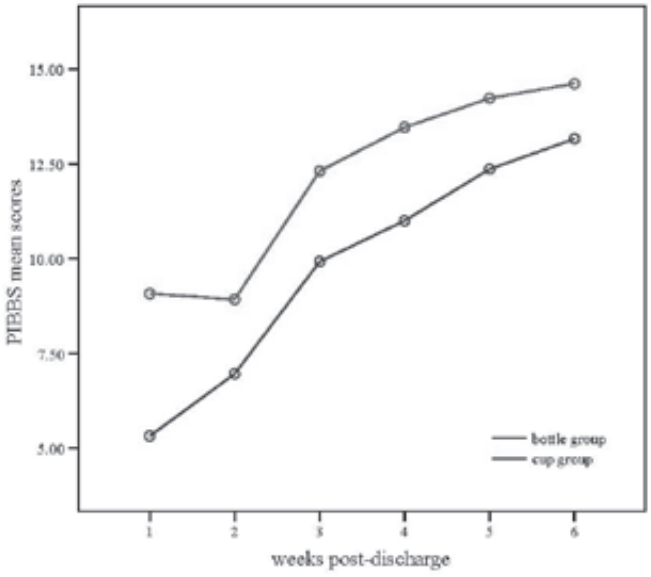

Figure 4. Group and time interaction of PIBBS mean scores over six weeks post-discharge.

skin-to-skin contact was terminated. The PI sat near the mother in a position which provided the best possible visibility of the infant's face and chin, and the infant's behavior at the breast was recorded using the PIBBS. At the end of the first breastfeeding session the PI asked the mothers the questions included in the Maternal Breastfeeding Questionnaire. It included questions about the frequency of breastfeeding during the day and the night, if any bottle feedings were given to the infant since discharge from the hospital, what was given (i.e. infant formula) and the frequency.

Results

Demographic characteristics for the cup and bottle feeding infants and their mothers are presented in Table 1. For the entire sample the mean duration of hospitalization was 17.5 days (Standard Deviation (SD) = 9.1 days) with no significant difference between cup and bottle groups. Infants had few direct breastfeeding experiences during hospitalization that ranged from one to ten times (mean = 2.8, SD = 3.1) and a mean duration of cup or bottle feeding of 9.1 (SD = 5.6 days) and 12.5 days (SD = 8.2 days) respectively with no statistically significant differences between the two groups for their breastfeeding experience or days on cup or bottle feedings during hospitalization.

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Figure 2 depicts the exclusivity of breastfeeding (direct breastfeeding and expressed breast milk) for infants in both groups one week after discharge. More infants in the cup feeding group were almost exclusively breastfed at one week after discharge when compared to infants in the bottle fed group (47% & 33% respectively). However, no statistically significant differences between the two groups in relation to the type of breastfeeding (either exclusive breastfeeding or partial breastfeeding were found ($\chi^2 = 1.1$, $p = 0.29$).

Do premature infants supplemented by cup during hospitalization demonstrate more mature breastfeeding behavior at 1, 2, 3, 4, 5, and 6 weeks after discharge when compared to premature infants supplemented by bottle?

Maturation of breastfeeding behavior was measured using the PIBBS. Figure 3 demonstrates the mean PIBBS scores for the both groups from week one through week six. Statistically significant differences in infant's age at discharge existed between infants in the cup feeding and bottle feeding groups, reflecting the younger age of infants in the intervention (cup feeding) group ($t = 3.16$, $p < 0.01$) (Table 1). Infants in the cup feeding group had a higher PIBBS score than infants in the bottle feeding group from the first week after discharge through the sixth week after discharge. Repeated-measures analysis of variance, using the general linear model, was used to examine the differences in the infants' breastfeeding behavior over time for the two groups. Because the assumption of compound symmetry was not met, the multivariate results (Wilks' Lambda) are reported (Table 3). An overall statistically significant difference in PIBBS Score existed between the bottle and the cup feeding groups, with the higher PIBBS scores occurring in cup feeding group ($p = < 0.01$). Also, there was a statistically significant difference for time effect (over six weeks after discharge) ($p < 0.01$), reflecting increasing scores for both

Table 3. Repeated measures analysis for the PIBBS scores over six weeks post-discharge.

Variable	Factor	F	df	p
PIBBS scores	Group	11.86	1.00	< 0.01
	Time	157.90	2.47	< 0.01
	Group*time	3.21	2.47	0.04

groups across the six time points. The interaction between group and time was also statistically significant ($p = 0.04$). This interaction is presented in Table 3 and illustrated Figure 4.

Discussion

Findings of the current study should be interpreted in the light of the following limitations. First, a randomized experimental design could not be used because the introduction of cup feeding would have been a threat to internal validity through the possible diffusion of cup feeding to the control group. Consequently, randomization was not possible. Second, the principal investigator collected all of the data, including the assessments of breastfeeding behavior after discharge. Thus, the PI was not blinded to group assignment or to the purpose of the study. Further study using independent data collectors who are blind to group assignment and purpose is required to overcome these limitations. Third, it was intended that determination of breastfeeding practices would have continued longer after discharge. However, 56% of the mothers had either only some or no education so that long term written documentation was not feasible. Additionally, concerns regarding accuracy of maternal verbal recall were present. These concerns were minimized by recording breastfeeding practices for the first week after discharge only. Use of a simple feeding diary is recommended for future studies. Finally because of the loss to follow up, the sample was too small to adequately answer the primary research question. Future research needs to be planned using a larger sample size to account for attrition. Despite the limitations, the current study was the first to implement cup feeding for preterm infants in Egypt and was one of the few studies to use cup feeding as the only oral feeding method for preterm infants during hospitalization.

All 60 mothers intended to breastfeed after discharge. Even though, only 17 infants in the bottle feeding group and 20 infants in the cup feeding group had breastfeeding experiences during hospitalization. The low incidence of breastfeeding during hospitalization is most likely a result of many factors, including infrequent visiting and lack of encouragement of the mothers to be actively involved in their infants' care during visitation. Consequently, 38% of the infants were discharged with no breastfeeding experiences during hospitalization. Despite this, the overall mean proportion of feedings that were breast feeding for the entire group one week after discharge was 72%, with a significantly higher proportion in the cup feeding group when compared to the bottle feeding group. Infants in the cup feeding group had significantly more breastfeedings per day one week after discharge from the hospital than infants in the bottle feeding group, suggesting that the transition to breastfeeding progressed more quickly for cup feeding infants than for bottle feeding infants. The lack of exposure of cup fed infants to oral mechanisms used during bottle feeding, which are different than the oral mechanisms used during breastfeeding, might facilitate adaptation to breastfeeding. However, the explanation for this finding is unclear.

Sipping and lapping used during cup feeding has been theorized to enhance development of tongue movements needed for breastfeeding. However, the mechanisms of sipping and lapping differ from those required during breastfeeding. Sipping and lapping require the lips to be closed, rather than open, as required during breastfeeding and to a lesser extent during bottle feeding. Differences in mouth contour, activity of the masseter, temporalis and buccinators muscles, and the position of the lips between cup, bottle and breastfeeding may contribute to subsequent breastfeeding difficulties. A recent electromyographic study carried out during cup feeding, bottle feeding and breastfeeding found that the range of contraction and mean contraction of the masseter muscle were greater during cup feeding than during bottle feeding. This finding supported the recommendation that if breastfeeding is not possible at certain times, cup feeding may be indicated, as it allows the participation of the masseter and temporalis muscles in a way that is similar to the participation of these muscles during breastfeeding. These differences in oral mechanisms underlie the differences found in breastfeeding patterns when alternative methods such as bottle feeding have been used for supplementation of the breastfeeding infant.

An increased prevalence of breastfeeding has been reported when bottle feeding was replaced by cup feeding for preterm infants as well as full term infants. The findings of the current study are consistent with a recent randomized controlled trial that found that cup feeding significantly increased the odds of breastfeeding at discharge. Additionally, Collins et al. reported a significant increase in the prevalence of breastfeeding at three and six months after discharge for infants fed by cup during hospitalization when compared with bottle supplementation. In contrast, another randomized controlled trial provided unclear evidence of the effect of using cup or bottle for feeding preterm infants on breastfeeding. No differences in breastfeeding prevalence at the first return visit between infants fed by cup and infants fed by bottle during hospitalization were found. At the first visit, 56% of bottle fed infants and 57% of cup fed infants had already been weaned and both groups presented similar breastfeeding prevalence. However, the percentage of infants still breastfeeding was two times greater in the cup fed group.

Although there were no statistically significant differences in the current study between cup feeding and bottle feeding groups regarding their breastfeeding type (full or partial) one week after discharge, more infants were exclusively breastfed in cup feeding group than in the bottle feeding group. These results are consistent with previous cup feeding studies that reported that cup feeding significantly increased the likelihood that the preterm infants would be fully breast fed at hospital discharge. Additionally, it has been demonstrated that exclusivity of breastfeeding at one month after birth predicted the likelihood of continuing breastfeeding at six months. In the current study it is possible that the shorter duration of cup feeding (9.1 days ± 5.61) than bottle feeding (12.5 days ± 8.20) resulted in these more optimal findings, as infants in the cup feeding group had less exposure to a feeding method other than breastfeeding. However, these findings were not significantly different, suggesting that it is the process of cup feeding rather than the duration of the feeding method that contributed to the better breastfeeding for the cup feeding group. In contrast to the suggestion of a recent Cochrane review, the length of hospital stay was shorter for the cup fed infants.

The second research question examined the maturation of breastfeeding behaviors from one through six weeks after discharge for both cup and bottle groups. The study findings demonstrated statistically significant differences between the cup and bottle feeding groups in their total breastfeeding behavior scores from the first-to-the sixth week after hospital discharge, reflecting higher mean PIBBS scores at each time point for the cup fed infants than the bottle fed infants.

Additionally, infants in both groups showed an increase in their PIBBS scores over the six weeks, indicating a maturation of breastfeeding behavior over time. These findings are consistent with those of Nyqvist.

There was a significant interaction effect between group and time, demonstrating that, although both groups demonstrated expected maturation of breastfeeding behaviors, cup fed infants were significantly more mature in their breastfeeding behaviors at all time points than bottle fed infants, despite the cup feeding infants having statistically significant younger ages at discharge. The finding of improved breastfeeding behavior maturation among cup fed infants may be related to the higher breastfeeding proportion for this group, in that more breastfeeding experience may promote the maturation of breastfeeding behaviors. Conversely, more mature breastfeeding behavior may promote the frequency of breastfeeding.

Most previous studies have been concerned only with descriptions of infants' sucking and swallowing behavior, physiologic responses, and milk transfer. Nyqvist, (1996) developed the PIBBS and used the instrument to describe the behaviors of breastfeeding preterm infants. However, the current study is the first to use the PIBBS to compare groups of breastfeeding preterm infants in relation to the method of supplementation. A recent report used the PIBBS to evaluate breastfeeding behaviors for two groups of term infants to determine if epidural anesthesia had an effect on breastfeeding behaviors. There were no statistically significant differences found between the groups. However, the PIBBS was not an appropriate instrument for use in that study as it had been developed for use with preterm infants. Future research should focus on the use of the PIBBS to compare preterm infants in relation to a variety of different experiences this population may have during the transition to full oral feeding.

Conclusion

Cup fed infants were more exclusively breast-fed after discharge, supporting the Baby Friendly Hospital Initiative recommendations for using cup feeding and avoiding bottle feeding when providing supplementation for preterm infants. The current study provides initial evidence for the implementation of cup feeding as a method of supplementation during hospitalization. If cup feeding is implemented in Egypt it will be necessary to first educate the medical and nursing staff. All healthcare personnel need to promote breastfeeding as the best and natural feeding method for all infants. Additionally, healthcare providers need to accept cup feeding as a safe, efficient feeding method and to learn safe cup feeding techniques. The finding that most mothers in both groups were able to initiate breastfeeding after discharge is interesting. Mothers did not have access to an electric breast pumps and did not provide breast milk to infants during hospitalization. Therefore, it is not known how mothers established and maintained their milk supply. These findings draw attention to the need for further exploration of the methods used by mothers of preterm infants to maintain their milk supply during infant hospitalization.

HME…continued from page 26

American National Standards Institute (ANSI), and the Internal Organization for Standardization (ISO). The AARC's minimum standard for an HME states that it should deliver no less than 30mg H2O/L at 30 degrees C 3, however, most HMEs do not meet this minimum standard. In fact, only 12 of the HMEs tested by the researchers met this minimum standard.

This study can be used by clinicians as an important guide to help them make informed decisions about what adult HMEs may be best suited for their clinical environment. It provides the available manufacturer data for the devices by name as well as the data obtained from the bench test apparatus. Further, it provides humidity efficiency data obtained from the bench test apparatus, and ranks the devices from highest efficiency to lowest efficiency. How effective is your HME?

* The Medisize Green and Red product lines came in first and tied for second in a field of 48 products. This study was performed in France. When reviewing the report please note that the products are listed under their European product line names (Hygrovent) and under the Medisize French distributor, Peters. In the US, Medisize products are distributed by Hamilton Medical.

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Maturation of Gastric Electrical Activity, Gastric Emptying and Intestinal Permeability in Preterm Newborns During the First Month of Life

Giuseppe Riezzo, Flavia Indrio, Francesco Raimondi, Osvaldo Montagna, Gennaro Salvia, Bisceglia Massimo, Lorenzo Polimeno, Luciano Cavallo and Ruggiero Francavilla

Abstract

Introduction: Immaturity of motility, intestinal epithelial barrier function and absorptive capacity may play a role in the pathophysiology of intestinal diseases in preterms. We determined the gastric electrical activity and emptying, and intestinal permeability, in preterm newborns to verify if a maturation pattern exists in preterm newborns during the first month of life.

Patients and Methods: Eighteen preterm newborns (median 34 wks, range 2 wks) completed the study. They underwent the recording of gastric electrical activity by means of cutaneous electrogastrography, the ultrasound examination of gastric emptying, and the lactulose-to-mannitol ratio from permeability-absorption test on days 3, 7, 15, and 30 after birth.

Results: Gastric electrical activity and emptying showed only slight changes between day 3 and day 7. On the contrary, an evident maturation in permeability, expressed as L/Mratio, was evident over time (Friedman Repeated Measures Analysis, p = 0.004).

Conclusion: In preterm healthy newborns of 34 weeks gestational age, electrical and motor activity are completely developed at birth whilst the intestinal epithelial barrier clearly improves during the first week of life.

Introduction

Feeding intolerance is a recurrent problem in the clinical care of preterm infants and occur mainly in the first week of life, suggesting the presence of a maturation pattern of gastrointestinal tract.[1] It is known that functional maturation of the gastrointestinal tract is quite different over time with respect to its anatomical development.[2-4] Adequate levels of some digestive enzymes are reached only at the end of gestation and lactase activity at 34 weeks gestation is only 30% of the level of full-term newborns.[3] To date there is little data available about the development of the motility function and of the mucosal barrier in newborns during early days of life.

Gastrointestinal motility can be recorded as a measure of gastric electrical activity, of the wall movements, and of gastric emptying time. A reliable method for recording gastric motility is cutaneous electrogastrography (EGG);[5-7] electrogastrographic studies in newborns have demonstrated the absence of normal slow waves at birth and a maturation process modulated by enteral feedings.[8-11] Gastric emptying (GE) can be assessed by ultrasonography which is considered a non-invasive technique particularly suitable for young patients.[12]

The functional integrity of the mucosal barrier of the intestine partly depends on the close interaction of adjacent mucosal cells. The most reliable in vivo method to study this functional integrity is the sugar absorption test (SAT), which has been performed on adults[13] and newborns, both preterm[14] and term ones.[15] Some of the key events involving permeability actually take place in the neonatal period, when the barrier is leakier. Coordinated motor function in the gastrointestinal tract plays a crucial role in the intestinal transportation, absorption and maintenance of the enteric bacterial ecology.[16] In particular, delayed intestinal transit time may contribute to increased mucosal permeability, and even to facilitated bacterial translocation.[17]

Table 1: Baseline anthropometric and clinical data of the newborns which completed the study (n = 18)

Gestational age	34 [2]
Birth weight (g)	2140 [305]
Apgar score	8 [1]
Male/Female	8/10
Vaginal/caesarian delivery	7/11

Data are expressed as Medians and range or numbers

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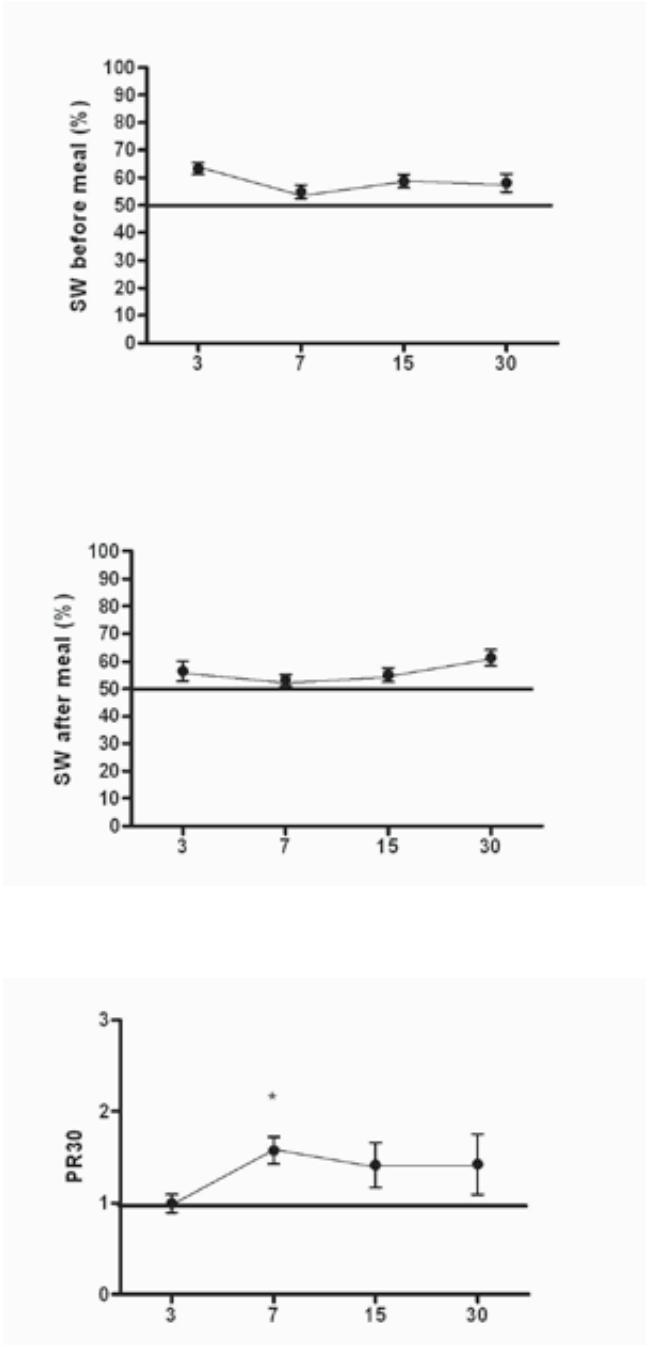

Figure 1. Gastric electrical activity are reported as percentage of gastric slow waves (SW) at baseline (a), after meal (b), and power ratio (PR) (c). Repeated measurements analysis did not demonstrate any improvement in power ratio over time. Only a difference at day 7 respect to day 3 is evident. Data are means ± SEM.

The aim of the study was to investigate gastric motility and intestinal permeability to verify if a maturation pattern exists in preterm newborns during the first month of life.

Methods

Infants and protocol: The study was performed at the Neonatology Section of the Department of Pediatrics at the University of Bari. Healthy preterm newborns, born at a gestational age of 28–36 weeks, a birth weight > 1800 g, normal Apgar score, and a post natal age ≤ 24 h, were eligible to participate in the study. Newborns with: a) respiratory distress, b) congenital malformation, c) inborn errors of metabolism, or d) proven sepsis or infection, were not included. From an initial

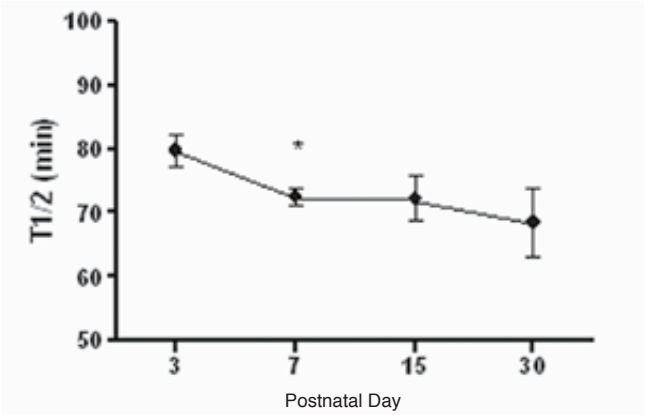

Figure 2. Gastric emptying time is reported as the half emptying time (T1/2). Repeated measurements analysis did not show any improvement in T1/2 over time. A slightly difference at day 7 respect to day 3 is only evident. Data are means ± SEM.

group of 38 preterm newborns, 18 entirely bottle-fed infants completed the study. The others were excluded for various reasons: a change in milk formula (4 newborns); an infectious disease (1 newborn); withdrawal from the study (7 newborns); inability to perform the scheduled SAT due to early transfer to another hospital (1 newborn) and/or failure to collect urine within the scheduled collection day (7 newborns). All the newborns enrolled reached the total amount of enteral feeding within the first week of life. All the preterm newborns were exclusively bottle-fed with the same preterm standard formula throughout the intervention period. The daily formula intake was approximately 30 ml/kg/day at baseline and 180 ml/kg/day at the end on the study.

Gastric electrical activity, gastric emptying time and intestinal permeability were recorded on days 3, 7, 15, and 30 after birth in order to evaluate the time changes in motility and permeability. The range of the data collection period was rigorously narrow (± 1 day). From birth until the end of the study, episodes of regurgitation, vomiting, number of evacuations, the time of complete emission of meconium, and the daily amount of feedings, were recorded. Written informed consent was obtained from the parents, and the study was approved by our local institutional ethics committee.

Assessment of gastric electrical activity: The EGG recordings were performed using portable equipment before and 120 min after meal, following a fasting period of 4 hours. Two silver-silver chloride bipolar electrodes (Clear Trace, ConMed, Utica, NY) were placed on the cleaned abdominal surface overlying the antro-pyloric axis to obtain the best signal-noise ratio. The reference electrode was placed to form an equilateral triangle.[18] Electrogastrography was performed using a portable EGG recorder (UPS 2020, Medical Management Systems, MMS, The Netherlands). The recordings and analysis of the EGG parameters (dominant frequency and normal slow wave percentage, power ratio) were previously described in different papers.[11,19]

Assessment of gastric emptying: The ultrasound gastric emptying examinations were always performed by the same investigator using a real-time apparatus (Image Point HX, Hewlett Packard Company, Palo Alto, CA) equipped with a 3.5 MHz linear probe. The ultrasound examination and the measure of the antral area were performed according to the

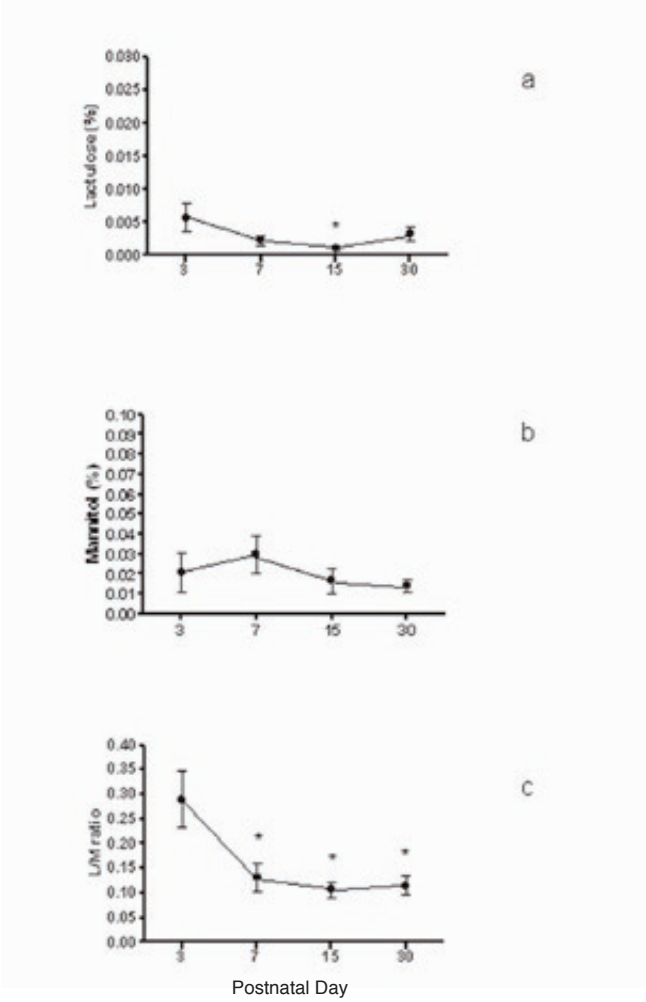

Figure 3. Intestinal permeability pattern as determined by urinary excretion of orally administered lactulose (a), mannitol (b), and L/M ratio (c) respectively. L/M ratio persistently and significantly reduces after day 3 (see text). Data are means ± SEM.

procedure reported in a previous work.[11] The EGG and GE were simultaneously recorded to avoid differences due to the rapid changes in physiological parameters. During the same EGG recording session, antral measurements were made before the test meal, and at regular 30-min intervals up to 180 min after the meal. In each patient, the half emptying time (T1/2) was calculated.[11,12,20]

Assessment of intestinal permeability: The SAT was performed after oral ingestion, by suckling, of a solution containing 5.0 g of lactulose and 2.0 g of mannitol (Sigma Aldrich s.r.l., Milano, Italy) per 100 ml water (375 mosml/l) at a dose of 2 ml/kg of body weight. The newborns fasted two hours before and after the oral administration of the solution. All the urine passed in the subsequent five hours was collected in an adhesive urine bag (Sincrolag srl Italy). The complete urine volume was measured and stored at -80°C until analysis. Urinary concentration of lactulose and mannitol were determined by ion exchange chromatography with pulse amperometric detection.[21] Lactulose is a disaccharide that crosses the intestinal epithelium by passive diffusion through the paracellular tight junctions. Mannitol is a monosaccharide that crosses the intestinal epithelium mainly by transcellular passive diffusion through aqueous pores.[22] The evidence of an exclusively transcellular permeation of monosaccharides is still controversial. Mannitol is used for osmotic shrinkage of membrane vesicles, which would not be possible if permeation across cell membranes were unrestricted, and many experimental physiologists use it as an extracellular fluid volume marker suggesting a paracellular route of permeation for this probe.[23]

The urinary excretion percentage of lactulose and mannitol are markers for paracellular and transcellular diffusion respectively. To correct for non-mucosal factors that may affect the intestinal uptake of these saccharides, including rate of gastric emptying, intestinal transit time and renal clearance, the urinary percentage of lactulose and mannitol were expressed as the L/M ratio.

Data analysis: The data were first analyzed using simple descriptive statistics of centrality and dispersion. Clinical parameters are expressed as median and range and physiological data are expressed as mean ± SEM. However, because of the sample size and absence of a normal distribution of the data, only non-parametric statistical analysis tests were performed. The overall effect over time of EGG, GE and SAT parameters was determined by a repeated measures analysis (Friedman Friedman Repeated Measures Anova). Because of missing data at some points, multiple comparisons were not available and differences among the recording points of EGG, GE and SAT parameters were made using the Wilcoxon signed rank test. All the differences were considered significant at a 5% level. The software package used for the statistical analysis was STATA (STATA ver 4.0 Statistical Software, Stata Corporation).

Results

Anthropometric and clinical parameters: These parameters are reported in Table 1. It clearly shows that a homogeneous group was collected. None of the newborns presented significant regurgitation and/or vomiting from birth until the last day of examination and all passed the meconium within the second day of life. All newborns reached the total amount of enteral feeding (140 ml/kg/day) within the seven days.

Electrogastrographic and Gastric emptying data: Figure 1(a,b,c) shows the pattern over time of the percentage of normal slow waves recorded before and after meal, and the pattern of power ratio (Power ratio: Friedman Repeated Measures $p = 0.18$; Wilcoxon signed rank test, day 3 vs day 7 $p = 0.02$). Figure 2 plots the ultrasound T1/2 over time (Friedman Repeated Measures Analysis $p = 0.69$; Wilcoxon signed rank test day 3 vs day 7 $p = 0.08$). Both power ratio and gastric emptying time did show a slightly difference comparing day 3 and day 7, without a significant improvement over time.

Intestinal permeability data: Measurement of lactulose excretion demonstrated an evident reduction at day 7 and the subsequent recording days (Figure 3a). On the other hand, measurement of mannitol excretion demonstrated a fluctuation over time and an increase on day 7 without reaching a significant difference (Figure 3b). The L/M ratio showed a deep decline between day 3 and day 7, then the ratio became constantly low (Friedman Repeated Measures Analysis $p = 0.004$; Wilcoxon signed rank test: day 3 vs day 7 $p < 0.05$, day 3 vs day 15 $p < 0.05$, day 3 vs day 30 $p < 0.05$ (Figure 3c).

Discussion

In preterm newborns the gastric electrical activity is quite stable with slight differences in power ratio and emptying at given recording days. On the contrary, intestinal permeability showed a persistent improvement over the first week of postnatal life.

A few studies have investigated the gastric motility and intestinal permeability in preterm newborns. We studied the gastric electrical activity, gastric emptying and intestinal permeability in a time series in order to account for the effect of the different physiological variables over time. The pattern of slow wave percentage in the normal neonates showed a stable 3 cpm activity over time. During the first month of life the slow wave percentage was usually reported to be about 38%[24] from birth to 4 weeks, whilst according to others the slow wave percentage was about 50%.[25] Our data from premature newborns showed a higher percentage of normal slow wave, probably as a result of our broad interval in the normal EGG frequency ranges.

Intestinal immaturity is limited largely to infants of less than 34 weeks gestation but may extend to older gestational ages. Intestinal immaturity could explain poor gastroduodenal coordination and excessive quiescence in motor activity reported in very immature infants as poor gastric emptying, duodenogastric reflux and gastroduodenal hypomotility.[26,27] Our group of healthy newborns were of about 34 weeks gestation and showed a normal EGG parameters and gastric emptying time, even if subtle differences between the recording days were found. These findings confirm that gastric development is complete in late preterm infants.[28-30]

Different sugar-absorption tests for measuring intestinal permeability for sugars have been studied in a variety of gastrointestinal diseases. In vivo mannitol is absorbed via the transcellular pathway and serves as a marker of transcellular uptake[22,23] while lactulose is only slightly absorbed, but exclusively across the intestinal membrane through the intercellular junctions, and serves as a marker for mucosal integrity.[31] In our study L/M ratio was sharply reduced at day 7, then it remained stable. The clinical significance of an increased intestinal permeability is still under investigation. Although alterations in intestinal permeability could cause bacterial translocation and septic complications, no evidence is reported in humans to support this assumption.[32,33] A close relationship between luminal factors and permeability was demonstrated only for IgA, ovoalbumin, and bacterial peptides.[34-36] Overall, the human neonate shows a developmental pattern of sugar intestinal permeability that resembles gut closure observed in other mammals; intestinal permeability decreases faster in breast-fed newborns than in those fed with adapted or hydrolysed formula.[37,38] However, both decreased and increased permeability during the first months of life have been reported.[14,39,49] The reasons for such discrepancies lie in the differences in study design such as gestational age, clinical condition, feeding regiments and postnatal age at the time of the studies. Our data are similar to that of Van Elburg, actually preterm newborns permeability is higher during the first 2 days of life than up to 6 days later, independently of birth weight and gestational age.[41] Our data showed a slight increase in mannitol permeability in day 7 and a dramatic reduction of L/M ratio between day 3 and day 7 related to reduced lactulose permeability. Even if the relationship between feeding and intestinal maturation was not studied in our paper, some authors have demonstrated that the starting of enteral feeding induces an increase in intestinal barrier function.[42] The fact that adult patients fed with total parenteral nutrition showed an impaired intestinal permeability confirms the link between enteral nutrition and permeability.[43]

In conclusion, healthy late preterm newborns showed mature EGG and gastric emptying and a rapid improvement in intestinal permeability. The role of enteral nutrients is not merely linked to nourishing the developing intestine of the premature infants but may represent a kick off point. Optimization of nutrition in preterm infants could have major implications for health and outcome.

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Posthemorrhagic Hydrocephalus of Infants: A review of the current treatment methods

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Abstract

Posthemorrhagic hydrocephalus (PHH) is a major problem for premature infants, generally requiring lifelong care. It results from small blood clots inducing scarring within CSF channels impeding CSF circulation. Transforming growth factor – beta is released into CSF and cytokines stimulate deposition of extracellular matrix proteins which potentially obstruct CSF pathways. Prolonged raised pressures and free radical damage incur poor neurodevelopmental outcomes. The most common treatment involves permanent ventricular shunting with all its risks and consequences. This is a review of the current evidence for the treatment and prevention of PHH and shunt dependency. The Cochrane Central Register of Controlled Trials and PubMed (from 1966 to August 2008) were searched. Trials using random or quasi-random patient allocation for any intervention were considered in infants less than 12 months old with PHH. Thirteen trials were identified although speculative interventions were also evaluated.

The literature confirms that lumbar punctures, diuretic drugs and intraventricular fibrinolytic therapy can have significant adverse effects and fail to prevent shunt dependence, death or disability. There is no evidence that postnatal phenobarbital administration prevents intraventricular haemorrhage (IVH). Subcutaneous reservoirs and external drains have not been tested in randomized controlled trials, but can be useful as a temporising measure. Drainage, irrigation and fibrinolytic therapy as a way of removing blood to inhibit progressive deposition of matrix proteins, permanent hydrocephalus and shunt dependency, are invasive and experimental. Studies of ventriculo-subgaleal shunts show potential as a temporary method of CSF diversion, but have high infection rates.

At present no clinical intervention has been shown to reduce shunt surgery in these infants. A ventricular shunt is not advisable in the early phase after PHH. Evidence exists that pre-delivery corticosteroid therapy reduces mortality and IVH and there may be trends towards reduced disability in the short term. There is also evidence that postnatal indomethacin reduces IVH but with no effect on mortality or disability. Overall, there is still no definitive algorithm for the treatment of PHH or prevention of shunt dependence. New therapeutic approaches in neonatal care, including those aimed at pre-empting PHH, offer the best hope of improving neurodevelopmental outcomes.

Introduction

Intraventricular hemorrhage (IVH) remains a serious complication of premature birth. Despite many treatment options, there is still no consensus on the management of post-hemorrhagic hydrocephalus (PHH) in the very low birth weight baby. Although improvements in obstetric and perinatal care have decreased the incidence and severity of IVH in low-weight preterm infants from 40-50% in the 1980s, to 20-25% in the 1990s, the problem still remains important as the survival rate of very immature newborns increases. Moreover, there is a direct correlation between increasing prematurity and severity of the IVH. A 1998-2000 study reported IVH grade III in 32% of premature infants born at 24-26 weeks' gestation and IVH grade IV in 19% of this group, whereas in infants born at 31–32 weeks gestation the incidences of IVH grades III and IV were 11% and 5% respectively. Additionally, the percentage of patients developing hydrocephalus secondary to this haemorrhage varies greatly. In the last 20 years different medical and surgical treatments have been put forward to prevent both the occurrence of hemorrhage and the development of hydrocephalus. In this study we reviewed the literature on the different treatments used to control and treat PHH.

Background: With improvement in neonatal intensive care, more children with PHH are surviving. Murphy et al. provided evidence that posthemorrhagic ventricular dilation in the 1990s had a more aggressive course than previously. This is presumably due to the increasing survival of infants of progressively lower birth

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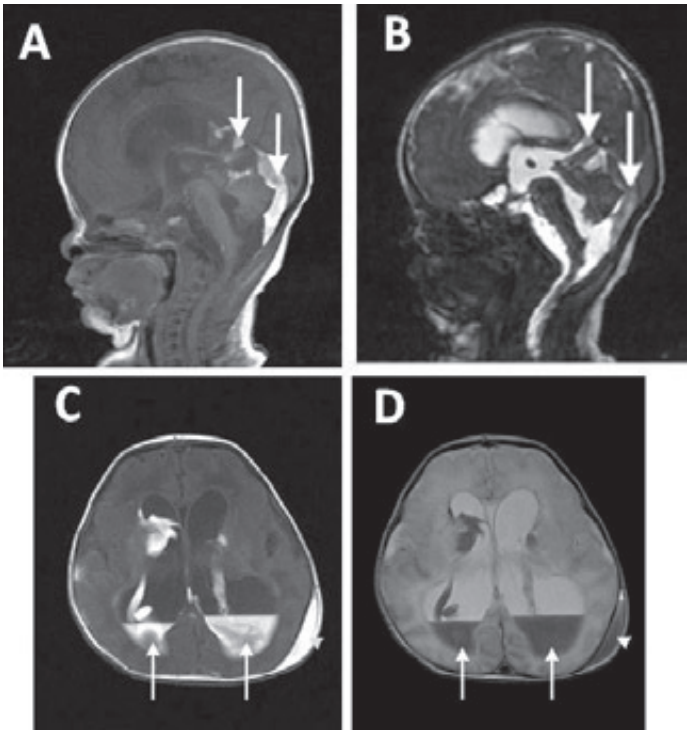

Figure 1. MR images of the head of a very low birth weight infant nine days after birth. A: Sagittal T1-weighted MRI showing layering of the intraventricular haemorrhage within the venticles and in the posterior fossa (arrows). B: CISS (Constructive Interference in the Steady State) sequence giving heavily T2-weighted high resolution images with excellent fluid contrast demonstrating the dilated ventricular system in white and the dependent haemorrhage (arrows). C: T1-weighted axial MRI scan showing layering of the intraventricular haemorrhage (arrows) and a left scalp haematoma (arrowhead). D: T2-weighted axial MRI showing layering of the intraventricular haemorrhage (arrows) and a left scalp haematoma (arrowhead). The most striking features on these scans are hydrocephalus with intracranial haemorrhage, which is seen layering within the lateral ventricles.

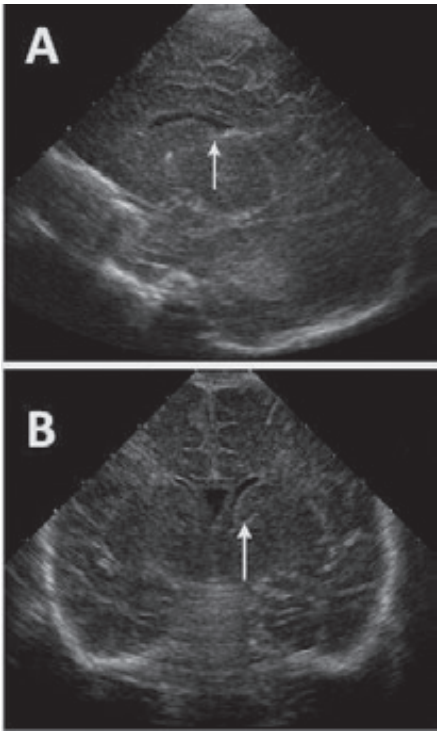

Figure 2. Ultrasound images of the head of a 2 week old normal term infant scanned with an 8V5 ultrasound probe on an Acuson Sequoia 512 ultrasound machine (Siemens, Erlanger, Germany). A: Sagittal view, arrow indicates the caudo-thalamic groove used as a reference point. B: Coronal view, again arrow referencing the normal caudo-thalamic groove.

weight and gestation followed by improvements in neonatal care, such as the widespread use of antenatal steroids and surfactants. However the less well-developed brain in these very premature neonates may also be more readily damaged by haemorrhage or increased intracranial pressure (ICP).

Hemorrhage into the ventricles of the brain is amongst the most serious complications of preterm birth despite improved survival rates. Large IVH has a high risk for neurological disability, and more than 50% of these children go on to develop progressive ventricular dilation. Extreme prematurity associated with PHH results in high morbidity and considerable mortality. The hydrocephalus is usually ascribed to fibrosing arachnoiditis, meningeal fibrosis and subependymal gliosis, which impairs the flow and reabsorption of cerebrospinal fluid (CSF). Initially, multiple blood clots may obstruct the ventricular system or CSF reabsorption channels, such as from thrombus formation within the cisterna magna. This leads to a chronic arachnoiditis of the basal cisterns, involving deposition of extracellular matrix proteins in the foramina of the fourth ventricle and in the subarachnoid space.

Recent experimental studies have suggested that acute parenchymal compression and ischemic damage, with increased parenchymal and perivascular deposition of extracellular matrix proteins, are the important contributors to the development of arachnoiditis and hydrocephalus. Transforming growth factor beta (TGF-beta) is a cytokine that up regulates the production by fibroblasts of extracellular matrix proteins. TGF-beta is involved in the initiation of wound healing and fibrosis. TGF-beta elevates the expression of genes encoding fibronectin, various types of collagen, and other extracellular matrix components. There is evidence that TGF-beta may be a mediator of the pathological process.

Previous studies suggest that these changes take place over weeks. Heep et al in 2004 confirmed that TGF-beta CSF concentrations are in fact not elevated in the acute phase of fibroproliferative reactions in patients with PHH. However, this study demonstrated that vascular endothelial growth factor (VEGF) is highly expressed in the CSF of neonates with PHH and may serve as an indicator of brain injury from progressive ventricular dilation. Further studies confirmed that intraventricular blood and ventricular expansion may have adverse effects on the immature periventricular white matter by a variety of other mechanisms, including physical distortion, raised ICP, free radical generation facilitated by liberated iron, and inflammation. The haemorrhage can be isolated or it can rupture through the ependymal lining into the ventricular system. If the haemorrhage is large it may extend into the parenchymal tissue adjacent to the germinal matrix. The majority of hemorrhages occur within 72 hours of birth.

Despite all the difficulties in isolating a pathogenetic mechanism, there is little doubt that IVH is associated with damage to periventricular white matter and this damage is exacerbated by the development of hydrocephalus. Combinations of pressure, distortion, ischaemia, inflammation, and free radical-mediated injury are the main contributors. Importantly, damage to white matter accounts for the high frequency of cerebral palsy and

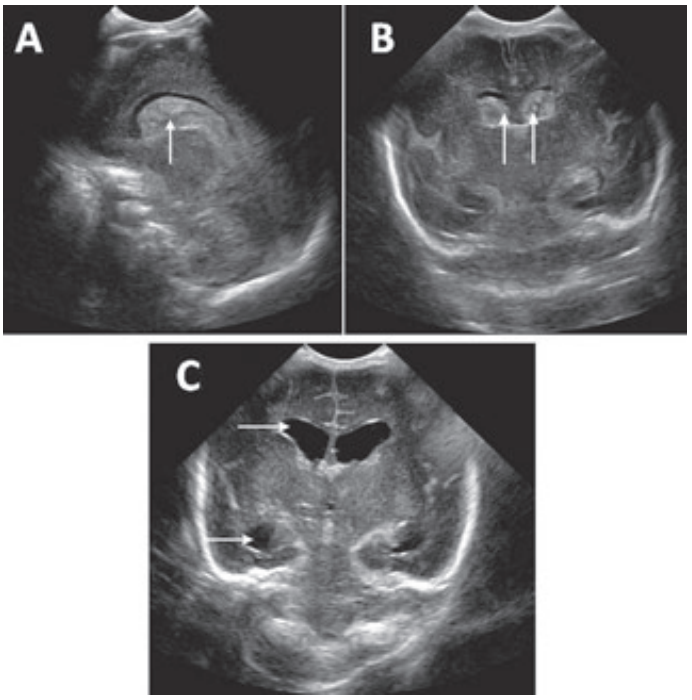

Figure 3. Ultrasound images of a 2 day old premature infant born at 28 weeks scanned with a C8-5 ultrasound probe on a Philips iE33 ultrasound machine (Philips Medical Systems, Eindhoven, Netherlands). A: Sagittal scan presenting with bilateral grade III intraventricular haemorrhage, with blood in the caudo-thalamic groove (arrow). B: Coronal ultrasound scan presenting bilateral grade III intraventricular haemorrhage (arrows), with greater than 50% filling of the lateral ventricles. C: Coronal ultrasound scan with bilateral grade III post haemorrhagic hydrocephalus in the same infant six weeks later. The dilated anterior and temporal horns of the right lateral ventricle are apparent (arrows).

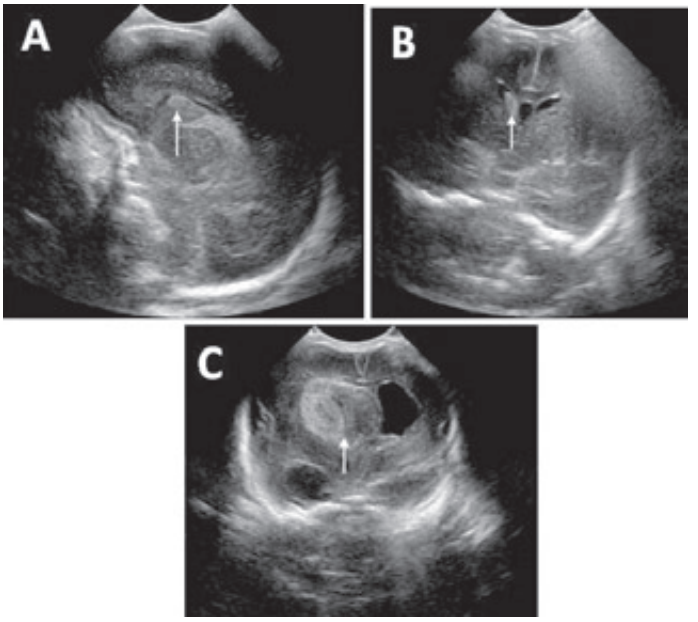

Figure 4. Ultrasound images of infants with different grades of intraventricular haemorrhage scanned with a C8-5 ultrasound probe on a Philips iE33 ultrasound machine. A: Coronal view of a 2 week old term infant with grade I intraventricular haemorrhage highlighted in the left caudo-thalamic groove (arrow). B: Coronal view of a 1 day old premature infant born at 24 weeks with grade II intraventricular haemorrhage in the right caudo-thalamic groove (arrow) which fills less than 50% of the ventricle. C: Coronal view of a 2 day old premature infant born at 24 weeks with a right grade IV intraventricular haemorrhage with hydrocephalus and extension into periventricular white matter (arrow).

poor neurodevelopmental outcome, in this group of infants. The aim of much of past and ongoing research is to identify mechanisms and mediators of hydrocephalus and white matter damage, which may enable new treatments that avoid permanent hydrocephalus, with its potential neurological sequelae, and avoid shunt dependence.

Treatment is more difficult than with other types of hydrocephalus. The large amount of blood and protein in the CSF, combined with the small size and instability of the patient, makes early ventriculoperitoneal (VP) shunt operations unrewarding, due to the high incidence of blockage and infection. There is a considerable complication rate throughout later life from such surgery, and the child is generally permanently dependent on the shunt system. Several studies act as testament to this difficulty. Pikus et al evaluated 52 patients with Grade IV IVH and progressive hydrocephalus treated between 1977 and 1987. These patients averaged 6.9 shunt revisions over 18 years. Mortality was 60%; 78% of survivors had intellectual function more than 2 standard deviations below the mean for age and all survivors had some form of spasticity. Boynton et al reported outcomes for 50 preterm infants with PHH, 92% with Grade III or Grade IV hemorrhages. Mortality was 7% with a median shunt revision rate of 4 per patient and shunt infection rate of 19% per procedure, with a failure rate of 92% for those treated in the first 3 weeks of life. Neurodevelopmental outcomes included strabismus (40%), blindness (28%) and hearing loss (24%). Seizures occurred in 38% and most required long-term anticonvulsants. Additionally, significant limitations in motor function occurred in 49%. More recently, a large cohort study by Adams-Chapman et al into 6,161 extremely low birth weight children, confirmed that those with severe IVH that require shunt insertion are at greater risk for adverse neurodevelopmental and growth outcomes at 18 to 22 months, compared with children with and without severe IVH and with no shunt. These poor outcomes reinforce the need for more alternative treatments, though they are not necessarily caused by the shunt, perhaps being due to the underlying processes leading to shunt dependence.

Anatomy and pathophysiology: Germinal matrix hemorrhage (GMH) and IVH are the most common and most important events that cause neurological injuries in preterm neonates. The homeostatic compensatory capacity of a premature infant is limited. Fluctuations in cerebral blood pressure and flow can rupture the primitive germinal matrix vessels or lead to infarction of the metabolically active germinal matrix. The damage can extend into the periventricular white matter, resulting in significant neurological sequelae, including cerebral palsy, mental retardation, and seizures. As has been mentioned, injury to the germinal matrix results in substantial mortality and morbidity rates.

The germinal matrix is located in the subependyma of the ventricular walls. At 8-28 weeks' gestation, the germinal matrix initially produces neurons and subsequently glial cells, which migrate to populate the cerebral cortex. Involution of the germinal matrix toward the caudothalamic groove begins late in the second trimester and is nearly complete by 32 weeks' gestation. The germinal matrix is metabolically active with a rich supply of blood via thin, fragile capillary networks, supplied by branches of the anterior cerebral artery. The arterioles flow from

the recurrent artery of Heubner at the level of the foramen of Monro and the terminal branches of the lateral striate arteries, which are located more superiorly. Venous blood flows through the terminal vein, which drains via the internal cerebral vein into the vein of Galen.

The neuropathology of GMH/IVH is characterised by bleeding into the subependymal germinal matrix, with or without subsequent rupture into the lateral ventricle. The pathogenesis of GMH is multifactorial. The influences can be divided into intravascular, vascular, and extravascular factors. The autoregulation of blood flow in response to changes in blood pressure in the germinal matrix circulation is underdeveloped in premature infants, and the thin microvasculature is susceptible to rupture. The immature mesenchymal and glial supportive tissues also influence the extent of GMH. Large fluctuations in blood flow and blood pressure can lead to injury to the germinal matrix vessels and subsequent haemorrhage. Moreover, the highly metabolically active germinal matrix is particularly vulnerable to hypotension and hypoperfusion, and this can lead to focal or diffuse infarction. Consequently, hemorrhage can occur in the infarcted regions after reperfusion. Hemorrhage from any cause can be confined to the subependymal layer, can extend into the ventricles or arise from the brain parenchyma. The aetiology is probably due to obstruction of venous drainage by blood clot in the germinal matrix. Thus, interventions aimed at prevention or treatment of IVH might be aimed at any of the above mechanisms. Sequelae of GMH/IVH include germinal matrix destruction, periventricular hemorrhagic infarction with subsequent encephalomalacia, and PHH. The major risk factors for GMH include a young gestational age, low birth weight, acute amnionitis, and not receiving antenatal steroids for at least 48 hours. Other neonatal risk factors include the use of general anesthesia for cesarean delivery, Apgar scores that are less than 4 in the first minute or are less than 8 by 5 minutes, respiratory distress, patent ductus arteriosus, anemia and arterial catheterization.

More evidence for the deleterious effects of PHH comes from studies by near-infrared spectroscopy (NIRS). NIRS permits continuous measurement of changes in the cerebral concentration of oxygenated and deoxygenated hemoglobin and oxidized cytochrome oxidase at the bedside of infants. A recent study showed that cerebral perfusion, cerebral blood volume, and oxidative metabolism are all compromised in infantile PHH to the degree whereby removal of any volume of CSF led to a significant improvement in these parameters. This further demonstrates how harmful the resultant PHH can be to the cerebral haemodynamics of infants.

Diagnosis and grading of IVH and PHH: Ultrasonography is the primary imaging modality for the screening and diagnosis of GMH/IVH, and CT scanning and magnetic resonance imaging are used as supplementary tools. Figure 1 shows MRI sequences of a VLBW infant nine days after birth with hydrocephalus and intraventricular and caudo-thalamic groove haemorrhages. Cranial ultrasound can be carried out at the cot side and does not expose the infant to ionizing radiation. This enables whole populations of infants to be safely examined. The classification of IVH by Papile in 1978 was originally developed for CT scanning, but has been adopted by ultrasonographers. Figures 2A and 2B demonstrate coronal and sagittal US images in a normal infant, and Figures 3A-C show views of grade III IVH and subsequent hydrocephalus six weeks later.

Four grades identified for IVH are Grade I or mild hemorrhage is confined to the subependymal germinal matrix with no blood clot in the ventricular lumen. Figure 4A shows a coronal US image with grade I IVH highlighted in the left caudothalamic groove. Grade II or moderate subependymal haemorrhage involves minimal filling (10–40%) of the lateral ventricles with little or no ventricular enlargement. Figure 4B is a coronal US image pointing out grade II IVH in the right caudothalamic groove. Grade III or severe subependymal haemorrhage is associated with substantial filling of the lateral ventricles (> 50%) with significant ventricular enlargement (Figure 3).

Grade IV or periventricular hemorrhagic infarction is IVH plus intraparenchymal venous haemorrhage. Figure 4C is a coronal US highlighting a right grade IV large IVH with hydrocephalus and extension into periventicular white matter.

Although US diagnosis of GMH is not perfect, with sensitivity of 61% and specificity 78%, the diagnosis of IVH shows high sensitivity (91%) and specificity (81%) as does identification of parenchymal haemorrhage (sensitivity 82% and specificity 97%).

Literature search: Literature searches were performed using PubMed and the Cochrane Central Register of Controlled Trials. Randomized or quasi-randomized controlled trials were considered as primary (level 1) evidence for treatment. Other small-scale studies were considered to affirm potential and understudied therapies. All types of intervention were considered in infants of less than 12 months of age with hydrocephalus following IVH.

Shunt treatment and complications: At the present time, the best definitive treatment for hydrocephalus in preterm infants is still the VP shunt. The most suitable time for surgery is when the newborn infant exceeds 1,500 g and the CSF has a protein content below 200 mg/dL. However, alongside poor long term outcomes, there are many problems with this method. Firstly, the surgical treatment is still complicated by high revision rates. Secondly, the prematurity of the patients and their relatively incompetent immune system favours shunt infections. The infection rate varies across the studies and is usually between 5-15%. Also increased CSF protein levels predispose to shunt obstructions which are the most common cause of shunt failure in these children, with the rate of shunt failure reportedly being higher in ventriculoatrial shunts. Furthermore, physiologically very low ICP levels in premature infants necessitate special shunt systems, which bring more potential problems. For low birth weight infants, low pressure valves or even valveless shunts are recommended. Problematically, low pressure valves may have to be converted later to higher pressure valves, or include systems with a component to prevent over drainage when upright as the child starts to sit and stand. Therefore, there is a high rate of shunt revision even in the absence of blockage, unless externally programmable valves are used. In addition, shunt over drainage with collapsed ventricles and eventual subdural fluid collections and/or secondary craniostenosis can occur in children with low pressure valve systems. Some authors, therefore, advocate shunts with programmable valves as the first choice although there is in fact limited evidence as to the superiority of one valve over another in addressing these risks, which only underlines the uncertainties in using these devices. There is also controversy about the setting for the surgery. Some authors advocate the neonatal intensive care unit (ICU) as the most comfortable and safest for premature patients.

Finer et al demonstrated that the unstable neonate can undergo surgery in the neonatal ICU with a surgical morbidity and mortality comparable to that seen in theatre, as transportation predisposes the critically ill neonate to hypothermia, frequently results in dislodgement of intravascular catheters, and is likely to increase postoperative pain. However, these studies apply to general procedures with no specific evidence for relevance to shunt operations. Therefore, given the high infection rate of shunting preterm neonates with PHH, this is an environment probably best limited to external ventricular drain (EVD) placement, unless evidence of safety emerges.

Nevertheless, VP shunting is clearly still a treatment with many problems in preterm infants with PHH, and prevention or alternative therapies are undoubtedly needed.

Medical and minimally invasive treatments: Diuretic therapy: Medical treatment of PHH consists of oral or intravenous administration of drugs that reduce CSF production. Acetazolamide and furosemide, which both reduce the production of CSF, have been suggested as non-invasive therapies to reduce hydrocephalus and the need for VP shunting. There are two level 1 trials of acetazolamide and/or furosemide compared with standard therapy in infants with IVH or post-hemorrhagic ventricular dilatation (PHVD); one randomized with 16 infants and the other with 177 infants. Neither study showed a decreased risk for VP shunt or death with acetazolamide and furosemide therapy. In the multicenter trial with 177 infants by the International PHVD Drug Trial Group acetazolamide in doses of 100 mg/kg/day, and furosemide 1 mg/kg/day were administered. None of the measures of outcome in this study suggested any advantage from drug treatment. They concluded that substantial future reductions in the adverse consequences of PHVD were most likely to come from continuing changes in neonatal care that contribute to its prevention rather than to its treatment. In total, 65% of infants receiving the drug treatment died or required shunt insertion and 46% of infants in the control group died or required shunt insertion. In the drug treatment group, 79% of infants were impaired or disabled at 1 year, whereas 53% of those in the control group were impaired or disabled at 1 year. The CNS infection levels were similar in both groups. Additionally, this large trial demonstrated that acetazolamide and furosemide treatment resulted in a borderline increase in the risk for motor impairment at one year. However, when the combined outcomes of death, developmental delay, disability or impairment at one year were considered there was no significant increase in risk. Another finding was that diuretic treatment increased the risk for nephrocalcinosis and a meta-analysis has confirmed the significance of this result. Thus the diuretic therapy increased nephrocalcinosis and biochemical anomalies, which led to the cessation of treatment. Additionally, the available evidence supports the assertion that diuretic therapy increases the risk of motor impairment and disability. As the results clearly showed a worse outcome in the drug-treated infants, the data-monitoring committee prematurely halted the trial.

The rationale for treatment with these drugs is to decrease the rate of CSF formation, but they have other effects. There is the potential to cause cerebral vasodilatation and impairment of autoregulation, leading to enhanced risk of secondary cerebral injury. Moreover, data from experimental studies suggest that acetazolamide may be toxic to the developing oligodendrocyte. The adverse effects seen in these trials, however, are probably best explained by alterations in cerebral perfusion pressure. Therefore, available evidence shows that acetazolamide and furosemide do not reduce the need for VP shunting in infants with PHH, being neither effective nor safe.

Fibrinolytic agents: Treatments involving fibrinolytic agents carry a high risk of triggering new hemorrhages, but in recent years their use has been taken up again in combination with ventricular drains. The effect of intraventricular streptokinase was determined on the risk of permanent shunt dependence, neurodevelopmental disability or death in neonates at risk for, or actually developing PHH. Two randomized trials, both evaluating intraventricular streptokinase in 12 infants who developed PHVD were identified. When intraventricular streptokinase was compared with conservative management of PHVD, the numbers of deaths and babies with shunt dependence were similar in both groups. No information on the effect of intraventricular streptokinase on disability is available. There is cause for concern about meningitis and secondary IVH, but numbers are insufficient to quantify the risks. Overall, therefore, intraventricular fibrinolytic therapy with streptokinase starting before one month of age in infants developing PHVD is not recommended.

Drainage, irrigation, and fibrinolytic therapy (DRIFT): Recently, Whitelaw and colleagues piloted a method involving intraventricular administration of tissue plasminogen activator (tPA) and 72 hours drainage via two ventricular catheters (one frontal on the right, and one occipital on the left). The procedure, DRIFT (drainage, irrigation, and fibrinolytic therapy) attempted to remove intraventricular blood and the cytokines that are associated with hydrocephalus before it could become established. They randomly assigned 70 preterm infants who had gestational ages of 24 to 34 weeks with progressively enlarging cerebral ventricles after IVH to two groups, (1) drainage, irrigation, and fibrinolytic therapy to wash out blood and cytokines and (2) tapping of CSF by reservoir as required, to control excessive expansion and signs of raised ICP (standard treatment). The results were that DRIFT did not reduce VP shunt surgery or death in preterm infants with ventricular dilation after IVH when compared with tapping of CSF to control excessive head expansion or raised ICP. Tapping a ventricular reservoir was relatively safe and effective in controlling hydrocephalus even in extremely small infants. Unfortunately, it was concluded that secondary IVH is a factor that counteracts any possible therapeutic effect from washing out old blood. Therefore, the conclusion was that this innovative intervention could not be recommended until more objective evaluations can provide less equivocal findings.

Therefore, neither the DRIFT procedure nor acetazolamide and furosemide are effective in reducing the need for shunting, and both forms of therapy have adverse effects. It may be that the results to date of intraventricular fibrinolytic therapy have been negative because the treatment (starting nearly two weeks after birth) had been administered too late. Fibrosis, deposition of extracellular matrix proteins and chronic inflammatory changes may already have become irreversible. Furthermore, very low levels of plasminogen and the presence of Plasminogen Activator Inhibitor-1 (PAI-1) would be expected to limit the fibrinolytic effect of intraventricular streptokinase. As we have alluded to, there is evidence that the cytokine, TGF-beta plays a major role in the development of PHH. Whitelaw et al further demonstrated that intraventricular injection of tPA, on its own, increases the

concentration of TGF-beta in ventricular CSF. This could help to explain the failure of intraventricular injection of fibrinolytic agents to prevent hydrocephalus. Thus, therapeutic strategies need to continue to consider ways of removing, blocking or preventing release of this and other cytokines such as VEGF.

Preventative measures for IVH: As has been mentioned, approximately 80% of IVH occurs by 72 h after birth but a considerable proportion of IVH is visible on the first scan within a few hours. This means that interventions to prevent IVH should ideally be commenced prior to, or immediately after delivery.

Postnatal phenobarbital: The rationale for administration of postnatal phenobarbital to prevent IVH in low birth weight infants is underpinned by: a) the observation that phenobarbital may dampen fluctuations in systemic blood pressure in premature infants, b) evidence that treatment with phenobarbital reduces the incidence of intracranial haemorrhage in newborn beagles made hypertensive with phenylephrine, c) experimental evidence that barbiturates can partially protect the brain against hypoxic-ischaemic damage and d) the suggestion that phenobarbital's free radical scavenging capacity may protect after hypoxia-ischaemia. However, the results of three trials which used posthemorrhagic ventricular dilatation or hydrocephalus as an outcome, reported no significant difference between the control or treatment groups. The typical estimates from a meta-analysis of these studies provide little evidence of a reduction in the risk of posthemorrhagic ventricular dilatation (typical relative risk 0.89). Moreover, a large double-blind randomised controlled trial by Kuban et al., found that in VLBW infants, phenobarbital was actually associated with an increased risk of developing any subependymal-intraventricular-intraparenchymal haemorrhage. Although they did not use PHH as an independent outcome measure, this study complements our assessment that the published evidence is very much against postnatal phenobarbital preventing IVH. Furthermore, phenobarbital suppresses spontaneous breathing in infants, causing a need for mechanical ventilation. In spite of the lack of efficacy for this intervention, there is still scope for researchers to consider perinatal intervention with other modalities.

Surgical treatment other than shunt placement: As regards surgical treatment of PHH other than shunt surgery, some authors have recommended ventricular drains in preference to subgaleal reservoirs, due to the levels of reported infection rates, but the numbers reported are too small for any confidence. The standard treatment varies from centre to centre, and few have built up a large series for analysis. The standard arms of the Ventriculomegaly Trial and the PHVD Drug Trial into acetazolamide and furosemide both used selective tapping of CSF to control signs of raised ICP or excessive head enlargement. Inserting a subcutaneous ventricular access device (VAD), to facilitate repeated tapping of adequate CSF volumes is widely practiced, without having been tested by a randomised trial. All these measures are considered here.

Lumbar puncture and ventricular taps: Repeated early lumbar puncture (LP) or ventricular taps have been advocated as a way of avoiding hydrocephalus and protecting the brain from excess pressure. It was thought that the risk of hydrocephalus and the need for a VP shunt might be reduced by the removal of protein and old blood from the CSF. In practice, the decision to employ this strategy is taken from head circumference changes, fontanelle examination, neurological signs, and sequelae of raised ICP and from US measurement of ventricular dilatation. In line with the Levene criteria for ventricular indices, intervention usually occurs when the ventricle reaches a diameter > 4 mm above the 97th percentile, although this is controversial as dilatation may already be too great for subsequent taps to be effective and there have been reports of better outcomes with taps performed before this cutoff. A common practice is to remove sufficient fluid to render the fontanelle soft and depressed, typically in the region of 10 ml/kg/tap. This hypothesis has been tested in four randomised trials involving premature infants in whom IVH (with or without established enlargement) was diagnosed by US. In total, four controlled trials, were identified, three being randomised and the fourth using alternating allocation. Two trials evaluated repeated LPs in neonates with IVH and two trials evaluated repeated CSF tapping in infants with IVH followed by progressive ventricular dilatation. The total number of infants in the four studies was only 282, with 157 coming from the Ventriculomegaly Trial. None of the trials found a significant effect from CSF tapping on: a) need for shunt, b) death, c) major disabilities in survivors, d) multiple disabilities in survivors, or e) death or disability. Similarly, a meta-analysis by Whitelaw of the results of all included trials showed no significant effect of CSF tapping on any of these outcomes. Nevertheless, this does not take into account the potential benefit of tapping to delay shunt implantation until such time as the skin in VLBW babies matures sufficiently to reduce the risk of shunt erosion.

Repeated CSF tapping of preterm infants carries a theoretical risk of introducing infection. None of the infants in Dykes' 1989 study developed CSF infection during tapping but 11 of the 157 infants in the ventriculomegaly trial developed CSF infections, all having had some CSF taps (the infants in the control group were eventually tapped if they developed symptoms or signs of raised ICP). CSF infection (meningitis/ventriculitis) can be a serious adverse effect of early repeated CSF tapping. There is no information about the frequency of needle-track lesions from repeated ventricular taps, though anecdotal evidence does exist. For example, a large (presumed traumatic) aneurysm of the pericallosal artery in an infant has been observed after repeated ventricular taps by the senior author (OS) (unpublished). Although it was a reasonable hypothesis that early CSF tapping would reduce ICP and remove protein and blood to clear the CSF pathways, the meta-analysis by Whitelaw of the four controlled trials failed to demonstrate any evidence of benefit. Moreover, the secondary risk of infection and the discomfort of the procedures were reiterated.

Assessment of the infants in the ventriculomegaly trial at twelve months included an analysis in two groups: a) infants who had a cerebral parenchymal lesion visible on US at entry, and b) infants with no cerebral parenchymal lesion at entry. In the group with parenchymal brain lesions at entry, there was a difference in neurodevelopmental outcome at 12 months in favour of those who had early CSF tapping. This difference just achieved significance at the 5% level, but caution was expressed in the paper as to whether this finding could be due to chance. The neurodevelopmental examination at 30 months in the infants with parenchymal brain lesions at entry, showed no difference between the two treatment groups. Thus, this paper emphasised the importance of basing clinical recommendations on consistent findings among large groups of subjects. Therefore, there is no evidence that early tapping of CSF by LP or ventricular tap reduces the risk of poor neurodevelopmental outcome, shunt

dependence or death after 30 months follow up. The use of repeated taps was associated with an increased risk of central nervous system infection. Thus, the use of early tapping is not a recommended treatment modality, and removing CSF should be reserved for cases where there is symptomatic raised ICP, for example while temporising before more definitive CSF diversion.

External ventricular drainage: After LPs prove to be unsuccessful, external ventricular drainage (EVD) is often the next invasive step in the management of PHH. The catheter is typically inserted into the dilated anterior horn of the right lateral ventricle under sterile conditions. The end of the proximal catheter is subcutaneously tunneled to a site on the scalp (or body) distant from the initial incision and connected to an adjustable drainage system. EVD appears to be much more effective than repeated LPs or ventricular taps in evacuating sufficient volumes of CSF.

The infection rate with EVD ranges from unacceptable levels to very low rates reported by some authors, despite long periods with an EVD. One study by Cornips et al. reported no infections in 14 patients with an EVD for PHH. They put this down to vigilant monitoring and insertion of the EVD within the relatively clean and stable environment of a neonatal ICU. Studies by Berger et al. and Rhodes et al. each with 37 patients, reported infection rates of 5.4% and 6%, respectively. Reinprecht et al studied 42 preterm patients recording a 7.1% infection rate. Weninger et al. cultured CSF and/or the tip of the ventriculostomy catheter in each of their 27 patients, reporting a 26% contamination rate but with no clinical or laboratory evidence of ventriculitis. Importantly, these studies confirmed infection via CSF drainage catheters as an independent predictor for poor neurodevelopmental outcomes.

Other problems such as over drainage and the development of subdural hygromas can occur but may be minimised by careful control of ICP. EVD also has the advantage of allowing easy intrathecal administration of drugs. The effect of EVD on shunt dependency and neurological outcome is at present not actually known. Long standing EVD may encourage the need for subsequent shunt insertion by decreasing natural CSF reabsorption. On the other hand, the need for permanent shunting may be reduced by the continuous removal of bloody and protein rich CSF. Nevertheless, the rate of permanent shunting after EVD is 64–68%.

Subgaleal shunts: Ventriculo-subgaleal shunts have been recommended as a more physiological and less invasive means of achieving CSF diversion until VLBW infants gain adequate weight, and the blood and protein levels in CSF are low enough, before a permanent shunt can be placed. In one study of this procedure to evaluate the effectiveness and complications over a 1-year period, the ventriculo-subgaleal shunt controlled the progression of hydrocephalus in all 6 premature infants, as assessed by clinical and imaging parameters, and a permanent shunt was avoided in 1 patient (16.6%). However, 4 patients developed shunt infections, 1 involved the ventriculo-subgaleal shunt itself, and 3 occurred immediately after conversion to VP shunt. The total infection rate in these cases was two thirds, though there was only a 1% shunt infection rate for primary implantation in their institution at that time. Therefore, according to this study, placement of ventriculo-subgaleal shunts for interim CSF diversion in neonates with posthemorrhagic hydrocephalus is effective as a temporary method of CSF diversion. However, it is associated with a worryingly high CSF infection rate. This study suffers from a small sample size in an understudied area, and thus cannot yet be treated as a standard therapeutic option, though it seems worthy of further study.

A potential cause for infection in this study may have been CSF stasis just beneath the extremely thin skin of the premature infants, promoting colonisation by skin flora, as all the infections were staphylococcal. It is postulated that CSF sampling before conversion to a permanent shunt and replacement of the proximal hardware, which may have been in situ for a prolonged period, may decrease the infection rates. However, until this is researched further, it cannot be a recommended treatment.

Subcutaneous reservoir: The subcutaneous reservoir or VAD is another frequently used option in the management of PHH. This avoids repeated needle tracks through the brain and potential injury. Reservoirs are tapped up to three times a day and the amount of CSF removed can be adjusted to the opening pressure. An important drawback of VADs (and LPs) is that the removal of CSF is intermittent. The fluid buildup and resulting rise of ICP between taps might be detrimental. The major complications of VADs are ventriculitis, shunt infection, skin necrosis, CSF fistula, or subdural hygroma. One recent study found hyponatremia to be a consequence of serial CSF punctures in preterm infants with a Rickham VAD. This has also been found in studies performed less recently, and has also been reported as a consequence of EVDs. However, hyponatremia as a consequence of CSF tapping or drainage is totally predictable and preventable, and can easily be treated with diligent monitoring and replacement. The rates of infection in VADs reported in the literature are actually very low. However, among patients who received a subcutaneous reservoir, subsequent shunting was necessary in 75-88%.

On balance, therefore, the current evidence for VAD use is conflicting. A study by Hudgins et al. in 149 infants with PHH recorded an 8% infection rate and concluded that the device can be recommended for several months with acceptable rates of infection, blockage and wound complications. On the other hand, a study by Richard et al into 64 infants recorded a 22% infection rate and did not suggest an Ommaya reservoir was beneficial in terms of mortality, prevention of shunt placement or neurological outcome. Nevertheless, a contemporary study by Brouwer et al. assessed two separate groups, 26 infants admitted during 1992-7 and 50 admitted during 1998-2003, treated with a ventricular reservoir. Their results suggest a learning curve reflecting the benefits of experience, whereby significantly fewer complications were recorded in the second period. It is also important to emphasise that the repeated punctures need to be undertaken with meticulous aseptic technique in order to minimize introduction of organisms from the skin. They suggest that in experienced hands, a ventricular reservoir is a safe treatment to ensure adequate removal of CSF in preterm infants with PHH.

Ommaya reservoir followed by shunt or ETV: A 2007 study has taken this a step further and evaluated treating PHH with an Ommaya reservoir, followed by VP shunt and/or endoscopic third ventriculostomy (ETV). There were 18 premature babies affected by IVH grades II to IV implanted with a reservoir. CSF was intermittently aspirated percutaneously from the VAD according to clinical requirements and ultrasonographic follow-up. Fourteen of the patients suffered progressive ventricular dilatation and underwent VP shunt implantation (5 patients) or

ETV (9 infants). One of the infants died during the study, and at the end of the follow-up period, 10 out of 17 premature neonates affected by PHH were shunt free (59%). They concluded that the combination of Ommaya reservoir, VP shunt, and the aggressive use of ETV, as either a primary treatment or as an alternative to shunt revision, allowed for a significant reduction of shunt dependency in a traditionally shunt-dependent population. Therefore, this is a promising approach, deserving of further study.

Improvements in antenatal and perinatal care: A general decrease in IVH has been noted in developed countries over the last 10 years despite an increase in survival of very immature infants. This may in fact be due to dedicated neonatal teams who are becoming experienced at handling premature babies. Maternal corticosteroid administration before preterm delivery has been mainly responsible for this decrease in IVH as demonstrated in a 2006 Cochrane review. Indeed, in a meta-analysis of previously published trials, antenatal corticosteroids have been confirmed to reduce the incidence of IVH in premature children. The combined odds ratio for the development of IVH was 0.38 when comparing antenatal corticosteroids with placebo. A promising randomized control trial by Liu et al evaluated whether combined antenatal corticosteroid and vitamin K administration has a benefit, over and above that of corticosteroid or vitamin K used alone, in reducing the frequency and the degree of periventricular-intraventricular haemorrhage (PIVH) in premature newborns of less than 35 weeks' gestation. More infants in the control group had grades III or IV intracranial hemorrhage after birth ($p = 0.049$). After antenatal supplement of dexamethasone and vitamin K1, both the total incidence of PIVH and the frequency of severe PIVH decreased significantly. Thus, many of the advances for treating PHH may be preemptive and the focus for research into improving antenatal care and interdisciplinary approaches is encouraging.

Of the other pharmacological interventions assessed, antenatal indomethacin appeared promising. However, results of a multicentre trial by Pringle et al of indomethacin in 1200 infants with birth weights < 1100 g showed that the reduction in IVH was not accompanied by an improvement in survival without disability, and a similar trial from Dani et al. showed ibuprofen to be ineffective in preventing IVH. Nevertheless, although the long-term benefits are unproven, the therapeutic value of indomethacin in reducing the incidence of IVH, and hence PHH, should be noted. It has been demonstrated in multiple single-centre studies to decrease the incidence of IVH in VLBW preterm infants and, therefore, presumably, improves long term outcome. Furthermore, initial studies of neuromuscular paralysis with ventilation seemed to have a favourable effect on incidence and severity of IVH, but there is still uncertainty regarding its long term pulmonary and neurological effects. Evidently, stronger evidence is required before this can be recommended.

Future surgical trends for PHH might include contributions from the fields of robotics, image-guided neuroendoscopy, in utero therapies and the applications of stem cell research, though these remain speculative.

Implications for practice: On the basis of available evidence, routine use of early CSF tapping for infants at risk of, or actually developing PHH cannot be recommended. It would seem wise to be conservative in the management of infants developing PHH to reduce the risk of iatrogenic damage. Routine scanning is important to determine the presence or absence of parenchymal brain lesions, as they affect prognosis. The infant should be followed with repeated measurements of head circumference and ventricular width, as well as clinical examination of neurological status and fontanelle tension. Despite the lack of evidence from randomized trials, CSF drainage is obviously important if there is symptomatic raised ICP, as shown by either a deterioration in neurological signs with a tense fontanelle, or directly measured CSF pressure > 12 mm Hg. Some evidence supports CSF drainage also in the presence of either decreasing diastolic velocities on cerebral artery Doppler waveforms or deteriorating sensory evoked potentials. However, neither of the latter can be regarded as routine clinical tools, so require further evaluation before contemplating adding to the routine criteria for draining CSF.

Many infants need few, if any CSF taps but continue to expand their ventricles and heads at a rate that is clearly above normal. If this excessive expansion continues until the clots have largely absorbed, shunt surgery should be considered. The surgeon may wish to postpone surgery if the infant is still extremely small, particularly if skin quality is poor, if there is infection, or if the CSF still has visible blood or high protein. If it has been necessary to tap the CSF repeatedly, then the case for earlier shunt surgery is stronger, because repeated CSF taps, particularly ventricular taps, create morbidity.

Conclusion

Neither treatment by repeated lumbar or ventricular tapping, nor the use of acetazolamide and furosemide to reduce CSF production, are proven to prevent the need for shunt surgery or improve neurodevelopmental outcomes. Additionally, both have appreciable adverse effects. Phase 1 clinical trials of intraventricular fibrinolytic therapy and a small randomized trial have not given encouraging results. There is insufficient evidence for postnatal phenobarbital in preventing IVH, and drainage, irrigation, and fibrinolytic therapy to wash out blood and cytokines is both highly invasive, experimental and showed no benefit, so cannot be recommended routinely. However, it may be that earlier use of an implanted reservoir for tapping could improve outcomes. Overall, therefore, although the proportion of premature infants suffering IVH has declined, PHH is still a serious complication for which we do not have a definitive treatment. Research clearly needs to focus more on the mechanisms of hydrocephalus and radically new therapeutic approaches will have to be considered. In the interim, advances in pediatric intensive care and neonatal medicine offer hope in preventing PHH.

Can Muscle Ultrasound Density in Early Life Predict Motor Outcome in Spina Bifida Aperta?

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Background: Spina bifida aperta (SBA) is associated with neurological function loss caudal to the meningomyelocele (MMC). At birth, leg movements are transiently present, but they do not reliably predict motor outcome. Pediatric neuromuscular studies have shown that muscle ultrasound density (MUD) reflects neuromuscular condition. In the present study, we investigated whether MUD assessment can predict motor outcome in SBA.

Aim: To determine the relationship between neonatal MUD and motor outcome in SBA.

Materials and Methods: We included 20 SBA neonates with MMC at thoraco-lumbar (n = 2), lumbar-sacral (n = 13) and sacral (n = 5) level. At 0, 6 and 12 months, MUD in SBA children was determined and compared with the morphological and neurological deficit (MRI and sensory/motor assessment, respectively) and compared with MUD in controls (n = 9). In neonates with MMC caudal to L4 (n = 7), we also associated the intra-individual increase in MUD caudal to the MMC (iMUD%) with motor outcome. iMUD% was characterized by: [(MUDgastrocnemius – MUDquadriceps)/MUDquadriceps ×100%]. At one year, motor outcome was assessed by neurological examination.

Results

From birth onwards, MUD In SBA myotomes (cranial and caudal to the MMC) were higher than controls [SBA, gastrocnemius 66 (57–76) and quadriceps 75 (67–88); controls, 51 (21–70) and 67 (55–71), resp., each $p < 0.05$]. From 6 months onwards, MUD correlated with the morphological and functional level of the MMC ($p < 0.05$). MUD cranial to the MMC was higher than caudal to the MMC [SBA, gastrocnemius 59 (15–81) and quadriceps 67 (35–135); $p < 0.05$]. In 6 of 7 neonates with MMC caudal to L4, leg movements caudal to the MMC were present at birth. In all (7/7) neonates, a higher MUD caudal than cranial to the MMC could be visually assessed and confirmed by calculation [median iMUD% 43% (10–394%)]. This intra-individual increase in MUD caudal to the MMC either concurred with (1/7) or preceded (6/7) gastrocnemius muscle function loss.

Conclusion

In early life, MUD is higher in SBA than in controls and MUD caudal to the MMC is higher than cranial to the MMC. MUD parameters (like iMUD%) appeared associated with motor outcome. Our data indicate that assessment of MUD may provide additional information on motor outcome in SBA.

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Undocumented Migrants Lack Access to Pregnancy Care and Prevention

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Abstract

Background: Illegal migration is an increasing problem worldwide and the so-called undocumented migrants encounter major problems in access to prevention and healthcare. The objective of the study was to compare the use of preventive measures and pregnancy care of undocumented pregnant migrants with those of women from the general population of Geneva, Switzerland.

Methods: Prospective cohort study including pregnant undocumented migrants presenting to the University hospital from February 2005 to October 2006. The control group consisted of a systematic sample of pregnant women with legal residency permit wishing to deliver at the same public hospital during the same time period.

Results: 161 undocumented and 233 control women were included in the study. Mean ages were 29.4 y (SD 5.8) and 31.1 y (SD 4.8) ($p<0.02$), respectively. 61% of undocumented women (controls 9%) were unaware of emergency contraception (OR 15.7 (8.8;28.2) and 75% of their pregnancies were unintended (controls 21%; OR 8.0 (4.7;13.5)). Undocumented women consulted for an initial pregnancy visit more than 4 weeks later than controls and only 63% had their first visit during the first trimester (controls 96%, $p<0.001$); 18% had never or more than 3 years ago a cervical smear test (controls 2%, OR 5.7 (2.0;16.5)). Lifetime exposure to violence was similar in both groups, but undocumented migrants were more exposed during their pregnancy (11% vs 1%, OR 8.6 (2.4;30.6)). Complications during pregnancy, delivery and post-partum were similar in both groups.

Conclusions: Compared to women who are legal residents of Geneva, undocumented migrants have more unintended pregnancies and delayed prenatal care, use fewer preventive measures and are exposed to more violence during pregnancy. Not having a legal residency permit therefore suggests a particular vulnerability for pregnant women. This study underscores the need for better access to prenatal care and routine screening for violence exposure during pregnancy for undocumented migrants. Furthermore, healthcare systems should provide language- and culturallyappropriate education on contraception, family planning and cervical cancer screening.

Background

An estimated 8,000 to 12,000 undocumented migrants live and work in the canton of Geneva, representing 1.8 to 2.9% of the 440,982 resident population. These socalled undocumented migrants live in Geneva without a legally mandatory residence permit. Undocumented migrants arrive in Switzerland in general as tourists but do not leave Switzerland, which ordinary tourists are required to do after a maximum stay of three months. The restrictive Swiss immigration policy makes it almost impossible for low-qualified migrants from countries outside the European Union to receive a legal residency permit. Because of difficult living conditions, separation from their families, frequent exploitation by employers, permanent threat of being caught by the police, and exclusion from the usual healthcare system, undocumented migrants are at increased risk of poor health. Pregnancy can be of particular concern, as it may imply loss of work and of income just when these resources are sorely needed to pay for medical care.

However, there is a striking scarcity of direct evidence on these issues and study results are controversial. Some, but not all studies show that lack of health insurance, illegal status, and low

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Table 1. Birth outcomes and complications of undocumented migrants vs. women with legal residency status (control group) who delivered at the Geneva University Hospital, Switzerland between February 2005 and October 2006

Characteristic or measurement	Undocumented births (n=106)	Missing n (%)	Control group (n=229)	Missing n (%)	p-value
Gravidity (SO)	2.3 (1.4)	-	2.4 (1.4)	-	0.97
Parity (SO)	1.7 (1.0)	-	1.7 (0.9)	-	0.99
Mean gestational age (SO)	38.9 (1.9)	-	39.4 (1.4)	-	0.02
Pre-term births «37 weeks)	8.5%	-	3.9%	-	0.09
Post-term births (>40 weeks)	15.1%		21.0%		0.20
Delivery:		-		-	0.14
Vaginal spontaneous	59.8%		63.9%		
Forceps	3.7%		4.3%		
Vacuum	11.2%		10.9%		
Cesarean	25.2%		20.0%		
Complications during pregnancy	31.1%	-	33.6%	-	0.70
Complications during delivery*	26.3%	-	32.8%	-	0.36
Complications during post partum	3.7%	-	2.2%	-	0.41
Sex of the child (male)	50.5%	-	54.6%	1 (0.4)	0.48
Health of the child:		-		-	
Good health	96.2%		95.6%		0.53
Bom dead	0.9%		0.4%		0.58
Transfer to Neonatology for serious health hazard)	3 (2.8%)		9 (3.9%)		0.44
Birth weight in g (SO)	3293.9 (521)	-	3380.9 (495)	-	0.15
Low birth weight (<2500 g)	4.7%		2.6%		0.24
Apgar 1 (mean (SD)	8.5 (1.4)	-	8.7 (1.3)	1 (0.4)	0.43
Apgar 2 (mean (SD)	9.7 (0.8)	-	9.7 (0.6)	1 (0.4)	0.73
Apgar 3 (mean (SD)	9.9 (0.5)	-	9.9 (0.4)	1 (0.4)	0.86
Neonatal Complications	2.8%	-	6.6%	-	0.07

income increase maternal and newborn morbidity. On the other hand, a "healthy migrant effect" has been postulated to explain the lower prevalence of low-birthweight newborns in foreign-born compared to US-born women. In a previous study on pregnant, undocumented migrant women in Geneva, we found a high percentage of unintended pregnancies (83%), and a low use of important preventive measures, such as rubella immunisation or cervical cancer screening; however, comparison with the general population was difficult because control group data were not available.

The objective of the present study was to describe detailed information about contraception, intendedness of pregnancy, health status and behaviour, violence exposure, and birth outcomes of undocumented migrant women and to compare them to those of women having a legal residence permit.

Methods

Setting: In Switzerland, healthcare insurance is legally mandatory and every legal resident has to arrange for coverage on their own. However, as the cost of healthcare insurance is high, more than 90% of Geneva's undocumented migrants in Geneva lack such insurance. Since 1996, a healthcare unit has offered medical care for free or at low cost to undocumented migrants in Geneva, where no similar site for free gynecological or general healthcare exists. Over the years undocumented migrants have learned to trust the unit which does not transmit information to the police or other official agencies. The consultations in general medicine of the facility reached 10,000 in 2006 for over 3,000 undocumented migrants. Because of its high visibility for the local undocumented population and of the absence of formal administrative requirements, the unit reached the majority of pregnant, undocumented and uninsured women.

This prospective cohort study included all pregnant, undocumented women presenting to the healthcare facility between February 2005 and October 2006 as the exposed group. All pregnant women wishing to deliver were included independently of their stage of pregnancy and systematically referred to a coordinating midwife providing free pregnancy care in collaboration with the women's University Hospital, which is the only public women's hospital in Geneva. Some pregnant undocumented women who presented directly to that hospital were also referred to the same midwife. The women's hospital is well known and frequented by the majority of the female population of Geneva. In 2006, 67% of the 5,892 newborn of Geneva were born in this hospital.

The control group comprised a systematic sample of women with a legal residency permit who were directed by their gynecologist to the antenatal consultation at the women's hospital. They were seen by the same midwife as undocumented migrants. These women were selected during predetermined days between November 2005 and May 2006. On each selected day, every woman who saw the midwife was asked to participate in the study.

A socio-demographic questionnaire was completed during a face-to-face interview by a fluently Spanish and French-speaking midwife for both groups. The data were collected during

Table 2. Sociodemographic characteristics of undocumented pregnant migrants vs. pregnant women with legal residency status (control group) who delivered at the Geneva University Hospital, Switzerland between February 2005 and October 2006.

Characteristic or measurement	Undocumented (n=161)	Missing n (%)	Control group (n=233)	Missing n (%)	p-value
Mean age in years (SO)	29.4 (5.8)		31.1 (4.8)		0.02
Continent (%)	Latin America 83.9, Asia 6.2, Europe 5.6, Africa 4.3		Europe 80.3, Latin America 9.0, Africa 7.3, Asia 1.3, N.-Am. 2.1		<0.001
Nationalities (%)	Bolivia 34.8, Brazil 23.0, Columbia 8.7, Equator 6.2, Peru 5.6, Philippines 3.7		Switzerland 49.4, Portugal 13.7, France 9.0, Spain 3.4, Brazil 3.0		<0.001
Civil status (%):					<0.001
Single	71.4%		20.6%		
Married	20.5%		72.9%		
Oivorced	6.8%		5.2%		
Widowed	1.2%		1.3%		
Education:		39 (24.2)		3 (1 .3)	
Years of schooling (SO)	12.7 (2.7)		13.5 (4.2)		0.07
Highest achieved education:					<0.001
Primary school	3.7%		2.2%		
Secondary school	31.5%		47.4%		
High school degree	40.7%		15.2%		
University	24.1%		35.2%		
Years living in Geneva (SO)	2.5 (2.2)	39 (24.2)	16.4 (11.8)	18 (7.7)	<0.001
Father not living in Geneva	18.2%	39 (24.2)	4.3%		<0.001
Having a family member in Geneva	46.7%	39 (24.2)	67.7%	1 (0.4)	<0.001
Having children	41.8% (of whom 56.9% in Geneva)	39 (24.2)	52.8% (of whom 99% in Geneva)		0.05
Absence of emotional support	15.0%	39 (24.2)	0.4%		<0.001
Living conditions:		39 (24.2)			
Living in a single-room (%)	62.5%		18.0%		<0.001
Total number of persons of those living in a single room (SO)	3.1 (SO 1.8)		2.3 (SO 0.83)		0.01
Moves during the last year (SO)	1.5 (1.2)		0.4 (1.2)		<0.001
Lack of health insurance	100%		0%		<0.001
Insured during pregnancy follow up	25.2%		0%		<0.001

pregnancy follow-up (first to third trimester) for undocumented migrants and during the last trimester for control women. The socio-demographic questionnaire included 31 items concerning health insurance, nationality, children, housing and working conditions, duration and aim of the stay in Geneva, education, occupation, social support, major difficulties in daily living and social support, which was evaluated by: civil status, presence of a family member in Geneva, and relation of the father with the child. The health questionnaire concerned contraceptive history, health problems during pregnancy and post-partum as well as intendedness of pregnancy, meaning that pregnancies are begun without planning or intent. Cervical and breast cancer screening histories and substance abuse were also assessed. Prenatal aneuploidy screening, cytomegalovirus (CMV), venereal disease research laboratory test (VDRL), human immunodeficiency virus (HIV) Hepatitis B, as well as rubella and Toxoplasma gondii immunity status were assessed by blood tests. Information concerning delivery and neonatal outcomes was obtained from medical records.

The main study outcomes were unintendedness of pregnancy, knowledge of the emergency pill, cervical and breast cancer screening, delayed prenatal care, violence exposure during pregnancy and complications during pregnancy, delivery and postpartum. As the main confounding factors we considered age, Latin American origin, civil status, education, duration of residence in Geneva, and having emotional support and/or a family member in Geneva.

Results

During the 20 month study period, 163 undocumented women wishing to deliver were referred to the midwife. None had valid health insurance at time of their first pregnancy visit. Two-hundred-forty-six women with a regular residency permit were selected to participate in the control group. Two undocumented women (age unknown) and 13 controls (mean age 28.5) refused participation for the following reasons: had no time (n=6); did not want to participate without giving a reason (n=4); husband didn't want (n=2); didn't want to reply to questions (n=2); was afraid (n=1). Thus, the final study group consisted of 161 undocumented women and 233 women with a legal residency permit.

The large majority (84%) of undocumented migrants came form Latin America. Reported reasons for migration were mainly economical (84%), but also were related to family (7%) (to join a husband or a relative), education (2%, to study French), and 7% for political or tourism reasons.

Fifteen percent of the undocumented pregnant migrants indicated lack of emotional support (controls 0.4%, p<0.001). Furthermore they reported less social support than controls: 71%

Table 3. Preventive aspects and voluntary termination of pregnancy (TOP) history of undocumented pregnant migrants vs. pregnant women with legal residency status (control group) who delivered at the Geneva University Hospital, Switzerland between February 2005 and October 2006.

Characteri stic or measurement	Undocumented (n=161)	Missing n (%)	Control group (n=233)	Missing n (%)	p-value
Unintendedness of pregnancy (%)	75.2	12 (7.5)	20.6		<0.001
Of those with unintended pregnancies:					
No contraception	47.7%		33.3%		0.13
Insecure contraception (condom calendar, retraction)	31.2%		33.3%		0.51
No knowledge of emergency pill	61.2%	40 (24.8)	9.0%		<0.001
Previous voluntary termination of pregnancy (TOP)	27.0%	13 (8.1)	24.0%	4 (1.7)	0.51
Pap-test:		15 (9.3)			
Never	13.0%		0%		<0.001
> 3 years ago	4.8%		2.1%		0.15
Never breast examination by physician	29.7	16 (9.9)	3.9%		<0.001
Tobacco never	65.5%	13 (8.1)	48.1%		0.001
Alcohol consumption:		16 (9.9)			
Before pregnancy	65.0%		73.8%		0.06
During pregnancy	11.7%		30.0%		<0.001
Binge drinking (>4 glasses /occasion):					
Before pregnancy	6.3%		15.5%		0.007
During pregnancy	4.2%		0.9%		0.03
Other substances abuse	3.4%	14 (8.7)	17.4%	3 (1.3)	
Exposure to violence:		16 (9.9)		2 (0.9)	
Lifetime	26.4%		32.2%		0.21
During pregnancy	11.2%		1.3%		<0.001
Type of violence, if exposed to violence:					
Physical	53.7%		46.0%		0.45
Sexual	24.4%		28.6%		0.63
Psychological	53.7%		53.9%		0.98

were single (controls 21%, p<0.001); 18% lived separately from the father of their future child (controls 4%, p<0.001); and 8% had no relationship with the father (controls 0.4%, p<0.001). Twenty two percent of the undocumented migrants had no or only an occasional relationship with the father of their child (controls 1.3%, p<0.001). Forty three percent of the undocumented women with children lived separately from them (controls 1%, p<0.001). Moreover, only 47% of undocumented women had a family member living in Geneva (controls 68%, p<0.001).

Sixty percent of undocumented women (controls 18%) shared a single room with on average two (controls one) other persons. Over two-thirds (70%) of the undocumented were employed, mostly (95%) in the domestic sector (childcare and house keeping). They worked a mean of 23.9 hours a week (SD 15.8) and earned 13 SFr (SD 8.4; ≈8 Euro) per hour, which is 40% lower than the minimal mandatory hourly wage in Geneva.

To the open-ended question "which is actually the most important difficulty in your life?", 46% of the undocumented migrant women answered illegality, 25% housing, 14% finding work, 9% the language (French), 5% absence of the family, and 2% other. The control women reported: housing (22.9%), lack of money (22.9%), to find work (15.7%), and language (7.2%). Other sociodemographic characteristics are summarized in Table 2.

In undocumented women, unintended pregnancies were significantly more frequent and accounted for 75% compared to 21% in the controls (adjusted OR 8.0 (4.7;13.5)). Sixty-one percent of the undocumented migrants were unaware of emergency contraception (Levonorgestrel) compared to 9% among the control group (adjusted OR 15.7 (8.8;28.2)). Moreover, 79% of the undocumented women with unintended pregnancies did not use any (48%) or used unreliable (31%) contraceptive measures, such as condoms, retraction, or the temperature method. Reasons for absence of contraception among undocumented migrants were: infrequent intercourse (25%), believed that they were infertile (18%), and stopped contraception (run out of pills, side effects, lack of money) (12%). Other less frequent reasons were: "didn't think about it", "latent wish of pregnancy but planned for later", "lack of knowledge about contraceptive methods", and "presumed sterility of the partner". Undocumented migrants declared their pregnancies as unintended 73.2% of the time when asked during the first and 78.8% during the second and third trimesters (p=0.45).

There was significant under-use of preventive measures such as cervical smear (Pap) test and breast examination by undocumented migrants (Tables 3 and 4): they had more than a six-fold higher risk of under-use of Pap-test screening (never or >3 years ago) (adjusted OR 5.7 (2.0;16.5) and a ten-fold higher risk of never having had a breast examination by a physician (adjusted OR 9.6; CI:4.5;20.5). When considering alcohol, tobacco, and other substance abuse, undocumented migrants showed a healthier pattern compared to the control group. Lifetime exposure to violence was similar in both groups, but undocumented migrants were more exposed during their pregnancy (11% vs 1%, adjusted OR 8.6 (2.4;30.6)).

Table 4: Unadjusted and adjusted relationships of pregnancy care or preventive aspects of undocumented migrants vs. women with legal residency status (control group) who delivered at the Geneva University Hospital, Switzerland between February 2005 and October 2006.

Characteristic or measurement	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Unintended pregnancy	11 .7 (7.2;19.0)	8.0 (4.7;13.5) †
Delayed prenatal care (>12 weeks of amenorrhea)	13.3 (6.3;27.9)	10.8 (4.8;24.2) †
Violence during pregnancy	9.6 (2.7;33.5)	8.6 (2.4;30.6) ¡
Pap-test never or more than 3 years ago	9.9 (3.7;26.4)	5.7 (2.0 ;16.5) †
Never breast examination by physician	10.5 (4.9;22.3)	9.6 (4.5;20.5) ¡
No knowledge of emergency pill	15.9 (8.9;28.3)	15.7 (8.8;28.2) ¡

¡ adjusted for age
† adjusted for age and civil status

Undocumented migrants had an 11-fold higher risk for delayed prenatal care, meaning that their first pregnancy consultation occurred after the first trimester (adjusted OR 10.8 (CI 4.8;24.2)). Significant differences were also observed for Toxoplasma gondii and CMV immunity (Table 5).

During the study period 106 undocumented women (66%) delivered at the women's hospital. Fifty four women left Geneva and one had an early abortion (week 16). Mean gestational age was lower in undocumented migrants and preterm births seemed to occur more frequently but lacked statistical significance (p=0.09). Birth weight was similar in both groups. No significant differences between the exposed and control groups were found for complications during pregnancy, delivery, or post-partum. The main complications during pregnancy among undocumented migrants (controls) were: urinary infection 12% (11%), anaemia 8% (3%), risk of preterm delivery 7% (7%), vaginal bleeding 3% (4%), hypertension 3% (4%), and diabetes 2% (1%). Complications during vaginal delivery were similar in both groups: vaginal tear 11% (controls 18%), retention of the placenta 3% (4%), pre-eclampsia 2% (2%), and fever 1% (2%). Other birth outcomes are shown in Table 1.

Discussion

Compared to women who are legal residents of Geneva, undocumented migrants had more unintended pregnancies, use preventive measures less frequently, delayed prenatal care more, and were exposed to more violence during pregnancy. Delayed use of prenatal care remains problematic among undocumented migrants in Geneva: the first pregnancy visit occurred more than 4 weeks later than for women with a legal residence permit, and prenatal care began during the first trimester in only 63% of the undocumented compared to 96% of controls. Similar difficulties were observed for undocumented pregnant migrants in Colorado, US. The United Nations has indicated that one high priority "Millennium goal" is to improve maternal health throughout the world. Even if the existence of a free healthcare unit facilitates access to care, there is clearly a need to find ways to improve use of care and particularly early pregnancy care for undocumented women. In our experience, the cost of healthcare is a major barrier, particularly in countries like Switzerland where each individual has to arrange and pay for their own health insurance and where over 90% of the undocumented migrants lack health insurance. Improved healthcare access for undocumented migrants requires creative financial solutions, including being free or of minimal charge, but also language competencies of healthcare providers and administrative staff. Furthermore, protection has to be guaranteed: undocumented migrants would hardly be likely to contact a healthcare provider if they feared potential notification of their stay to the police and any other subsequent legal sequelae.

Undocumented pregnant migrants in Geneva were mostly

Table 5. Pregnancy characteristics of undocumented migrants vs. women with legal residency status (control group) who delivered at the Geneva University Hospital, Switzerland between February 2005 and October 2006.

Characteristic ar measurement	Undocumented (n=161)	Missing n (%)	Control group (n=233)	Missing n (%)	p-value
Weeks of pregnancy at first		9 (5.6)		-	
control (SO)	12.6 (6.1)		8.0 (3.1)		<0.001
Trimester care began		9 (5.6)		-	<0.001
First	63.2%		96.1%		<0.001
Second	32.2%		3.4%		<0.001
Third	4.6%		0.4%		0.007
No Toxoplasma gondii immunity	31.2%	9 (5.6)	57.9%	-	<0.001
No Rubella immunity	10.0%	9 (5.6)	4.7%	-	0.046
No CMV immunity	7.8%	10 (6.2)	40.8%	49 (21)	<0.001
VORL positive	1.3%	10 (6.2)	0.4%	1 (0.4)	0.71
HIV positive	1 woman	10 (6.2)	1 woman	5 (2.1)	0.79
0'Sullivan test positive	7.8%	10 (6.2)	7.4%	17(7.3)	0.96
HBV (Ag Hbs+)	0	9 (5.6)	0	-	
HCV	0.6%	10 (6.2)	0.4%	1 (0.4)	0.79
Prenatal screening (p.s.):		8 (5.0)		6 (2.6)	
Without p.s.	17.0%		6.2%		0.001
If p.s., double test (1.trimester):	54.6%		85.5%		<0.001
Double test (2.trimester)	14.5%		7.5%		0.028
Amniocentesis	3.3%		9.7%		0.001

young and single Latin-American women of whom an important percentage lacked social and emotional support. They were living in poor housing conditions and one in five of them had no or only an occasional relationship with the father of their child.

Despite our findings that prenatal care was delayed and preterm births were more frequent in undocumented migrants (9%vs.4%, p=0.09), health outcomes such as complications during pregnancy, delivery, and post-partum were similar in both groups, and neonatal outcomes even tended to be slightly better in the undocumented. These relatively good health outcomes might be explained by a selection of the fittest women during migration, which has been conceptualized under the "healthy migrant effect." Alternatively, it could be hypothesized that good birth outcomes might be explained by the fact that women who were lost to follow-up might have had worse risks. Nonetheless, when comparing undocumented women who delivered to those who left the country, no particular risk profile could be identified.

Considering drugs and alcohol abuse, undocumented pregnant migrants showed a healthier pattern than control women. Prenatal alcohol exposure is a major cause of foetal defects and neurodevelopmental problems and the most frequent cause of avoidable mental retardation. In our population, most women stopped their alcohol intake with the onset of pregnancy. Nevertheless, 30% of the control group and 12% of undocumented migrants consumed alcohol during pregnancy with a notable proportion of binge drinking (16% versus 6%). Healthcare professionals must be aware of this major problem.

Seroprevalences in undocumented women corresponded to their countries of origin, mainly Latin-America. They were better immunized against Toxoplasma gondii and CMV but less so against rubella than controls. Toxoplasma immunity prevalence among controls was 42%, similar to what has been found for the Swiss general population (46%), whereas the Toxoplasma immunity prevalence in Latin-America (67%) is similar to that of the undocumented migrants in this study. Seroprevalence of rubella is known to vary across countries, with lower rates in Latin-America, where congenital rubella syndrome is an under recognized public health problem.

The high prevalence of unintended pregnancies among undocumented migrants (75%) highlights an important public health issue and confirms our previous study where we found a similar rate among undocumented migrants in Geneva. In contrast, the control group reported only 20% of unintended pregnancies. To our knowledge, this is the first time that unintended pregnancies resulting in live births have been studied for women with a legal residency permit in Switzerland. International comparisons show large differences between and uncertainties within countries, which indicates the complexity of measurement of unintended pregnancies: 10 to 31% in Great-Britain, 16 to 20% in France, and up to 55% in Colombia resulting in live births. In the US 49% of all pregnancies are estimated to be unintended, of which 33% to 49% result in live births, with large differences between the states. Known factors associated with unintendedness, such as delayed prenatal care, not being married, or exposure to violence were also observed in our study.

Exposure to violence has frequently been reported, particularly among women with unintended pregnancies and during pregnancy, as was the case for 11% of the undocumented migrants in our study. Consequently, it is important to ask pregnant women systematically and repeatedly about violence exposure. It was unexpected that only 1.3% of the controls reported being exposed to violence during pregnancy, which contrasts with 7% found in a survey conducted 10 years before at the same hospital. The latter study investigated violence prevalence as a major outcome, which could have influenced the women's responses and explain the higher prevalence.

Seventy-nine percent of the women with unintended pregnancies did not use any (48%) or used unreliable (31%) contraceptive measures, and 61% were unaware of emergency contraception (Levonorgestrel) which can prevent pregnancy up to 72 hours after intercourse and can be obtained without medical prescription in Geneva. The important difficulties concerning knowledge, access, and use of preventive measures are also illustrated by the under-utilisation of cervical smear (Pap) tests and breast examination. Pap test under-use corresponds to the wellknown lack of lifetime screening in many parts in Latin-America and underlines the need for language- and culturally-appropriate education.

The relationship between residency permit and the main outcomes might be influenced by age, origin, civil status, education, duration of residence in Geneva, and having emotional support and/or a family member in Geneva. Using multiple logistic regression analysis we found that civil status was an important confounder of the relationship between residency status and three main outcomes: unintendedness of pregnancy, delayed prenatal care, and less use of Pap tests by undocumented migrants. Other potential confounders had no significant influence on the main outcome in our study and were therefore not included in the adjusted analyses.

Our study confirms the close relationship between illegality and poverty. Undocumented migrants earned 13 SFr per hour (≈8 Euro) which is 40% lower than the minimal mandatory hourly wage in Geneva. Furthermore, undocumented migrant status is associated with isolation, stigma, and fear. Further research is needed to better elucidate these complex influences in order to implement effective programmatic solutions for the main problems pointed out here.

Conclusions

Compared to women who are legal residents of Geneva, undocumented migrants have more unintended pregnancies and delayed prenatal care, use fewer preventive measures and are exposed to more violence during pregnancy. Not having a legal residency permit therefore suggests a particular vulnerability for pregnant women. This study underscores the need for better access to prenatal care and routine screening for violence exposure during pregnancy for undocumented migrants. Furthermore, healthcare systems should provide language- and culturally-appropriate education on contraception, family planning and cervical cancer screening.

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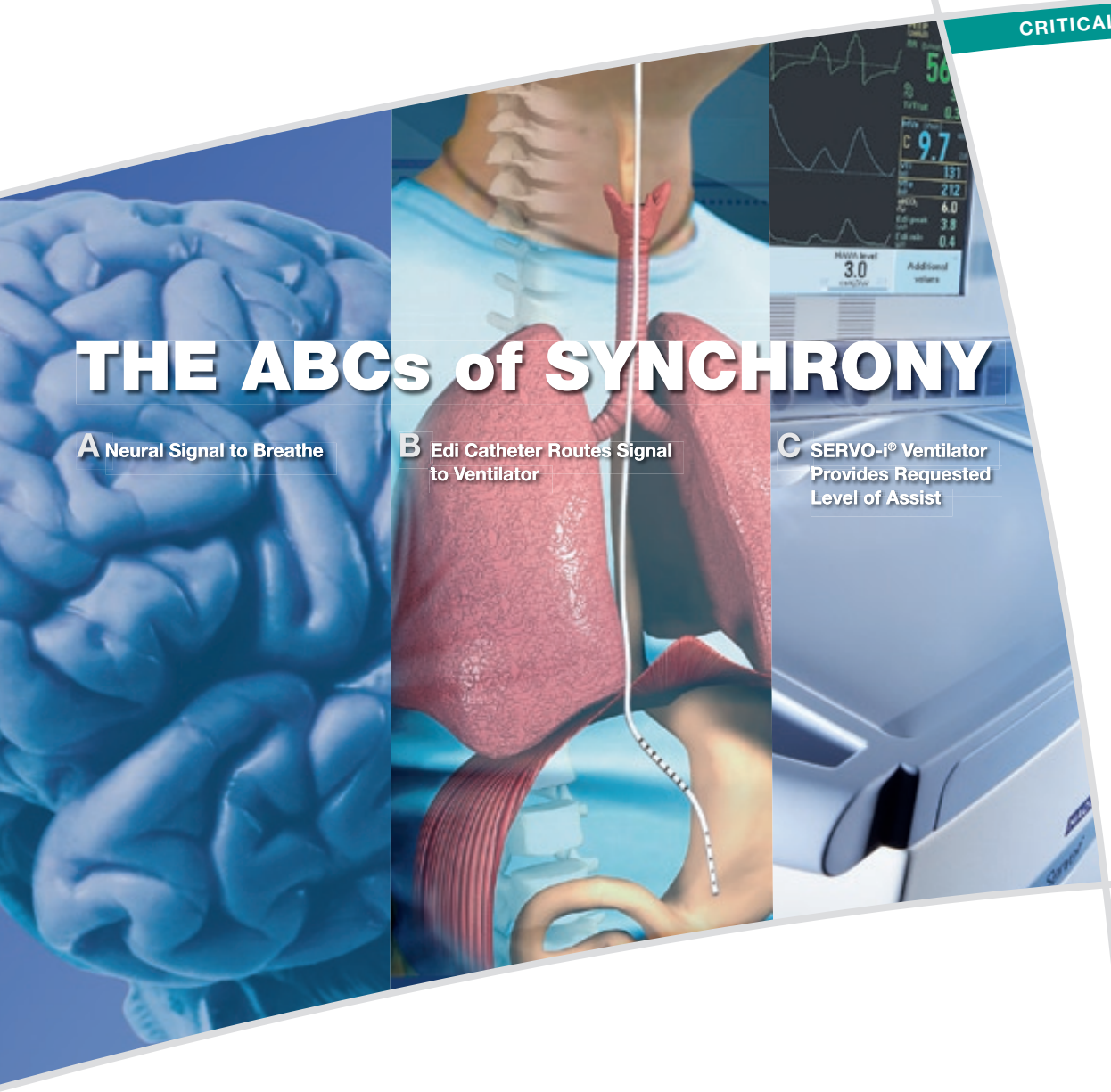

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* See, for example: Thille, A; Rodriguez, P; Cabello, B; Lellouche, F; Brochard, L; "Patient-ventilator asynchrony during assisted mechanical ventilation," Intensive care med., (226), 32:1515-1522, DOI 10. 1007/s00134-006-0301-8

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