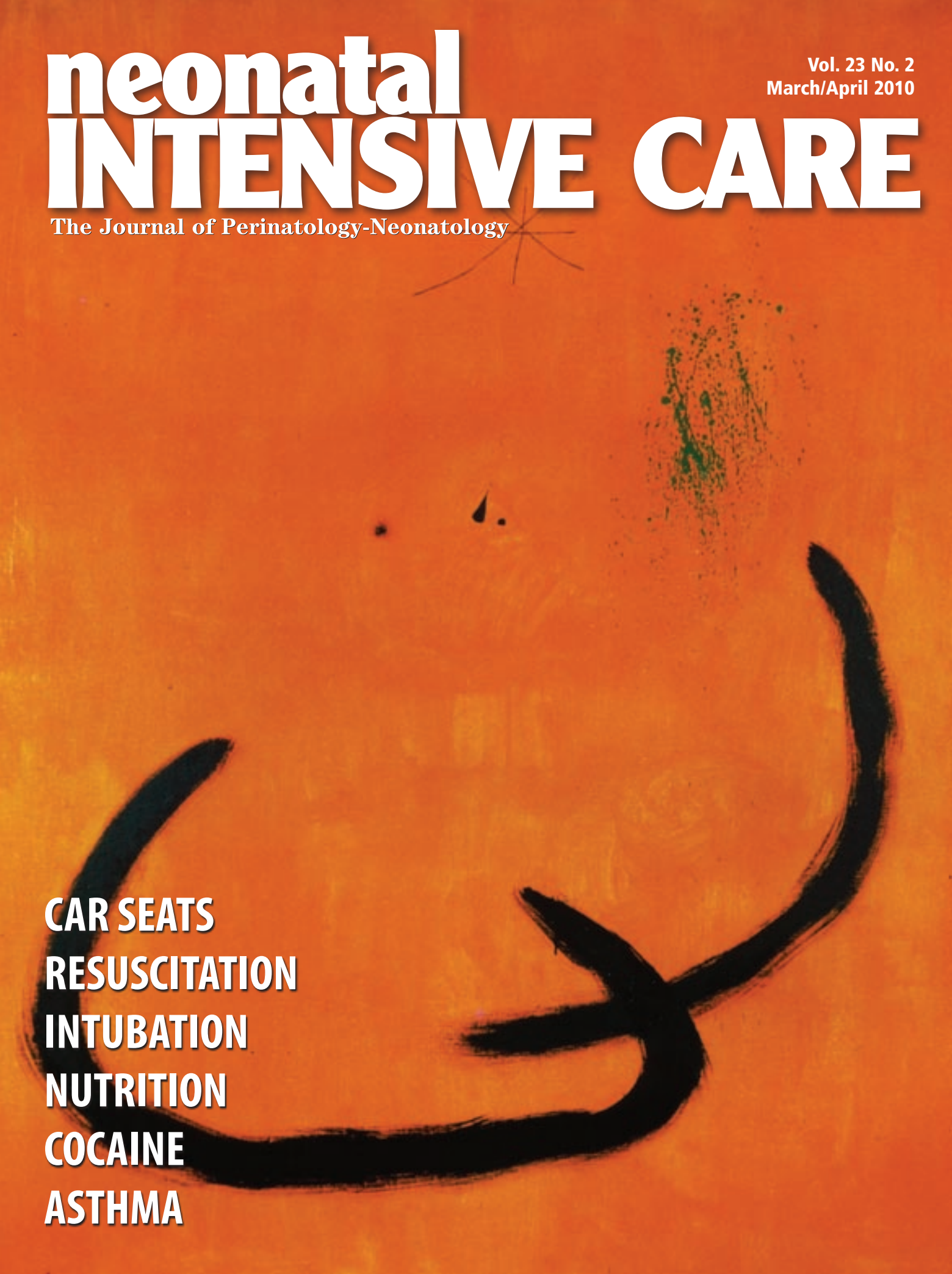


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Vol. 23 No. 2
March/April 2010

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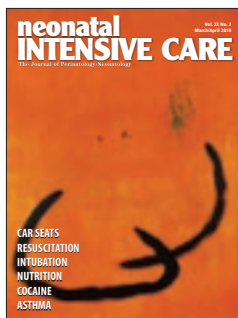
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Editorial

The Barn Door

What do the following have in common? The H1N1 epidemic, the bomb in the terrorist's underwear, the new healthcare bill, surrogates as parents (see page 6), and preemie viability. The above are all issues which have resulted in conundrums about the proper course of action in response to an event or a situation. In every case, all sides have weighed in with regulatory "solutions." The topics above are all examples of an occurrence, followed by an attempt to deal with it. In all of the foregoing, mitigating procedures have been introduced that are, in effect, attempting to lock the barn door after the horses have already fled. And, to stretch the metaphor, more often than not with a Rube Goldberg contraption that may or may not actually lock that barn once the next horses are inside. This is the way large bureaucracies and governments operate, when competing interests are involved.

Of course what is of primary concern to neonatologists is item #5, preemie viability, and decisions about when to offer treatment, and when to back off. Now that viability has been radically extended, of course we're up against a whole new paradigm.

In Italy, one solution has been to issue formal guidelines about care at the limits of viability. The authors of the article on page 18, "How Old Are You," put the issue succinctly: "The crux of the matter is whether strict guidelines based on the parameter of gestational age and authority rules are necessary." The authors note, "Concerning the decision to interrupt or not to initiate resuscitation procedures on low gestational age newborns or on newborns affected by severe and highly invalidating diseases, physicians do not need rigid rules based on inflexible gestational age and birth weight guidelines. Guidance in addressing the difficult and trying issues associated with infants born at the margins of viability with a realistic assessment of the infant's clinical condition must be based on the infant's best interests... The assessment at birth of vital parameters cannot have a rigorous prognostic value and cannot justify an aprioristic decision to desist from therapy. One can and must have doubts... about diagnosis and prognosis made in the first hours of life... We believe [that in] a decisional sphere burdened by such limited prognostic certainties, an individual approach is infinitely more acceptable than a statistical approach: any decision ought to be based upon the individual circumstances of each newborn rather than on references to guidelines, especially if these are based on gestational age."

While there is always a temptation to set down strict guidelines, one must also keep in mind the law of unintended consequences, as well as Murphy's Law. Americans, especially, have an aversion to risk, to contingency, to undecideability, and expect regulations and rules to solve problems that are intrinsically fluid and nuanced. While parameters and guidelines are a necessary component of healthcare, and neonatal care, it is ludicrous to imagine that a one-size-fits-all approach will ever work when it comes to dealing with issues of viability, and concomitant ethical issues. Practicing neonatologists are best served by procedures that allow for flexibility, that don't over-react to perceived problems, and that don't over-regulate commonsensical approaches to neonatal care.

Les Plesko, Editor

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News

□ March-April 2010

PHEW!

A Minnesota woman gave birth to a 15-lb 6-oz baby boy late last year. The kid was born three weeks premature and weighed in at twice the average for Minnesota. The mom was big too, at her own birth, that is—10 pounds, and she noted that doctors had to break her shoulder to get her out. The world baby weight record was set in 1955, with an Italian mom giving birth to a 22-lb, 8-oz boy.

PRIVATE ROOM

Los Angeles' first private-room NICU opened at the Providence Little Company of Mary Medical Center Torrance, CA. It took three years to build, at a cost of \$5 million. Each room allows the lighting to be dimmed according to the baby's sleep cycle, and is equipped with a sleeping chair for parents. Each room also has a mini-refrigerator for the mother's breast milk. In 2009, 183 babies were patients in the old NICU. The new one has 20 rooms, able to accommodate 34 babies at once (since twins will be in the same room).

NO CLOSURE

Researchers at Munich's Technischen University have come up with a clearer understanding of ductus arteriosus patency. Working on mice, the Munich team found that platelets congregate at the ductus arteriosus during closure, promoting the formation of a clot as the vessel contracts. They showed that failure of the ductus arteriosus to close in mice was associated with defective platelet function. The researchers also showed that in preemies, not having enough platelets also leads to the failure of patency. It was posited that a transfusion of platelets may mitigate the condition.

SINGLETONS ONLY

Preimplantation genetic diagnosis (PGD) is safe for the children of singleton pregnancies, but not for multiples, according to researchers at University Hospital Brussels. They looked at 581 children over 13 years who had been screened using the PGD technique. Rates of birth defects and deaths were similar to those of children born using other IVF methods, but there were considerably more deaths just after or before birth in multiple pregnancies following PGD. In total, 2.13% of PGD children had birth defects compared with 3.38% of the other children. For multiple pregnancies there was a greater difference. In the PGD group it was 11.73%, whereas among the others it was 2.54%. Researchers had no explanation for the variance.

STORY-TIME

Narrative medicine is a new approach to patient care, according to an article in the New York Times by Gina Kolata. She reports on her interview with Dr Rita Charon, professor of clinical medicine at the College of Physicians and Surgeons of Columbia University. Charon, with a PhD in literature, was interested in how stories are built and told, and how to apply them to patients' descriptions of their symptoms as they relate to a larger life narrative. Charon proposed a course at Columbia, a Master of Science in narrative medicine, and the program began last

fall. The specialized degree, at \$50,000, enrolled 28 students, including doctors, nurses, social workers, lawyers, literary scholars, and medical students. Courses cover philosophy, literary theory, psychoanalytic theory, autobiography and the close reading of literature involving experiences of illness. Charon said there's no obvious job market for people with a master's degree in narrative medicine, at least not at this time, but that the specialty would prepare graduates to become, at the least, better doctors. (Information is from The New York Times, Jan 3.)

WIKI-WATER

When Leroy Smith's wife's water broke and she went into labor, he went to his BlackBerry and the website wikiHow to fill him in on how to deliver the baby. As reported by the Baltimore Sun, Smith said, "I wasn't sure what I was going to do so I just looked up the instructions on the internet. I was very, very nervous. I never thought I'd actually have to do it. The BlackBerry told me that when I saw the head, I had to support it. And when the baby actually comes out, I had to place her on [the mom's] chest, then cover them both with a blanket and make sure they were both comfortable and relaxed." The mom said, "It was amazing. It was just us two in the house." The newspaper reported that the mom had disapproved of daddy's BlackBerry, since he was always playing with it, but has now changed her tune.

BIOMED CENTRAL

The National Institute for Health Research (NIHR) is funding Supporter Membership of BioMed Central. The NIHR has agreed to a membership arrangement with BioMed Central to support publication of research articles in the publisher's open access journals... EvoDevo is a new journal on evolutionary developmental biology, now open for submissions... BMC Health Services Research has published the abstracts, Patient Classification Systems International: 2009 Case Mix Conference Fukuoka, Japan... BMC Bioinformatics has published a collection of articles from Biodiversity Informatics... BMC Pharmacology has published the abstracts from the 15th Scientific Symposium of the Austrian Pharmacological Society (APHAR)... BioMed Central announced that the Chinese Academy of Sciences (CAS) is now a BioMed Central member. Contact bmc.com.

INDULGE!

Women should be allowed to eat and drink what they want during labor, according to researchers for The Cochrane Library, who carried out a systematic review of studies examining the traditional practice of restricting food and fluid intake during labor and found no evidence for any risk or benefit for women at low risk of complications. Throughout much of the last century, eating and drinking during labor was considered dangerous and many maternity units operated "nil by mouth" policies. This was largely due to concerns about possibly fatal damage to the lungs caused by Mendelson's syndrome. However, Cochrane researchers report, attitudes have begun to change and in many maternity wards, particularly in the UK, women are now allowed to eat and drink what they want. The Cochrane Systematic Review, which included five studies and a total of 3,130 women, looked at the evidence for restricting food and drink in women who were considered unlikely to need anesthesia. They found no evidence of any risk or benefit associated with eating or drinking, whether in studies comparing eating and drinking at will or just water with complete restriction, or in studies comparing specific foods, fluids, or carbohydrate drinks with

water. Source: Singata M, Tranmer J, Gyte GML. Restricting oral fluid and food intake during labor. Cochrane Database of Systematic Reviews 2010, Issue 1.

TRAUMATIZED

The 1st International Conference, Pediatric Psychological Trauma in Infants and Young Children from Illness, Injury and Medical Intervention was recently held at the University of Southern California, sponsored by the Keck School of Medicine and UC Irvine. It brought together an interdisciplinary group of distinguished healthcare professionals to discuss their work on behalf of young children, to identify the challenges they face and to build a vision and plan to minimize severe distress and pain while improving clinical practice and outcomes. The conference was designed to appeal to a wide audience: pediatricians, nurses, social workers, psychologists, psychiatrists, child life specialists, physical and occupational therapists, researchers and all others interested in the medical experience, science, and clinical care of the developing young child. Contact childdevelopmentmedia.com.

BRAVE NEW WORLD

In response to a New Jersey judge's ruling that a gestational surrogate who gave birth to twins is their legal mother, though she's not genetically related, The New York Times ran commentaries about surrogacy on its blog. (See the NYT's blog, Dec 31.) The Times asked: "as surrogacy becomes more common, should contracts for babies be subject to the strict vetting applied to adoption? Is there a public interest in regulating the process and deciding who can obtain a baby through surrogacy? Or is this a reproductive right that should be left to the private realm?" Several experts weighed in: Diane Kunz, exec director of the Center for Adoption Policy: "Medical tourism and the globalization of surrogacy make the case for regulation imperative." Arthur Caplan, professor of bioethics at the University of Pennsylvania School of Medicine: "There are more laws in the United States governing the breeding of animals than the use of surrogates to make people." Rebecca Dresser, professor of law and ethics in medicine, Washington University, St Louis: "Screen the parents: The intended social parents as well as the surrogate should meet standards for parental fitness." Bloggers also got to comment. Here's a sampling: "Regulated? If it becomes anything like the broken adoption process, where clearly qualified couples-in-waiting must wait years and jump through hoops, then absolutely not." ... "This surrogacy is another form of prostitution. The wealthy are paying women of lower station predetermined market prices for services that monopolize their sexual reproductive organs for the wealthy patron's benefit. Why is this even a question?" ... "Technology will march on (one day there will be an artificial uterus without the need to hire a human female) and profiteers will abound. There needs to be a balance in regulating the buying and selling of babies, both in adoption and surrogacy." ... "What a superbly egoistic and selfish thing to do. There are millions of children in this world whose lives would be saved by being adopted. What is so important about creating a baby that isn't even your own biologically? This practice needs to be severely curtailed." ... "It's not clear that one horrible case involving a surrogacy arrangement makes surrogacy a riskier or more dangerous way of achieving parenthood deserving greater scrutiny than other ways of becoming a parent." ... "Let's give up the silly notion that women can, and should postpone childbearing until their late thirties or even forties. Quite a bit of this silliness would be eliminated if we followed nature's own guidelines and returned

to childbearing in our early twenties." ... "Nature has decreed that the infertile should not reproduce. Using technology to create designer babies to satisfy the egos of these people is outrageous." ... "The entire Reproduction-Industrial Complex of fertility doctors, surrogates for hire and desperately seeking to be pregnant parents is degenerating into a twisted, selfish morass where the bottom line for most parties involved is simply the bottom line with selfishness on the part of all parties involved the rule rather than the exception."

DOULA DUEL

BBC News health reporter Clare Murphy reported on the trend of using doulas during birth. She reports that some docs are saying doulas are taking over duties that should be performed by midwives and compromising the relationship between the medical team and the mom. There are about 100,000 doula-assisted births each year in the US. One researcher said the use of doulas is "a sad reflection of failures in the delivery of medical and midwifery care, a sticking plaster concealing greater problems." Murphy said there's a broad consensus that "doulas are indeed stepping in to provide the support that midwives do not provide, either because they are overstretched [so to speak] or because they have no relationship with a mother they have never met before. Midwives are said to report mixed experiences, which on the down side was reported as aggressive or obstructive behavior. Another physician said many doulas have hardly any training and no code of ethics. However, others say they're providing much needed, high quality support, patching up the gaps in midwifery care. In the UK, a doula's services cost an average of £600, which includes antenatal, labor, and postnatal visits. Thus, they're used by those with cash to spare. One anesthetist said the problem is that caregivers are often perceived by doulas as enemies, but pointed out, "we don't come to work thinking 'how many needles can we stick in today.' Doctors are not the enemy but are sometimes portrayed as such." One doctor said the trend toward the use of doulas coincides with the desire among many women for "natural" birth, that is, without epidurals, or without invasive procedures. A physician interviewed for Murphy's article noted, "In no other field of life or medicine would you allow anyone to endure the pain that women endure in childbirth. And yet somehow women now feel failures if they have an epidural, or they end up having an instrumental or cesarean birth." Reported by the BBC, online.

EC-TOPIC

Researchers at Edinburgh University said activin B could be the key to early diagnosis and treatment of ectopic pregnancies. The researchers said they've established that women with these pregnancies have a much lower level of the protein, and they hope to develop a diagnostic test to check.

EARLY SEX

Babies who are small at birth are more likely to start puberty early, according to the World Cancer Research Fund. Rapid weight gain in the first two years of life is also associated with earlier onset of puberty. The cancer organization set up the study because early puberty has been associated with an increased risk of breast and testicular cancer. Researchers looked at a sample of 215 boys and girls who had height and weight measured regularly from birth to early adulthood. Those born at 2.5kg-3kg started puberty seven months earlier than heavier babies. Those who grew fastest as infants tended to have their puberty growth spurt four months earlier. The study also showed that for girls, rapid early weight gain was also related to starting their periods earlier.

Notably, the researchers did not find a link between birth weight, early puberty and childhood obesity, as previous studies had.

NO LO CAL

The Globe and Mail reported that pregnant women who drink non-alcoholic and low-alcohol beverages may be putting their babies at risk because some brands contain more alcohol than it says on the label, according to a study released today by the Hospital for Sick Children in Toronto. Researchers tested 45 beverages claiming to contain no alcohol or less than 0.5% alcohol for ethanol concentration using gas chromatography. Thirteen contained ethanol levels higher than on their labels. In three cases, ethanol levels of nearly 2% were recorded in beverages advertised as non-alcoholic. The researchers guessed that a potential contributor to the alcohol detected in the beverages may be the degradation of fruit. Reported in the Globe and Mail by Zosia Bielski.

HOW COME?

Erik Eckholm of the New York Times reported on a county in Wisconsin which has had a significant decline in the rate of infant deaths among blacks, countering recent trends. The rate of infant deaths among blacks in Dane County plummeted between the 1990s and the current decade, from an average of 19 deaths per thousand births to fewer than 5. In other parts of the state, including Milwaukee, Racine and two other counties, black infant death rates surpass 20 deaths per thousand. (Nationwide, the rate is 6 per thousand for whites and 13 for blacks.) The level of prenatal and birth care in the county was said to be the same as elsewhere in the state. Puzzled healthcare service providers said the likely explanation lay in "the interaction among a variety of interrelated factors," which is really saying nothing at all. A three year study compared the experiences of black mothers in the county to those in Racine County, which has the highest black infant mortality rate in the state. It was pointed out that Racine is more segregated and violent, and that Dane County has greater access to services. The director of county health said he thought it was "a community effect," and pointed to services for uninsured women, including the use of midwives, transportation to appointments, and anti-smoking programs. It was also noted that the black community in the county is close-knit, and that the area has a black leader and coordinator of Medicaid services.

MS-STOPPER

Giving birth seems to slow the progression of multiple sclerosis, according to Belgian and Dutch

researchers, who tracked 330 women with MS for 18 years and found that among those who had children, severe disability took longer to develop. Previous studies have suggested a worsening of MS just after birth. Commentators on the study noted that it was difficult to form any meaningful conclusions from the research, given the small size of the study. The women in the study had been referred to one specialist center and had had their first symptoms from the ages of 22 to almost 38. A quarter of the women were childless; 52% had given birth before their symptoms developed, 18% had their children after their symptoms developed, and 6% had children both before and afterwards. Researchers used the Kurtzke EDSS Scale, where 10 is death from MS and six is a limited level of ambulatory disability. After an average of 18 years living with MS, 55% of the

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women were categorized as EDSS six, meaning they could walk with a cane or crutches. The researchers found that both the likelihood and speed of progression were affected by childbirth. Women who had given birth to one or more children before or after the start of MS symptoms were 34% less likely to progress to EDSS six than childless women. Women whose children had been born after their MS began were 39% less likely to progress to EDSS six than women who had not had children. This held true even after taking account of the age at which symptoms began. Women who had no children after their MS symptoms started progressed to EDSS six within 13 to 15 years on average, but women who did have children took an average of 22 to 23 years to reach this stage. Researchers said it was possible that the hormones released in pregnancy had a beneficial effect on the immune system. The other possibility put forth was that lifestyle changes caused by having a baby somehow delayed the effects of MS.

MATERNAL MEETING

The Society of Maternal Fetal Medicine, a division of the American College of Obstetrics and Gynecology, recently held its annual Pregnancy Meeting in Chicago. Eighty-six papers were presented on topics that deal with high risk pregnancies. Subjects included: whether inducing birth or waiting is more effective with cases of intrauterine growth restriction, determining causes of stillbirth, whether staples or sutures are safer after cesareans, predictors of preterm birth, ways to reduce the number of induced births, ties between Atrazene and birth defects, whether screening for the genetic deficiency spinal muscular atrophy is cost-effective, and the risk of intrauterine fetal death and fibroids.

RATS

An international team of scientists led by Dr Bernard Thébaud, neonatal specialist at Alberta Health Services, has demonstrated that stem cells protect and repair the lungs of newborn rats. Thébaud's team simulated the conditions of prematurity, giving the newborn rats oxygen. The scientists then took stem cells, derived from bone marrow, and injected them into the rats' airways. Two weeks later, the rats treated with stem cells were able to run twice as far, and had better survival rates. When Thébaud's team looked at the lungs, they found the stem cells had repaired the lungs, and prevented further damage. The research team included physicians and scientists from Canada, France, and the US. The team is investigating the long-term safety of using stem cells as a lung therapy. The scientists are examining rats at 3 months, and 6 months after treatment, studying the lungs, and checking their organs to rule out any risk of cancer. Thébaud's team is also exploring whether human cord blood is a better option than bone marrow stem cells in treating lung disease, and are also studying the healing liquid produced by the stem cells, to see if it can be used on its own to grow and repair the lungs, which would make stem cell injection unnecessary. The study, *Airway Delivery of Mesenchymal Stem Cells Prevents Arrested Alveolar Growth In Neonatal Lung Injury In Rats*, is available at ajrcm.atsjournals.org/current.shtml.

RATS & TRANSPLANTS

Transplanted human-derived umbilical cord blood stem cells transplanted in an animal model had positive therapeutic effects on specific lung and heart disorders. In a study at Samsung Medical Center in Seoul, researchers investigated the therapeutic benefits of transplanting UCB mesenchymal stem cells (MSCs) into newborn laboratory rats with oxygen-deprived

lung injury, and found that MSCs have a protective effect against hyperoxia-induced lung injury, likely due to anti-inflammatory effects. The researchers noted that their findings are expected to have important therapeutic potential for BPD in premature human infants. The optimal route for transplantation had not previously been determined. The intratracheal, rather than the intraperitoneal transplantation of human UCB-derived MSCs significantly attenuated hyperoxia-induced lung injury, such as decreased alveolarization and fibrosis. Survival rate was not improved by the MSC transplants, however. Questions remain over whether the donor cells exert a therapeutic effect by inducing direct tissue repair and regeneration of damaged cells, said the researchers.

FLATHEAD

Researchers at Arizona State University have analyzed a database of 20,000 kids and found that the number of babies who have developed deformational plagiocephaly has dramatically increased since 1992. The increase coincides with the AAPs "Back to Sleep" campaign that recommended parents place their infants on their backs to reduce the risk of SIDS. The largest factor in flat-headedness was the sleep position of the baby, and comes from babies spending too much time in one position. Babies who slept on their right-side or left-side tended to have right-side and left-side flat spots, respectively. The study also found that boys were twice as likely as girls to have the condition and it was also more common in firstborn infants, babies with low birth weight, in breech and transverse positions in the womb, and in fraternal twins. The research was by Jessica Jorganic, for her undergrad honors thesis. She's pursuing a doctorate in physical anthropology at St Louis's Washington University.

HARVEST TIME

Stem cells that could provide therapeutic options for muscle and bone disorders can be harvested from the tissue of the umbilical cord, according to researchers at the University of Pittsburgh School of Medicine. Umbilical cord tissue cells can be multiplied and might not trigger strong immune responses. The cells can be obtained from Wharton's jelly and blood vessel walls. From 21 million to 500 million stem cells could be banked from a single umbilical cord. Researchers analyzed sections of two-foot-long human umbilical cords that were donated for research, looking for cells that displayed the characteristic protein markers found in stem cells derived from other sources. The researchers then sought to find the best way to isolate the cells from the cords, and tested them in the lab to confirm their ability to produce specialized cells while retaining their invaluable ability to renew themselves.

MIS-TIMED

Less than half of women with potential preterm labor deliver when they present at a hospital. However, for many of these women, antenatal admissions are common and many are subjected to unnecessary interventions, according to research presented at RCOG. However, a simple test may let doctors know if the mom will delivery early. When fFN is found to be leaking at a certain stage of pregnancy, a spontaneous preterm birth is more likely. A diagnostic fFN test has been developed though it is not commonly used in all maternity units. Relatively cheap and easy to perform, the test is done at the same time as a vaginal examination, which is routine when a woman is admitted with abdominal pain in pregnancy. A negative result means fetal fibronectin is minimally present and the chance of the woman having an imminent preterm birth is low. Researchers from

University College Hospital London conducted a two-stage audit to assess the effectiveness of the fFN test and the impact of its introduction. Over a two-month period, there were 95 hospital admissions that were at <37 weeks gestation. Out of 22 women who presented with threatened preterm labor, 17 didn't deliver during their admission. Sixteen received steroids or tocolytic drugs and three had an in-utero transfer to an NICU. The mean duration of hospital stay was 8.1 days. After introducing the fFN test, in 94 of the tests carried out, the negative predictive value for delivery within two weeks was 98.6%. Of the 78 women in threatened preterm labor with negative fFN, only seven were admitted for management of abdominal pain. Researchers said that women with a negative test can be reassured that they don't need inpatient care. The use of fFN tests can also reduce unnecessary in-utero transfers.

BELLY BANNED

Fat pregnant women may need their gastric band released to prevent pregnancy complications, according to doctors at Dewsbury District Hospital. A doctor was confronted by a belly-banded woman who suffered from severe morning sickness and weight loss at 17 weeks, after she'd undergone gastric banding. She was found to be severely malnourished. Release of the gastric band led to some improvement, but after more deterioration, it was removed after 21 weeks. The mom had a normal delivery. Doctors noted that pregnant women need to consider the fetus's nourishment needs, and should inform their doctors and midwives if they've had gastric banding.

A LEGAL MESS

A proposed ballot initiative to grant constitutional rights to cells at conception would raise a mess of questions, according to a report by The Advisory Board Company, in Medical News Today. For instance, would rapists have the right to ensure their children are born? Would a woman who smokes and drinks while pregnant face legal consequences? In any event, the point might be moot, because a state initiative can't override the US Constitution. Proponents of the legislation say it isn't an effort to stop legal abortions. However, the counterargument is that it's stupid to offer an initiative that *prima facie* won't accomplish what it's supposed to. (Information for the foregoing © 2009 The Advisory Board Company. All rights reserved.)

GET IT OUT

Umbilical oxytocin has no effect on the need for manual removal for women with retained placenta, according to researchers at the University of Liverpool. A retained placenta complicates 0.1 to 2.0% of deliveries. However, the rate of placenta removal has increased ten-fold in relatively affluent areas of Europe since the 1920s, perhaps because of higher induction rates and facilities for the procedure. Such facilities are often unavailable to poor women. As a result, this condition has a case fatality rate of almost 10% in rural communities. Large amounts of the oxytocin hormone are released after distension of the cervix and vagina during labor. Injecting oxytocin into the placenta via umbilical vein is a low-cost solution. However, in order to reach the placental bed, at least 30 mL of solution needs to be injected through an umbilical vein catheter. Until the current study, this technique hasn't been used for treatment of a retained placenta. For the study, women who were not bleeding or in shock, and with a placenta retained for more than thirty minutes, were recruited in a randomized controlled trial from thirteen sites in the UK, Uganda, and Pakistan. A total of 577 women were assigned to be given 30 mL saline containing either 50 IU

oxytocin or 5 mL water, which was injected into the placenta through an umbilical vein catheter. The primary outcome was the need for manual removal of the placenta. The researchers detected no difference between the groups in the need for manual removal of placenta: oxytocin 179/292 was 61.3% compared to placebo 177/285 which was 62.1%. When combining the groups, the authors showed that the need for manual removal was higher in the UK than in Uganda or Pakistan: UK: 69%, Uganda 47%, and Pakistan 62%. The researchers noted that in settings in which there are long waits for treatment and in which women are "tolerant of pain," there can be many attempts at placental delivery with prolonged cord traction, grasping of vaginal portions of the placenta, and uterine massage. In the UK, by contrast, operating theatres with regional anesthesia are easily accessible and so the woman does not need to undergo the discomfort of repeated attempts at placental delivery. Information for the above is from an article written by Stephanie Brunner, BA, copyright Medical News Today.

TREATED LIKE SH*T

Women who don't make a lot of money are discriminated against when seeking healthcare coverage, according to a study by Oregon State University. An analysis of Oregon data over a three year period showed that women who made less than 50-grand a year were three times more likely to report discrimination by healthcare providers because of the kind of insurance they had during pregnancy and childbirth. Insurance-based discrimination was three times more likely among moms on Medicare and four times as likely among moms who didn't have Medicaid or health insurance. Researchers analyzed data from 5,762 women and found that of women who reported insurance-based discrimination during prenatal care, labor or delivery of their babies, 43% had a yearly household income of less than \$15,000. The remainder of women reporting discrimination had incomes of \$15,000 to \$49,999. Only about 4% made more than \$50,000 a year. Women with employer health insurance who reported insurance-based discrimination reported much less breastfeeding support in the hospital. In addition, Hispanic women, regardless of income level, were much less likely to report insurance-based discrimination than other women.

ASTHMA AND AUTISM

Beta 2 adrenergic agonist drugs for the treatment of asthma in pregnant women as well as preterm labor may increase the incidence of autism-spectrum disorders, psychiatric pathology, cognitive problems and poor school performance in children, according to researchers at Johns Hopkins. Researchers observed that when given prenatally, these drugs can cause functional and behavioral disorders by permanently altering the balance of sympathetic and parasympathetic tone. Animal studies support the concept that in humans prenatal exposure to continuous high doses of beta 2 adrenergic agonists can permanently disregulate signaling from the beta 2 adrenergic receptor. Clinical investigators noted that given the risk of long-term neurophysiologic and behavioral impairment, the use of beta 2 adrenergic agonists should be limited to proven indications when alternate drugs are ineffective or unavailable and the risks of the untreated disease to the mother and fetus are greater than the risk of the beta 2 adrenergic agonist.

TOO DEEP

A recent study at the University of California, San Diego, showed that MRI is a highly accurate means of identifying placenta accreta. Due to the increase in c-sections and other surgeries

that leave scarring on the uterine wall, coupled with women giving birth later in life, the incidence of accreta has increased dramatically over the past 20 years. While routine prenatal ultrasound is often able to identify the presence of placenta accreta, it is not always able to definitively diagnose subtle cases. To evaluate the accuracy of MRI in diagnosing placenta accreta, 108 patients underwent MRI evaluation at UCSD between 1992 and 2009. The women were referred for MRI based on a suspicious prenatal ultrasound or clinical examination or significant risk factors for the condition. The researchers compared the MR images with surgical and/or pathology results in 71 of 108 cases. When correlated with surgical and pathology findings, MRI had a 90.1% accuracy rate in detecting accreta. A 2005 study analyzed data from 64,359 births over 20 years and reported an overall incidence of placenta accreta of one in every 533 deliveries. Women who have previously delivered a baby through a cesarean section have a greater risk for the condition by a factor of three. The risk escalates with each subsequent c-section. Researchers noted that while placenta accreta isn't necessarily a bad prognostic indicator for a pregnancy, not knowing about it can be life-threatening.

PRODUCTS

ADVENT-URE

Advent Product Development offers the Timer For Nebulizer Compressor, a modification to the design of nebulizer compressors comprised of a simple timer mechanism connected to an automatic shutoff valve. The Timer for Nebulizer Compressor will keep the machine from overheating and times out after a specified period set for the required treatment. The timer is activated and automatically shuts off the nebulizer, preventing it from overheating when the session is complete. The Timer was invented by Jesus Padilla of Rialto, CA, a respiratory therapist. To view a graphic of the Timer For Nebulizer Compressor, along with more information, go to adventproduct.net/24983/default.htm.

SHOWCASE

CareFusion showcased its ventilation technologies at the 55th AARC International Respiratory Congress. The company demonstrated its EnVe Ventilator, a high-performance critical care ventilator for pediatric and adult patients. Weighing only 10 pounds, the EnVe ventilator is 70-80 pounds lighter than other intensive care ventilators, allowing it to be easily moved with patients when they are transported into and within the hospital. The company also featured its LTV 1200 Ventilator, and announced that the CDC ordered 4,500 of them for the Strategic National Stockpile. Also highlighted was CareFusion's ReVel Ventilator, a lightweight, portable ventilator featuring advanced functionality and a four hour internal battery that can be hot swapped without disruption, offering intensive care ventilation in any environment. Contact carefusion.com.

BRIGHT NOT BLAND

At the 95th Scientific Assembly and Annual Meeting of RSNA, Siemens Healthcare presented "Healthcare Lighting," a concept for lighting design in medical facilities, aimed at creating a friendly and colorful environment instead of the common bland hospital atmosphere. Typical areas of application for light installations are CT, AX and MRI examination rooms. Light tubes—operated via computer to emit different light colors—can be mounted on walls. Walls and ceilings can be attractively

decorated with different motifs, such as a mountain landscape and a blue sky with white clouds. With a special software program, the operator can choose from the full color spectrum and combine different tints. A special system for the MRI room works with a large number of small LEDs mounted on the ceiling that light up the entire room in color. The Center for Diagnostic Radiology at Butzbach near Frankfurt, Germany, has achieved very positive experiences with Healthcare Lighting, because it helps keep patients distracted during CT scans. Economic figures from Butzbach clearly showed that only about 1% of patients had to be sedated before undergoing an MRI scan. Because of the lighting, claustrophobic patients can make it through the procedure without sedation. The distraction with colors also works well with children. Contact usa.siemens.com.

EXECUTIVE PROFILE

iMDsoft

Describe your product and its unique features.

The flagship product of iMDsoft, the MetaVision Suite, manages all the clinical data in critical, perioperative and acute care environments. MetaVision for NICUs facilitates the creation of a single continuous record for NICUs and step-down nursery units, with labor and delivery forms for easy data entry related to both baby and mother, highly accurate drug and fluid management, automated intake calculations enabling daily comparison to patient weight, precise compounding of neonatal nutrition, and newborn growth charts. MetaVision seamlessly integrates data from bedside devices, including IV pumps, hemodynamic monitors and incubators, to automatically create a complete electronic patient record. It arms healthcare professionals with timely, accurate, and actionable information, and fully supports the unique workflows of high-need, data-rich NICUs.

MetaVision features decision support and analysis tools: Event Manager—Smart alert system that uses predefined rule-engine algorithms to continually search system databases, issue clinical and administrative alerts, and execute predefined actions including targeted communications to relevant staff members; The Query Wizard—intuitive tool for query and report generation supporting clinical research, quality initiatives and cost analysis.

How does your product directly affect patient care?

MetaVision has proven that it helps to improve patient safety and care quality by providing clear, actionable information. It offers minute-by-minute patient data collection and display to create a complete electronic patient record. Precious minutes previously spent on filling in forms, manually recording key vitals, and calculating complex formulas and balances become time available to spend with patients. With MetaVision, the errors associated with hand charting are eliminated, enhancing patient safety. Data is instantaneously available, in just the required format, meaning healthcare professionals are better informed. Meanwhile, MetaVision's robust decision support options offer smart notifications to prompt you on changes in patient condition and enhance delivery of best practices.

Tell us about the latest advances in the area your product serves.

iMDsoft is dedicated to enhancing its product's existing functionality to retain its position as a provider of cutting-

edge technology. One of the latest advances in MetaVision is the Total Intake Calculator, part of the Order Management module. MetaVision includes the Order Management module, a comprehensive tool that facilitates building prescription packages, including drugs and clinical tasks. Treatments are planned and entered via the Total Intake view. This flowsheet view facilitates the management of daily intake of ingredients and drugs. Displaying this view alongside Order views on the flowsheet enables physicians to see changes made to the ingredients/drug amounts during the planning stages of ordering before committing to changes. The intake calculator will simulate multiple ingredient intakes over the next 24 hours at the planning stage before even signing the prescription. This allows clinicians to analyze their complete drug, fluid and nutrition plan before signing it.

What sets your product apart from others in the field?

For a system to create measurable, sustainable value through ICU automation, it must adapt to the complex, data-intensive, collaborative based nature of critical care, must support the caregiver through information capture, presentation, and decision support, must interoperate fully with the existing IT infrastructure, and overall must improve the working environment of the clinicians. MetaVision uniquely meets these requirements: MetaVision is a single application that meets all the disparate workflow needs of different patient types (NICU, PICU, GICU, Burn), different user types (nurses, physicians, respiratory therapists), and different workflows and clinical states. The fully configurable MetaVision Event Manager continually identifies opportunities to improve care, using branching, longitudinal logic to foster delivery of protocols and best practices. MetaVision offers full customizability of the user interface for workflow integration, standards-based device information capture, and service-oriented-architecture interoperability with ADT, lab, pharmacy, and other HIS systems. Further, because MetaVision is modular in its deployment, hospitals can leverage its CPOE and/or note-writing modules, or continue to use their existing technologies for these workflows.

MetaVision has the ability to wrap around the existing workflow stems from its parameter-based architecture, and its overall separation of the logical layers of the application. Thus, users can configure flowsheets, calculations, reports, forms, and pre-populated note templates without any modification to the underlying application.

Finally, beyond the features and functions and technology architecture, iMDsoft assigns to each implementation a dedicated team of professionals who focus solely on critical care information systems. With offices around the world, iMDsoft provides local support, while leveraging the expertise of a global installed base and active user group. MetaVision has a proven track record of producing positive outcomes. Hospitals have realized clinical, financial and operational benefits with the system, including significantly reduced patient mortality rate, fewer medical errors, and less time spent on documentation. Further, the MetaVision Suite has been proven to improve compliance with regulations and protocols.

Discuss the educational services you offer for use of your product.

iMDsoft has vast experience training clinicians in implementations that range from single units to multi-hospital. From our installations worldwide, iMDsoft has gathered a wealth

of experience in providing training that ensures that hospital staff will be able to comfortably and competently use and maintain the system independently. iMDsoft offers its customers a range of training options both during and after implementation. The training is delivered by an experienced staff and is designed to help make the most the MetaVision system. Documentation of all iMDsoft products is provided during the onsite training and can be accessed any time via the online training center. The materials are provided in a range of languages and cover both clinical and technical topics that are important to end users. Onsite training: During the implementation project, key users from the hospital staff undergo extensive onsite training by iMDsoft professionals. Following go-live, specific onsite training sessions can be held at the request of the customer. Online Training Center: The iMDsoft Training Center is a web-based system for various e-Learning solutions. It is designed to serve as a complete source for all the information customers need during and after going live with MetaVision. The center offers self-taught online courses, step-by-step demonstrations, on-demand, instructor-led training sessions (live and recorded), online help and a variety of knowledge tools that support the learning process.

iMDsoft also offers its customers advanced courses onsite or remotely via WebEx. The courses are designed to help optimize use of MetaVision to better support workflows and to introduce advanced application features, such as data mining and analysis. Customers can request a customized training program that is tailored to specific needs that they may have at a given time. iMDsoft also holds virtual and face-to-face workshops in different regions throughout the world. These workshops are attended by customers interested in enhancing their use of MetaVision and provide an opportunity to share knowledge and best practices with the rest of the MetaVision community.

Discuss the role of critical care providers in developing and upgrading your product.

iMDsoft employs both market and user data to further develop the MetaVision Suite system. We use a multifaceted approach to determine the content of future enhancements and upgrades to MetaVision. First and foremost, user feedback is central to the methodology used to gather information about enhancement and upgrade requirements. iMDsoft utilizes user groups and customer sites for suggestions about what improvements can be made to the product. Market trends and conditions are another key factor when considering the content and functionality of the upgraded software. iMDsoft gathers feedback from market analysts and draws on guidance from its Scientific Advisory Board (SAB) and its innovative, creative and highly experienced research and development team to generate new ideas and directions to focus on for future upgrades. By collecting input from all these important sources of information to create superior future versions of its products, iMDsoft remains a leader in the CIS market.

Tell us how you utilize conferences, seminars and such to promote your product.

iMDsoft attends over 40 trade shows a year presenting our offerings and new developments to clinicians, hospital executives and IT professionals worldwide. iMDsoft also initiates user group meetings for existing customers to present them with new features and services and to give them a chance to discuss their experiences using the application and to share information.

Assessment of Current Practices for Transitioning Infants from Car Beds to Car Seats: A Survey Study

Michele DeGrazia, PhD, NNP-BC; Ashley A. Wilkinson, MS, RN; Lawrence Rhein, MD

Objectives: Some premature and high-risk infants experience breathing problems in their car seats. Infants with breathing problems when positioned in their car seats are recommended for travel in a car bed by the American Academy of Pediatrics (AAP). However, no published guidelines for transitioning infants from car beds to car seats currently exist. This descriptive survey study was developed to gain a better understanding of the current practices used by primary care pediatricians for transitioning infants from car beds to car seats.

Study Design: We conducted a cross-sectional, anonymous survey of 1,585 Massachusetts pediatric primary care physicians about their current practices for transitioning infants from car beds to car seats.

Results: The response rate was 24% (N=376). Pediatricians used age (37%) and weight (15%) as criteria for repeating the ICSC or transitioning from a car bed to a car seat. Management strategies for transitioning infants from car beds to car seats varied dramatically among the respondents.

Conclusions: This study provides important information about current practice patterns of pediatricians when they transition infants from car beds to car seats and highlights the substantial practice variability by pediatricians who care for infants who fail the ICSC.

Introduction

Car seats have played a major role in the safe travel of the youngest motor vehicle passengers.¹ Since the widespread use of car seats, the risk of death from automobile accidents has significantly decreased.² However, some premature and high-risk infants experience breathing problems in their car seats.^{1,3-9} These breathing problems are detected by screening infants in their car seat prior to hospital discharge. Infants with breathing problems when positioned in their car seats are recommended for travel in a car bed by the American Academy of Pediatrics.¹⁰ Yet, no published guidelines for transitioning infants from car beds to car seats currently exist. This descriptive survey study was developed to gain a better understanding of the current practices used by primary care pediatricians for transitioning infants from car beds to car seats.

Background

Car seats protect infants from injury in the event of a motor vehicle accident. Yet several studies have documented unexpected respiratory compromise associated with car seat use in some infants.^{1,5,6,11-15} Both premature and selected term infants are at risk for breathing difficulties in their car seats.^{3,15} Based on these observations, the American Academy of Pediatrics (AAP) recommends that premature and at-risk newborns (ie infants with poor tone, history of respiratory illness, or airway anomalies) be screened for breathing problems for a period of time in their car seat, prior to hospital discharge.^{16,17} We refer to this screening as the Infant Car Seat Challenge (ICSC).¹⁸

Several studies have demonstrated logistical issues and inconsistencies (gestational age, length of test and oxygen saturation, respiratory rate/effort and heart rate parameters) associated with implementation of the ICSC which can be attributed to the lack of standardized guidelines.^{4,19} Furthermore, the lack of standardized guidelines for performing the ICSC has fueled debate about the significance of this test.^{20,21}

Despite the lack of standardization, the ICSC has become a routine pre-discharge screening procedure in response to the AAP's recommendation.¹⁹ Following the lead of the United States, other countries have also instituted the practice of pre-discharge ICSC.^{6,13,22} Recent estimates of compliance with the AAP guidelines for screening suggest that close to 90% of hospitals are performing the recommended pre-discharge ICSC, although the exact testing process varies.¹⁹

There are over 4 million births in the United States each year and almost 13% (over 500,000 infants) of infants are born prematurely (less than 37 weeks gestation), making them eligible for ICSC screening.²³ Approximately 27% (range 4-60%) of premature infants fail their ICSC; therefore even the lowest estimates for failed ICSC testing rates suggest that up to 20,000 infants or more fail the ICSC in the United States each year.^{6,7}

Infants who have breathing problems in a traditional car seat and fail the ICSC are subsequently screened for respiratory stability in the only available alternative for motor vehicle transport of infants, a car bed. Infants who experience oxygen desaturation in a crash-tested car bed are recommended to undergo further diagnostic evaluation for cardio-respiratory issues, while infants that demonstrate respiratory stability in a car bed are recommended to use this type of restraint for travel in motor vehicles.

DeGrazia is with the Division of Newborn Medicine, Wilkinson is with the Division of Nursing, Rhein is with the Division of Newborn Medicine and Division of Respiratory Diseases, Children's Hospital, Boston.

Table 1. Survey Questions

1. Please describe your practice.
2. Do you care for infants that were born prematurely (< than 37 weeks gestation)?
3. Are car seat screens performed at the institutions that you are affiliated with?
4. Approximately how many infants have you cared for that travel in a car bed due to prematurity and or breathing problems? (Per year/ in the last 5 years?)
5. Describe what management strategy you used in the past to transition infants from car beds to car seats?
6. Do you have any other comments that you would like to share with us about this issue?

Although a large number of infants are discharged home in car beds each year, guidelines for transitioning infants from a car bed to car seat are not available. Additionally, there have been no published studies to date that have examined follow-up care of infants who were sent home in car beds by their pediatric care providers.

Both the Newborn Intensive Care Unit and the Center for Healthy Infant Lung Development at Children's Hospital Boston receives frequent requests for guidance about transitioning infants from car beds to car seats from primary care pediatricians. This suggested a lack of available community resources for the evaluation of infants sent home in car beds. This descriptive survey study was developed to gain a better understanding of the current practices used by primary care pediatricians to transition infants from car beds to car seats, and to determine the need for an outpatient follow-up clinic to address this problem.

Methods

Sample: We conducted a cross-sectional, anonymous survey of 1,585 Massachusetts pediatric primary care physicians about their current practices for transitioning infants from car beds to car seats. Of the 1,877 pediatricians identified from the Massachusetts Board of Registration in Medicine registry, 292 (16%) were excluded because they were retired, pediatric subspecialists, or had moved out of the area.

Study Procedures: The Children's Hospital Boston Institutional Review Board approved this study. An anonymous survey instrument was designed by the researchers and mailed to the primary care pediatricians (Table 1). Surveys were mailed in February 2008; the last survey was returned in mid-June 2008.

Table 2. Number of Infants Traveling in Car Beds Requiring Management by their Pediatrician

Number of infants traveling in car beds per year: Range 0-50; Mean 4.27			Number of infants traveling in car beds in the last 5 years: Range 0-50; Mean 10.37		
N= 350			N=307		
Per Year	n	%	Last 5 Years	n	%
0	114	33	0	77	25
1-5	214	61	1-5	120	39
6-10	10	3	6-10	50	16
15	1	<1	12-25	38	12
50	1	<1	26-50	6	2
Missing	10	3	Missing	16	5

Table 3. Management Strategies of Pediatricians Who Transition Infants from Car Beds to Car Seats

Multiple Choice Answers (N=351)		
	n	%
Never an issue	124	35
Outgrows car bed	39	11
Timeframe		
• 1-2 weeks after discharge	1	<1
• 1 month of age	12	3
• 2 months of age	8	2
• after retesting in office	31	9
• after rescreening at birth or other facility	84	24
• other	52	15
Other (Free Text) Comments (N=52)		
	n	%
Transition at term, due date or 44 weeks gestation	19	37
Uses own weight criteria (i.e. 6.5 lbs, 8 lbs, 10 lbs, term weight)	8	15
Demonstrates improved head control/tone	6	12
Retest in office hospital or clinic	11	21
Parental decision	4	8
Not primary care pediatrician for the infant (filling in), so did not address this issue	4	8

No remuneration for participation was offered. Each survey was coded with a study ID number to ensure anonymity of the respondents. Completion of the questionnaire indicated the pediatrician's willingness to participate in the study. A Northeastern University graduate nursing student, supervised by the study's primary investigators, entered the data into SPSS 16.0. Data was rechecked for accuracy and data analysis was completed using descriptive statistics. Comments by the pediatricians were categorized.

Results

The response rate was 24% (N=376). Of the 376 respondents, a majority were primary care physicians in the community (84.5%, n=317), a small minority worked in a hospital-based practice setting (9.6%, n=36); the remainder were not pediatric primary care providers or did not respond to this question. Most physicians (94.9%, n=351) reported that they are involved in the care of at least some premature infants. Consistent with AAP guidelines, most physicians (92.6%, n=340) reported that ICSCs are performed at institutions with which they have affiliations. A very small number of physicians reported that they were not aware of whether car seat screening tests were performed at their affiliated institutions.

Most physicians reported that they cared for infants who travel in car beds, but management strategies for transitioning infants from car beds to car seats varied dramatically among the respondents (Tables 2&3). In addition to sharing their transition strategies, the pediatricians surveyed expressed several key sentiments (Table 4):

1. The need for evidence-based practice (n=41)
2. The need for hospital- or office-based programs for transitioning infants that are convenient for families (n=21)

Table 4. Sample of Key Sentiments by Physicians

Expressed need for evidence based recommendations and practice	<p>"This has been very unscientific to this point, it will be nice to have some data"</p> <p>"Guidelines most welcome"</p>
Expressed need for office or hospital rescreening programs	<p>"Car seat retesting is very cumbersome office procedure"</p> <p>"It has been hard to get infants rescreened at our affiliated community hospital"</p> <p>"Doing car seat tests in the office will waste valuable resources"</p>
Expressed need for more resources for primary care physicians dealing with this issue	<p>"I would like more education on what is the correct thing to do"</p> <p>"I have no clue when the best transition time is"</p>
Expressed need for more knowledge about car beds	<p>"What is a car bed?"</p> <p>"Do car beds work?"</p> <p>"I know nothing about car beds"</p>
Request that transitioning decisions be made by neonatal specialists	<p>"Stop sending home babies less than 4 lbs 8 oz; if you send home in a car bed, I'd appreciate you do the monthly follow up, not me"</p> <p>"I went to neonatologist for recommendations"</p> <p>"I guess I just assumed our neonatal follow up clinic would deal with this issue"</p>

3. The need for more resources for the primary care pediatricians dealing with this issue (n=7)
4. The request for more knowledge about car beds (n=8)
5. The need for assistance from neonatal specialists in decisions about transitions from car beds to car seats (n=6)

Discussion

Car seats provide safe motor vehicle travel for infants and toddlers; this is indisputable. When properly used, car seats have undeniably led to decreased mortality for our youngest travelers.² While car seat misuse has attracted substantial publicity over the past years,²⁴ the finding of unexpected respiratory compromise for select at-risk infants has received limited attention.

Many published studies support the AAP's guidelines recommending ICSC screening to identify respiratory compromise in at-risk infants, though lack of standardization of the ICSC has led to controversies about its validity.^{20,21} Despite these controversies, most hospitals and nurseries are compliant with the AAP recommendations.¹⁹ As a result, the ICSC has become an important part of hospital discharge. However failing the ICSC raises multiple issues for the pediatric primary care provider.

As highlighted by this survey study, no standardized guidelines for screening and follow up care of infants who fail the ICSC exist. This has led to varied management strategies for transitioning infants from car beds to car seats. Many pediatricians assume that a minimum weight or age confers protection from car seat-related respiratory compromise, but no data exists to suggest that these assumptions are accurate. These inconsistent management strategies may result in unsafe conditions for the infant motor vehicle passenger.

Standardization of ICSC combined with documentation and tracking infants who require the ICSC is essential to identify predictors of failure and the appropriate time to transition from car bed to car seat. Until these goals can be accomplished, a written plan for follow-up testing options, developed by the discharging neonatology team, may be useful to send home with the parents and include with the discharge summary sent to the pediatric primary care provider.

This study demonstrated that many physicians desire hospital- or office-based car seat challenge follow-up programs that employ clinicians with expert knowledge about the ICSC and infant motor vehicle restraints. Until an accurate assessment of risk factors for failure of ICSC can be determined, follow-up programs can provide an important service for pediatricians and families by offering an alternative, objective determination of success in repeat ICSC to guide safe transition from the car bed to the car seat. Providers who care for large populations of premature infants should explore whether establishment of a follow-up program is feasible and seek out local experts to assist with program development.

In addition, many pediatricians surveyed report that they lack knowledge about car bed restraints and their safety. Car bed manufacturers are required to meet the same safety standards as car seat manufacturers. Therefore, when used correctly, car beds provide the same protection as car seats. Special needs trained child passenger safety technicians listed on the National Highway Traffic Safety Administration web site, by state, can provide important information about car beds and can assist with proper installation of these devices.

Two primary limitations of this study were identified. First, this study included only primary care pediatricians. Family physicians, pediatric and family practice nurse practitioners, and physician assistants were not included in our study sample, but it is likely that their practice patterns would be similar to primary care pediatric physicians. Second, despite receiving over 300 responses, the response rate for this study was lower than we had hoped (24%). However, characteristics of non-responders did not vary significantly from responders, and the total number of responses enabled us to answer the main research question.

Conclusions

This study demonstrates the difficulties primary care pediatricians experience when discharging infants home in car beds following a failed ICSC. In addition, it provides important information about current practice patterns of pediatricians when they transition infants from car beds to car seats, and highlights the substantial practice variability by pediatricians who care for infants who fail the ICSC.

Pediatricians lack knowledge about the best methods for transitioning infants from car beds to car seats. In order to address these issues, continued research is needed so that evidence-based standardized national guidelines can be developed. Future research efforts should include (a) determination of the safest method and timing for transitioning infants from a car bed to a car seat; (b) identification of criteria for successfully passing the ICSC and (c) determination of long-term sequelae of a failed ICSC.

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How Old Are You? Newborn Gestational Age and Neonatal Resuscitation Practices in the Italian Debate

Emanuela Turillazzi, Vittorio Fineschi

Abstract

Background: Multidisciplinary study groups have produced documents in an attempt to support decisions regarding whether to resuscitate “at risk” newborns or not. Moreover, there has been an increasingly insistent request for juridical regulation of neonatal resuscitation practices as well as for clarification of the role of parents in decisions regarding this kind of assistance. The crux of the matter is whether strict guidelines, reference standards based on the parameter of gestational age and authority rules are necessary.

Discussion: The Italian scenario reflects the current animated debate, illustrating the difficulty intrinsic in rigid guidelines on the subject, especially when gestational age is taken as a reference parameter for the medical decision.

Summary: Concerning the decision to interrupt or not to initiate resuscitation procedures on low gestational age newborns or on newborns affected by severe and highly invalidating diseases, physicians do not need rigid rules based on inflexible gestational age and birth weight guidelines. Guidance in addressing the difficult and trying issues associated with infants born at the margins of viability with a realistic assessment of the infant’s clinical condition must be based on the infant’s best interests, with clinicians and parents entering into what has been described as a “partnership of care.”

Background

In recent decades a lively debate has developed concerning the decision to interrupt or not to initiate resuscitation procedures

on low gestational age newborns. The flourishing of rulings by multidisciplinary study groups is evidence of the importance of this debate, with neonatologists, pediatricians, obstetricians and bioethicists working together in the attempt to support decisions regarding whether to resuscitate “at risk” newborns or not.

At present, in Italy, there has been an increasingly insistent request for juridical regulation of neonatal resuscitation practices as well as for clarification of the role of parents in decisions regarding this kind of assistance. A look at the operative situation shows that adherence to neonatal resuscitation guidelines is low across Italian tertiary centers. The practice of and approach to the resuscitation of ELBW infants varies greatly between the centers surveyed, reflecting a paucity of evidence and consequent uncertainty among clinicians.

In this scenario emerged the so-called “Carta di Firenze,” compiled by a group of Italian obstetricians and pediatricians, which in addition to the need to ensure that the mother and the newborn are offered adequate assistance, aims to spare them useless, painful and ineffective therapies. The Carta di Firenze basically makes reference to the epidemiological data of the EPICure study, defining as “of uncertain vitality” infants born between 22 and 25 weeks of gestational age and classifying the therapies administered to the infant during this period as extraordinarily intensive therapies. The fundamental instructions of the chart can be summarized thus:

22 weeks’ gestational age (154-160 days’ intrauterine life).

Decisions regarding the treatment of the mother must be based on her health conditions. Cesarean section must be performed only when indicated by the mother’s clinical conditions; women requesting it for other reasons should be informed about its potential risks and discouraged. The newborn should be provided with comfort therapies except in those extremely exceptional cases in which significant vital capacities are shown.

23 weeks’ gestational age (161-167 days). Cesarean section based on fetal indication is not recommended. At birth the newborn’s vitality must be carefully assessed. Resuscitation must be performed; the decision must be shared with the parents if the newborn shows capacity to survive. When the newborn shows highly compromised clinical conditions the physician will have to take into consideration the advisability of not starting or continuing extraordinary therapies which would be out of proportion to the objective of the best interest of the patient. Obviously, this decision will also have to be shared and assessed

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with the parents. Ordinary therapies must always be provided to these infants, namely comfort assistance.

24 weeks' gestational age. Cesarean section may be exceptionally taken into consideration for fetal reasons. Intensive treatment of the newborn is more advisable than at 23 weeks, but always on the basis of favorable objective clinical criteria which suggest proceeding with extraordinary therapies, such as the presence of attempts at respiration, valid cardiac frequency, and recovery of skin color.

25 weeks' gestational age. Cesarean section may be performed for fetal reasons. Newborns must be resuscitated and subjected to intensive extraordinary therapies, except those cases presenting severely compromised clinical conditions suggesting the impossibility of survival.

An intense debate arose in response to the Carta di Firenze with the National Bioethics Committee (NBC) influentially taking sides, considering "ethically" and scientifically unacceptable the presumption of identifying a temporal threshold below which to refuse, a priori, any attempt at resuscitation. The NBC, however, recognize in the chart itself the merit of drawing attention to the problems of neonatology and of insisting on the importance of palliative therapies for extremely premature newborns and on their right to serious antalgic therapies and to a death with dignity. In the Carta di Firenze the time of intrauterine development is referred to as the most indicative parameter of maturation, that is to say of potential vitality, without taking into account the conditions which have caused such a premature birth (spontaneous interruption of pregnancy due to accidental or pathological causes; spontaneous or induced multiple pregnancy; uterine malformations; fetal malformations, etc). The chart explicitly chooses to make reference to extremely low gestational age newborns (22-25 weeks) for whom it proposes the "do not resuscitate order" as a rule of desirable behavior at 22 weeks and below, whilst allowing for departures in exceptional cases (such as the presence of spontaneous respiratory acts, efficient heartbeat, recovery of skin color). Moreover, it considers gestational weeks of 23-24 as a grey zone of uncertain vitality. The NBC, while acknowledging the exactness of the scientific premise of the extremely low survival rate at <22 weeks, admonishes that this may lead to behaviors prejudicially "not resuscitating." The critical point of the Carta di Firenze, according to experts at the NBC, is the difficulty of establishing truly reliable parameters which would provide the certainty of prognosis at birth. Therefore, the assessment at birth of vital parameters cannot have a rigorous prognostic value and cannot justify an aprioristic decision to desist from therapy. One can and must have doubts, obviously of a merely probabilistic character, about diagnosis and prognosis made in the first hours of life. Finally, it is the opinion of the NBC that the possibility of the newborn's life, once resuscitated, continuing with a handicap of major or minor severity, does not mean the treatment performed is futile. In other words, a treatment which prolongs the life of a disabled person cannot be defined as futile simply because it prolongs a life considered by some to be of low quality. On the opposite side many authors believe that the future quality of life of a newborn must be taken into account in deciding the best treatment for a very ill neonate.

Moreover, the NBC invites us to consider the modalities of treatment of extremely premature newborns in a way absolutely analogous to the assessment of any other form of treatment to

which handicapped people are subjected, regardless of their age. Finally the NBC refers to the Italian legal system. Law 194/1978, which allows the voluntary interruption of pregnancy, provides that, when there is the possibility of autonomous life of the fetus, regardless of gestational age, the physician who has performed the intervention must put into effect all the appropriate procedures to guarantee survival, in compliance with the principle of equality. Like any other person needing assistance, extremely premature newborns have full right to the adoption of all the appropriate procedures to ensure their survival. The Carta di Firenze instead seems to invert this principle for newborns between 22 and 23 weeks, who appear to deserve resuscitation practices only exceptionally, when there is evidence of significant vital capacities or of the capacity to survive. This inversion does not appear ethically acceptable to the NBC. Uncertainty about the prognosis of these newborns seems to give rise to an inversion of the general rule: not the duty to assist as a general rule anymore, except when there is evidence of the futility of the intervention given the incapacity of the newborn to live autonomously outside the mother's body, but the opposite prescription, according to which lifesaving assistance would not be due in general, but only in exceptional cases where the newborn shows significant vital capacities or evidence, at the 23rd week, of capacity to survive.

According to the chart, it seems that this requirement should be accompanied by the parents' consent. Starting from these assumptions, the NBC believes that with birth every newborn, albeit extremely premature, acquires the juridical status of a person and consequently has the full right to therapies. Therefore it is to be hoped that, in general, criteria to be adopted for resuscitation of newborns is no different from those adopted to resuscitate an infant no longer in the neonatal phase, or an adult.

The prognostic uncertainty of the time between 22 and 23 weeks of gestation cannot justify a rigid assumption of the futility of resuscitation and the impossibility of demanding the physician's duty to adopt every appropriate measure to protect the newborn's life. The physician may well abstain from this duty but only by considering each individual case and diagnosing the insufficient vitality of the newborn. The NBC believes that an extremely premature newborn should not be resuscitated when this practice objectively assumes the tones of therapeutic obstinacy, even if the prolongation of therapeutic interventions is strongly urged by the parents. Finally, a point of fundamental importance is the centrality of parents in the decision-making process regarding the therapies administered to their premature newborns. When parents disagree with the physician's assessments favorable to resuscitating the newborn it is the opinion of the NBC that the physician's opinion must prevail.

Other documents have been issued in the same period in Italy. We refer in particular to the so-called "Carta di Roma," drawn-up in February 2008 and signed by the Directors of the Obstetric and Gynaecologic Clinics and by numerous neonatologists from the four medical faculties of the Universities of Rome. This document suggests "treating extremely premature newborns as any person in a condition of risk and assisting them in an adequate way," regardless of their gestational age, thus suggesting an approach which is not based on a statistical criterion, like the rate of survival or disability, but which must be individualized. Almost contemporaneously, the Italian Superior Council of Health (March 2008) expressed their

opinion “regarding the advisability of identifying protocols for perinatal therapies in extremely low gestation ages, to define the temporal ranges and modalities of assistance most appropriate to guarantee the safeguarding of the health and dignity of the newborn and its mother, in accordance with more recent scientific evidence.” In the final recommendations we read that “taking into account that medical and resuscitative treatment cannot be confined in rigid schemes, but requires a careful and individualized assessment of clinical conditions at birth... after the assessment of their clinical conditions...the appropriate resuscitation procedures [must be] guaranteed to newborns, with the aim of revealing potential vital capacities which can predict the possibilities of survival following intensive care.” If clinical evolution were to show that the intervention is ineffective, intensive therapies turning to therapeutic obstinacy should be avoided. In any case newborns would be provided with nutrition and hydration compatible with their clinical conditions and with other compassionate therapies, always treating them with an attitude of respect, love and care. The therapies administered to newborns should always respect the natural person’s dignity, ensuring the most appropriate interventions to safeguard their potential development and the best quality of life possible. It being understood that resuscitation treatment requires immediate decisions and prompt and timely actions, the parents should be provided with understandable and exhaustive information about the newborns’ conditions and their life expectancy, offering them understanding and all possible psychological support. In the event of a conflict between the parents’ requests and the physician’s decision, a shared solution should be sought, taking into consideration the safeguarding of the fetus and newborn’s life and health.

The Italian Society of Gynaecology and Obstetrics underlined that at birth it is impossible to define a sure prognosis only on the basis of the newborn’s gestational age and weight, even taking into account the possibility of error in the assessment of gestational age and that at low gestational ages the possibilities of survival increase very quickly as days go on. Thus, besides gestational age and weight, it is necessary to consider every single case on the basis of the newborn’s vitality, of his/her reactions to tactile and environmental stimulation and of his/her development. Moreover, it is recommended as necessary to agree that medical intervention with the parents, having provided them with adequate information; neonatal resuscitation, pre-alerted and adequately shared by a multidisciplinary team (obstetrician, neonatologist and anaesthetist), offers the newborn increasingly improved resources.

Finally, in the scenario that animates the current Italian debate on these matters, the stance sustained with particular emphasis by the exponents of Catholic ethics appears strong. This assumes that the idea of the “holiness” of human life is fundamental and has expressed clear positions regarding the Carta di Firenze, emphasizing the fact that in this document the right to life gives way to its “quality.” To an increase in births of the premature infants corresponds a constant tendency to not resuscitate the most severe cases among them, despite the fact that they have the possibility to survive. Against this tendency is sustained an approach based on respecting the person and on the adequacy of the means to employ in order to avoid any form of therapeutic obstinacy which in any way can not include the assessment of the quality of the newborn’s future life. Many voices rise in the Italian panorama to underline how the abstention from neonatal resuscitation is an alarming phenomenon because it ends up

depriving the chance of someone who might have it. Without doubt, the importance attributed by a physician to religion in his or her life was also consistently associated with decision-making: being Protestant or having no religious background is consistent with a lower tendency to actively resuscitate premature neonates.

Discussion

From this scenario that reflects the current animated debate in Italy, derives the intrinsic difficulty of laying down any rigid guidelines on the subject, especially when gestational age is taken as a reference parameter for medical decisions. First, there is a fair margin of error in the estimation of gestational age, so that in dubious cases, the Carta di Firenze for example specifies the “fundamental importance of clinical evaluation of the newborn by a neonatologist, who should take into account particularly the newborn’s conditions at birth, obstetric history and response to resuscitation procedures.” Recent studies based on data of pregnancies induced with IVF programs (the only case in which dating can be absolutely sure), show that the best echographic performance in the dating of pregnancy may show an error oscillating between -10 and +7 days. The timing of the menstrual cycle is, obviously, even more inaccurate, reaching deviations of as much as 14 days. There are obvious repercussions of such a range of error on the subtle decisional distinction right in that grey zone in which even a temporal oscillation of a few days may lead to abstention from neonatal resuscitation procedures or, conversely, the initiation of resuscitation therapies. On the other hand, neonatal prognosis is conditioned by many independent predictive factors (birth weight, use of steroids before birth, multiplicity of pregnancy). It is therefore evident that the chronological criterion of gestational age alone might lead to a dangerous simplification in evaluating decisional paths, giving an excessive value to one single parameter. It is well known that the prognosis for very preterm children varies with the place of birth (level III perinatal center or not), the attitude of both obstetricians and pediatricians toward care and hence the interventions they use, gestational age, postnatal age, and later comorbidities. On the other hand, many authors still consider gestational age, although imperfect, the best parameter, indicator of the infant maturation (the means of the survival capacity) and all the existing guidelines refer to gestational age to recommend behaviors and clinical choices.

In the bioethical debate it was underlined how one of the unique features of neonatal bioethics is in its focus on guidelines that specify which extremely preterm babies should not receive resuscitation. No other area of medicine has been as focused upon such policies or as specific in delineating treatment limitations. Instead, in other areas, guidelines are broad and general, with much room for individual clinical judgment and professional discretion. What some authors find, in fact, is that policies for newborns appear very different from those for other patient populations. In fact, even in critical situations burdened by high mortality or morbidity, for example adult patients with cardiac arrest after trauma; cardiac arrest in children following severe trauma; adult patients with a primary hemorrhagic stroke), the low percentages of survival or even the prevision of long term significant and disabling sequelae certainly do not lead to abstention from the resuscitation procedures laid down in rigorous protocols or guidelines.

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Tracheal Agenesis as a Rare Cause of Difficult Intubation in a Newborn with Respiratory Distress: a case report

Raja Ahmad, Kahairi Abdullah, Lukman Mokhtar, Ahmad Fadzil

Abstract

Introduction: Tracheal agenesis is a very rare congenital airway anomaly. It may pose a great challenge to the first attending physician both in diagnosis and in establishing the airway during the first day of life.

Case presentation: We report a newborn Malay baby boy with trachea agenesis (type III by Floyd's classification) who presented with severe respiratory distress immediately after birth. Clinical diagnosis in this case was not straightforward, as it started with difficulty in intubation followed by an unsuccessful emergency tracheostomy in the neonatal intensive care unit. Urgent surgical neck exploration with endoscopic examination in the general operating theatre revealed the final diagnosis. The authors present a short description of the embryopathology and diagnostic criteria of the abnormality.

Conclusion: We hope this case presentation will be valuable in increasing the awareness of physicians about this rare cause of tracheal obstruction or difficult intubation.

Introduction

Tracheal agenesis is a rare congenital airway anomaly. There were 116 cases of tracheal agenesis reported in the literature between 1900 and (September) 2004.¹ Airway management in this abnormality poses a great challenge to otolaryngologists, anaesthetists and pediatricians. This condition is incompatible with life. At present there is no specific surgical management technique that is associated with survival of tracheal agenesis

The newborn with tracheal agenesis usually presents with immediate and severe respiratory distress, and the only way to provide ventilation is through the esophagus. Performing endotracheal intubation or tracheostomy does not normally help. Bag-mask ventilation and intubation of the esophagus may allow ventilation of the lungs. Neck exploration during the tracheostomy and endoscopic evaluation will establish the diagnosis. The ex-utero intrapartum treatment (EXIT) procedure is an excellent method developed for use in anticipation of possible airway compromises in newborn babies at birth.

Case Presentation

A 2.4 kg Malay baby boy was delivered after 37 weeks of gestation by spontaneous vaginal delivery. The pregnancy was complicated by polyhydramnios. The baby developed immediate respiratory distress at birth with an Apgar score of 1 at 1 min, 5 at 5 min, and 6 at 10 minutes of life. He was initially resuscitated with bag-mask ventilation, and subsequently transferred to the neonatal intensive care unit (NICU). Multiple oral endotracheal intubations were attempted in the NICU with no success. Bag-mask ventilation was continued and an otolaryngologist was consulted for emergency tracheostomy. Oxygen saturation was successfully maintained at above 85% with bag-mask ventilation. It was possible to pass a Ryle's tube through both nostrils.

During the surgical procedure, the trachea could not be identified. The baby was transferred to the operating theatre for neck exploration, and a complete endoscopic examination was performed to evaluate airway patency. During the neck exploration, it was noted that the larynx ended blindly at the cricoid level (Figure 1), while the trachea was absent. A laryngoscopic evaluation without muscle relaxant disclosed a cleft larynx with bilateral immobile vocal cords (Figure 2). A bronchoscope could not be passed below the vocal cords. An esophagoscopy was performed which revealed two openings at the distal portion of the esophagus, which communicated with the left and right bronchus, respectively (Figure 3).

At the end of the surgical procedure, an endotracheal tube was inserted into the esophagus and effective ventilation confirmed by visualization of normal chest expansion and good oxygen saturation. The baby also had persistent ductus arteriosus, dysplasia of the right radius and the right thumb, and an imperforated anus. A diagnosis of tracheal agenesis was made and the family members were counseled about the grim prognosis. Life support was discontinued with the agreement of the parents, and the baby was allowed to die.

Authors Ahmad and Abdullah are with the Department of Otolaryngology—Head & Neck Surgery, Faculty of Medicine; Mokhtar is with the Department of Anaesthesiology and Intensive Care, Faculty of Medicine, International Islamic University Malaysia; Fadzil is with the Department of Pediatric, Tengku Ampuan Afzan Hospital, Malaysia. Reprinted from BioMed Central, Journal of Medical Case Reports, © 2009 Ahmad et al, licensee BioMed Central Ltd. This is an open access article distributed under the terms of the Creative Commons Attribution License. The authors note: Written informed consent could not be obtained in this case since the patient was lost to follow-up. The authors believe that this case report contains a worthwhile clinical lesson which could not be made as effectively in any other way, and expect that the patient and her family would not have objected to the publication since every effort was made so that the infant remained anonymous.



Figure 1. Neck exploration revealed a normal larynx that ended in a blind pouch at the level of cricoid (black arrow). The dome-shaped cricoid occludes the lumen.



Figure 2. Laryngoscopy examination revealed a cleft larynx with immobile vocal cords bilaterally in midline position.

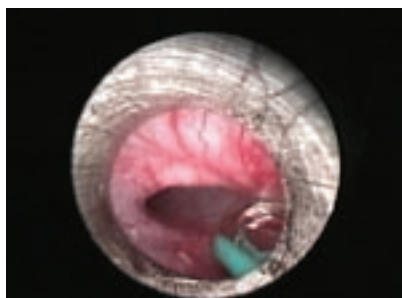


Figure 3. Esophagoscopy view showing one of the openings into the left bronchus at the distal end of the esophagus.

Discussion

At present, there is no specific surgical management that allows survival in cases of tracheal agenesis. Normally, a newborn with tracheal agenesis presents with immediate respiratory distress and an absent or very weak cry. This rare congenital anomaly might confound the attending doctor in the delivery room or operating theatre.

The embryopathology resulting in this abnormality occurs during the first eight weeks of gestation. The tracheo-pulmonary complex develops from the respiratory diverticulum at the ventral aspect of the primitive foregut. A compromised vascular supply to the developing trachea during this stage may cause tracheal agenesis or tracheal stenosis with complete tracheal ring.² According to Merei et al,³ the point of bifurcation between the developing trachea at ventral and developing esophagus at dorsal foregut remains fixed in relation to the cervical vertebra. Caudally, the respiratory diverticulum will develop into the carina and broncho-pulmonary tree. The cephalic aspect of the respiratory diverticulum will be elongated to form the trachea and the infra-glottic structure. Tracheal agenesis results when this normal elongation process fails to take place.¹ This anomaly is associated with relatively normal supra-glottic structures and pulmonary development, as seen in this case. The congenital abnormality is only limited to the region of the developing trachea. The severity of tracheal agenesis was described in detail by Floyd and colleagues and classified into three types.⁴ In Type I, a short segment of the trachea fails to elongate to fuse with the larynx. In Type II, the respiratory diverticulum fuses in midline to form the carina but tracheal elongation does not take place. And in type III, the respiratory diverticula does not

fuse in the midline, resulting in two fistula opening at the lower part of esophagus. The present case is compatible with a type III abnormality. Type II remains the most common abnormality (61%), followed by type III (23%) and type I (11%).¹

Tracheal agenesis is commonly associated with other congenital anomalies such as vertebral defects, anal atresia, tracheoesophageal fistula, esophageal atresia, cardiovascular defects, limb defects, duodenal atresia and renal defects. Tracheal agenesis can be a manifestation of several syndromes such as VATER (vertebrae, anus, trachea, esophagus, and renal), also known as VACTERL, and TARCD (total alkaloids from rhizoma corydalis decumbentis).

A high index of suspicion is required to diagnose tracheal atresia. Antepartum features that would corroborate such suspicion are the presence of polyhydramnios with multiple fetal anomalies. During birth, the baby may not cry or may have a weak cry. An acute severe respiratory distress develops and multiple attempts at intubations fail. Laryngoscopy will reveal immobile vocal cords lying in the midline position. Other findings are a cleft between the arytenoids, as well as associated congenital anomalies. Good oxygenation may be maintained with bag-mask ventilation or esophageal intubation. The diagnosis is made through neck exploration during emergency tracheostomy and an endoscopic evaluation of the larynx and esophagus. A pre-delivery procedure with three-dimensional ultrasound or fetal magnetic resonance imaging allows a complete evaluation of this upper airway abnormality. The ex-utero intrapartum treatment (EXIT) procedure can be planned based on the imaging results. EXIT procedure can reduce the risk of respiratory distress immediately after birth.⁵

Conclusion

Tracheal agenesis should be suspected in a newborn baby who presents with immediate respiratory distress, as well as extremely weak cry and failed intubation despite adequate ventilation with facemask. The establishment of airway after an insertion of endotracheal tube in the oesophagus will further enhance the index of suspicion before the definitive endoscopic evaluation.

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Can Prematurity Risk in Twin Pregnancies After In Vitro Fertilization Be Predicted? A Retrospective Study

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Abstract

Background: Assisted reproduction (ART) contributes to worldwide increases of twin pregnancies, in turn raising prematurity risks. Whether characteristics of ART cycles, resulting in twin gestations, can predict prematurity risks was the subject of this study.

Methods: One-hundred-and-six women, ages 20 to 39 years, with consecutive dichorionic-diamniotic (DC/DA) twin gestations were retrospectively investigated. All pregnancies investigated followed fresh ART cycles, with use of autologous gametes, and were delivered at a university-based high-risk, maternal-fetal medicine unit. Only premature deliveries (ie, <37.0 weeks gestational age), with viable neonate(s) of ≥ 500 grams, were considered for analysis.

Results: After 1.8 ± 1.2 ART cycles, 11.0 ± 5.4 oocytes were retrieved and 2.4 ± 0.9 embryos transferred in 106 women aged 31.6 ± 4.2 years. Indications for ART treatment were male factor in 51.9%, female infertility in 27.4% and combined infertility in 20.8%. Though maternal age significantly influenced prematurity risk ($p < 0.05$), paternal age, maternal body mass index, indications for fertility treatment, number of previous ART attempts, oocytes retrieved or embryos transferred, as well as stimulation protocols and previous ART pregnancies, were not associated with gestational duration in twin pregnancies.

Summary: Except for female age, baseline and ART cycle characteristics do not allow for prediction of prematurity risk in dichorionic twin gestations after assisted reproduction.

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Background

Since Louise Brown, the first in vitro fertilization (IVF) birth in 1978, more than three million IVF children have been born. Assisted reproduction (ART), nevertheless, has come under criticism due to the increased risk of multiple births associated with this fertility treatments. Twin pregnancies after spontaneous conception occur in Caucasians at a rate of 1:80. Assisted reproduction in Europe, in contrast, currently results in twin rates of 21.7% with wide variations across the countries. Twins (and higher order multiples), in comparison to singleton gestations, are at increased risk for prematurity-associated adverse perinatal outcome. A broader application of single embryo transfer (SET) has been suggested to reduce this rising incidence of multiple pregnancies in the course of assisted reproduction without compromising pregnancy chances.

Bechoua et al, for instance, describe comparable pregnancy chances after double embryo transfer (DET) when compared to elective single embryo transfer in a cohort of good prognosis patients. A Finnish group even report lower costs and higher cumulative live birth rates in good prognosis patients after SET and cryo-embryo transfers compared to DET. Others, however, claim that SET may after all reduce pregnancy chances. Veleva et al, for instance, differentiate between elective and compulsory SET. In their retrospective analysis, they describe considerably lower pregnancy rates in women undergoing SET of a non top quality embryo or compulsory SET in comparison to double embryo transfers or elective SETs of a top quality embryo. Roberts et al. go even further—they report a need for a 55% rate of SET to reduce twin rates to ten percent. By doing so, pregnancy rates would drop by 19%. In a recent meta-analysis, Gelbaya et al are in accordance with these data. They report a statistically significant reduction in the probability of live birth (-38%) and multiple birth (-94%) after e-SET.

The ability to prospectively identify IVF patients at increased risk towards twinning and premature delivery, would, therefore, allow for a more selective utilization of SET and therefore, possibly, more effectively contribute to the reduction of adverse perinatal outcome in IVF twins. Identifying such a subset of patients at risk, would then more than compensate for potentially impaired pregnancy chances in women who are not good prognosis candidates for SET.

While a variety of prenatal risk factors for preterm births in twin gestations have been established, conflicting data exist on the potential impact of controlled ovarian hyperstimulation

on prematurity risk and perinatal outcome. Griesinger and colleagues, for instance, fail to find an impact of controlled ovarian hyperstimulation on birth weight, while Shih et al. report lower birth weight in singletons after fresh embryo transfer when compared to frozen cryopreservation cycles. Abramov et al go even further, showing higher rates of prematurity, low birth weight, pregnancy-induced hypertension and placental abruption in pregnancies after ovarian hyperstimulation syndrome (OHSS). Aytoz concur with these observations, describing increased rates of intrauterine deaths in ART pregnancies with severe male factor infertility.

These publications point toward a potentially negative influence of IVF cycle characteristics, such as male factor infertility and good response to controlled ovarian hyperstimulation or OHSS, on pregnancy outcome and prematurity risk. Male factor infertility and OHSS are, however, considered risk factors for the occurrence of multiple gestations.

Whether other ART cycle characteristics, such as indication for fertility treatment and ovarian response to stimulation, serve as predictive for severe prematurity in twin gestations after ART was the subject of the here presented study.

Discussion

The present retrospective study involved 106 women, aged 20 to 39 years, with dichorionic-diamniotic (DC/DA) twin gestations after in vitro fertilization (IVF). All pregnancies were established with autologous oocytes/sperm in fresh IVF cycles and via the transfer of two or more embryos. To ensure IVF-related conception and a complete history of IVF-related parameters, such as the number of embryos transferred, only IVF-Fonds-covered pregnancies were included. [The IVF-Fonds provides governmental financial support of up to four IVF cycles per pregnancy in women under age 40]. To determine chorionicity, patients underwent first trimester ultrasound scans, performed by a small group of experienced, specifically and uniformly trained senior physicians. The detection of lambda signs served as proof of dichorionicity.

All women underwent prenatal care and delivery at the Department of Obstetrics and Gynecology at the Medical University Vienna, a University-based hospital unit for high-risk maternal-fetal medicine. To exclude potential prematurity-associated biases, neither monochorionic twin gestations, nor pregnancies that had undergone selective fetal reduction or pregnancies with vanishing embryos were eligible for enrollment. After 37 weeks of gestation, a number of twin pregnancies were delivered electively. To exclude this potential bias, only twin gestations that were delivered preterm (ie, gestational age <37.0 weeks) were included in the study. A comparison of IVF cycle characteristics between study patients and DC twin gestations that delivered at term (ie, ≥37 weeks; not eligible for enrollment) revealed no significant differences between the groups.

Statistical influences of maternal and paternal ages, numbers of previous IVF attempts and pregnancies, indications for fertility treatment, stimulation protocols, oocyte yields, fertilization procedure (IVF or ICSI), number of embryos fertilized/transferred, smoking status and body mass index on gestational ages were investigated. The data analyses of pregnancy- and delivery-related maternal and neonatal outcome data were based on retrospective chart reviews and computer-generated databases at the Department of Obstetrics and Gynecology at

the Medical University Vienna. Assisted reproduction technology (ART)-related data were collected by chart review and, where applicable, from of a computer-generated database at the IVF-Fonds.

Statistical analyses were performed utilizing SPSS version 10.0. Quantitative variables are summarized by their mean (standard deviation), while qualitative variables are summarized by frequency tables. Univariate and multivariate analysis were performed by (stepwise) linear regression. Pearson's Correlation was used to determine the sample size required to detect a correlation between gestational duration and ART cycle characteristics. In order to detect a correlation of 0.25 with a power of 80% and a Type I error of 5%, a sample size of 98 women was needed. Patient characteristics known to influence prematurity risk in spontaneous pregnancies (ie, age, smoking status, body mass index, parity) were investigated in univariate analysis and included in multivariate analysis if significant (i.e., $p < 0.05$). ART cycle characteristics (ie, numbers of previous IVF attempts and pregnancies, indications for fertility treatment, stimulation protocols, oocyte yields, fertilization procedure (IVF or ICSI), number of embryos fertilized/transferred) were also investigated in univariate regression analysis. While number of previous IVF-attempts, stimulation protocols, fertilization procedure (IVF or ICSI) and number of embryos transferred were only included in multi-regression analysis if significant in univariate analysis, factors previously described to be associated with prematurity risk, such as maternal age, number of previous IVF-pregnancies, indication for fertility treatment and oocyte yield, were included in multivariate regression analyses, irrespective of their statistical significance in univariate analysis. Univariate and multivariate regression analyses were then performed in the same fashion for women ≤30 years and >30 years, except for the exclusion of maternal age. A comparison of ART cycle characteristics between study patients and DC twin gestations that delivered at term (ie, ≥37 weeks; not eligible for enrollment) revealed no significant differences between the groups. P-values of <0.05 were considered statistically significant. Institutional Review Board (IRB) approval for data-linkage and retrospective data analyses was obtained from the IRB at the Medical University Vienna.

Results

Women demonstrated a mean age of 31.6 ± 4.2 years and a mean body mass index of 23.7 ± 4.34 kg/m². Men presented with a mean age of 33.9 ± 4.5 years. Indications for in vitro fertilization treatment were male factor in 51.6%, female infertility in 27.4% and combined infertility in 20.8%. Women with female infertility demonstrated with tubal infertility in 64.7%, 23.5% were patients with polycystic ovary syndrome (PCOS), 9.8% suffered from endometriosis and 2% had a history of tubal ligation. In addition to PCOS, one patient demonstrated with infertility-associated immunological factors. Due to the present distribution of fertility indications, intracytoplasmatic sperm injection (ICSI) was required in 68.9% of cases.

To achieve their dichorionic-diamniotic pregnancies, couples underwent a mean number of 1.8 ± 1.2 ART cycles. More than two ART attempts were required in 21.7% of patients. IVF attempts with concurrent twin pregnancy demonstrated a mean number of 11.0 ± 5.4 oocytes retrieved and 6.6 ± 3.5 oocytes fertilised. A mean number of 2.4 ± 0.9 embryos were transferred. No statistically significant difference was observed in the number of embryos transferred according to cycle number and previous

IVF outcome (first IVF attempts, 2.3 ± 0.7 ; previous IVF failure, 2.7 ± 1.1 ; previous IVF pregnancies, 2.4 ± 0.9 embryos). The couples' ages, their indications for fertility treatments, oocyte yields, fertilization rates and other IVF/ICSI cycle characteristics were also comparable between first ART attempts, previous ART failures and previous ART pregnancies.

Delivery occurred at a mean gestational age of 33.6 ± 2.9 weeks and resulted in 105 female and 107 male neonates. The mean birth weight for both twins was 2011.3 ± 527.9 gm (Twin A) and 1927.9 ± 549.2 gm (Twin B), respectively, with a mean discordance of 9.6 ± 13.4 percent. Mean perinatal arterial pH for both twins was 7.26 ± 0.1 (Twin A) and 7.26 ± 0.1 (Twin B). Delivery resulted in 99.1% live births for Twin A and B. Immediately post partum, 46.2% of first twins and 50.0% of second twins required neonatal intensive care at the neonatal intensive care unit (NICU) of the Department of Pediatrics at the Medical University Vienna.

When the impact of maternal and paternal age, maternal body mass index and tobacco usage, previous pregnancies and IVF attempts, stimulation (GnRH agonist or GnRH antagonist protocol), oocyte yield, fertilization rate and number of embryos transferred on gestational age were calculated in univariate analysis, only maternal age reached statistical significance ($p < 0.05$). In multi-regression analyses, including maternal age, oocyte yield and number of previous IVF-pregnancies, only maternal age demonstrated to be predictive for gestational duration.

When univariate and multivariate regression were performed according to age groups (ie, ≤ 30 years and > 30 years for female age), maternal age did not reach significance in univariate analysis and was, therefore, not included in multi-regression. When multi-regression analyses, including number of oocytes retrieved, number of previous IVF-pregnancies and indication for fertility treatment, were then performed for those age groups (ie, ≤ 30 years and > 30 years), none of those characteristics included proved statistically associated with prematurity risk in twin gestations.

Many improvements in perinatal and neonatal medicine have led to increased survival rates in premature neonates. Their neurodevelopmental outcomes, particularly of those with very low birth weight and/or very early gestational age, are, however, still concerning and often followed by a variety of lifelong disabilities. Assisted reproduction represents such a risk factor for prematurity in both, singletons and multiple pregnancies.

The uniformly agreed to goal of ART is the safest possible delivery of greatly desired offspring. SET, in its current form, focuses, however, on prevention of twin pregnancies, rather than on reduction of risks, associated with twin pregnancies. By doing so, single embryo transfer is mainly performed in good prognosis, ie young, IVF patients. Obstetrical data, however, demonstrate an exponentially increasing prematurity risk with advancing maternal age. If we could prospectively identify a subset of women at increased risks after twin conception, following ART, those patients would especially benefit from single embryo transfer. Even women with impaired pregnancy chances after SET, such as older patients and those with diminished ovarian function, would derive compensatory benefits to lower pregnancy chances by a possible reduction in prematurity risk.

Such risk-focused, rather than age-based, treatment policies have already been applied in prenatal diagnosis. While amniocentesis used to be a routine procedure in women above age 35, this approach was abandoned in favor of an individual risk calculation. This modification in approach increased diagnostic accuracy for fetal chromosomal abnormalities, but also saved a considerable number of prospective mothers of advanced age from the amniocentesis-related risks of a preterm premature rupture of membranes or miscarriage.

Our, unfortunately, negative findings in this study, may have a variety of explanations: (i) All women that were eligible for enrolment underwent close prenatal surveillance and delivery at a university-based high-risk, maternal-fetal medicine unit. Whatever ART-associated risk divergence may have been present, excellent prenatal care could have evened it out. (ii) This is further supported by IVF twins presenting with significantly lower perinatal mortality than spontaneously conceived twins. (iii) Women in this study also do not necessarily reflect a typical IVF population. Our study patients represented IVF-patients under age 40 with normal body mass index; they were either themselves fertile (male factor) or suffered from tubal infertility, and had only a limited numbers of previous IVF attempts.

This stands in contrast to other indications for fertility treatments, which are statistically highly associated with impaired pregnancy outcome, such as autoimmunity, uterine abnormalities or a history of repeated pregnancy loss. Moreover, our study population involved only fresh, autologous IVF cycles, reported associated with higher implantation potential and, consequently, higher risk for twin gestations, than cycles in which thawed embryos are used.

Summary

Standard ART cycle characteristics did not serve as predictive factors for severity of prematurity risk in our cohort of prematurely delivered dichorionic twin gestations after assisted reproduction. Since our study population consisted of a limited number of good prognosis patients, our results do not preclude that further research in more typical average IVF populations, at larger risk for prematurity, may after all, be able to define such risk factors. Further research is, therefore, warranted to develop a risk-focused approach to prevent, or at least reduce, adverse perinatal outcomes in twin pregnancies after ART.

Delivery of a Baby With Severe Combined Immunodeficiency at 31 Weeks Gestation Following an Extreme Preterm Prelabor Spontaneous Rupture of the Membranes

Sally J. Watkinson, Christopher C.T. Lee and Christopher V. Steer

Abstract

Introduction: If left untreated, severe combined immunodeficiency can lead to an acute susceptibility to infection. The intrauterine environment is sterile until the amniotic membranes rupture. The vaginal flora then ascends into the genital tract, thus increasing the risk of chorioamnionitis. An extremely premature and prolonged membrane rupture is associated with a dismal prognosis for an immunocompetent preterm fetus. There are no case reports to date that detail the outcome of an immunocompromised preterm baby following prolonged rupture of membranes.

Case presentation: We present the case of a 32-year-old Indian woman who delivered a 31-week gestational baby who had a severe combined immunodeficiency following premature prelabor prolonged rupture of the membranes at the 14th week of gestation.

Conclusions: Extreme preterm prelabor spontaneous rupture of membranes in an underlying condition of severe combined immunodeficiency does not necessarily lead to an unfavourable outcome.

Introduction

Severe combined immunodeficiency (SCID) is a combined cellular and humoral immunodeficiency resulting from a lack of functional T and B lymphocytes. In some cases, SCID is also combined with a deficiency of natural killer cells. This condition is extremely rare, affecting approximately only 1 in 100,000 live births. SCID is usually diagnosed after the 3rd month of gestation, during the onset of one or more serious infections such as recurrent or persistent infections despite conventional treatment, infections with opportunistic organisms such as *Pneumocystis*, and a failure to thrive. SCID is usually X-linked and can be diagnosed through genetic testing.

Babies in general are more susceptible to infections as compared to adults. This susceptibility is even more pronounced in preterm babies and those who have been potentially exposed to maternal flora following a breach in the amniotic membrane due to a

prolonged prelabor spontaneous rupture of the membranes (SROM). Pathogens gaining entry into the baby's system through the mucosa of the respiratory and gastrointestinal tracts are poorly localized. The preterm baby can thus easily become systemically unwell.

The sterile environment of the intrauterine amniotic sac limits the need for learned immune responses to specific antigens prior to birth. Upon birth, a normal baby has some immunoglobulins (Ig), with IgG as predominant because it is small enough to cross the placenta and be transferred from the mother. The level of IgG at birth is similar to that of the mother and provides passive immunity to mainly viral infections in the first few months of life.

Meanwhile, IgM and IgA do not cross the placental barrier but are produced by the normal fetus in utero from approximately 28 weeks of gestation. Levels of IgM at term are 20% of those present in adults, unless intrauterine infection develops and the fetus mounts an immune response to further elevate IgM levels. IgM provides a degree of protection to the neonate from enteric infections. While IgA levels are very low at birth, its production increases rapidly following delivery to reach adult values within two months. IgA protects against infection of the respiratory tract, the gastrointestinal tract and the eyes. The levels of both IgM and IgG at birth are lower in preterm than in term neonates.¹

There is no effect to the immune function of a female carrier of X-linked SCID. Thus, the fetus of such a woman generally has normal IgG levels in utero and at birth.

The prognosis for a normal pregnancy where the membranes rupture at 14 weeks is dismal due primarily to the risk of miscarriage secondary to infection. Even with appropriate treatment, approximately 50% of pregnancies are delivered each subsequent week following preterm SROM. Therefore, when the membranes rupture before 20 weeks of gestation the probability of reaching viability is <5%.²

A second reason for dismal prognosis is the risk of neonatal death secondary to pulmonary hypoplasia when pregnancy becomes viable. The chance of pulmonary hypoplasia is lessened if the fluid re-accumulates before 24 weeks of gestation. One study using a multivariate analysis suggested that the likelihood for neonate survival increases by 2.7 (95% CI 1.45 to 4.65) for every 5-mm increase in the depth of amniotic fluid during the follow-up from rupture up to the 24th week of gestation.³ Despite dismal prognosis, however, expectant management for preterm

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SROM at 14 weeks may be appropriate if the mother is well-informed of the risks for the neonate.

The conclusions of the ORACLE trials^{4,5} indicated that a course of oral erythromycin is the antibiotic of choice in the treatment of expectantly managed preterm SROM. This is because erythromycin is associated with a reduction in neonatal infection, slight prolongation of pregnancy with no increase in the likelihood of developing necrotising enterocolitis. Based on evidence from a study of preterm SROM conducted by the Maternal-Fetal Medicine Units of the National Institute of Child Health and Human Development, 7 days of antibiotics should be prescribed because longer courses have not been shown to be more effective and may actually promote antibiotic resistance.⁶

Maternal protein C deficiency is associated with an increased risk of poor pregnancy outcome including miscarriage, stillbirth and preterm delivery.

Case presentation

A 32-year-old Indian woman presented to our gynecology clinic with secondary subfertility. Routine screening found her to be positive for protein C deficiency. In 1999, the woman had previously delivered a son by elective cesarean section following a diagnosis of transverse lie at 39 weeks of gestation. The baby was subsequently diagnosed with SCID and died at 8 months due to this condition. A specialist genetic center indicated that this was an X-linked condition and the woman is a carrier of the mutation c.283G>A (W90X) in exon 2 of her IL2R γ C gene.

She was advised of a 50%-risk of any subsequent male offspring being affected by SCID and was thus offered preimplantation genetic diagnosis. However she subsequently conceived the index pregnancy spontaneously. She was commenced on aspirin, low molecular weight heparin (LMWH) and progesterone pessaries as soon as the pregnancy was confirmed by ultrasound at 6 weeks. Results of her nuchal translucency screening and first trimester anomaly scan were normal.

The woman presented with leakage of liquor at 14⁺⁵ weeks gestation. Spontaneous rupture of the membranes was confirmed clinically and through an ultrasonography. She was commenced on antibiotic prophylaxis with oral erythromycin and her medication of progesterone pessaries was discontinued. Serial specialist ultrasonography at 16, 18, 20 and 22 weeks confirmed a normally grown male fetus with no obvious structural defects. The placenta was posterior and low, and the severe oligohydramnios was persistent. In view of the oligohydramnios due to extreme preterm SROM, an invasive genetic testing was not felt to be appropriate. The risk of this male fetus being affected with SCID therefore remained at 50%. Because of the extremely poor prognosis for the baby, the couple was offered a termination of pregnancy but they declined. The pregnancy continued, septic markers remained negative, and she remained on continuous oral erythromycin, aspirin and LMWH.

At 24⁺⁴ weeks gestation, the woman self-referred with a history of unprovoked vaginal bleeding. She was given dexamethasone and was transferred to a center with Level 1 neonatal facilities. She stayed at the center until her transfer back to her local hospital at 28⁺⁵. Erythromycin was discontinued at 25⁺⁶ weeks gestation, maternal clinical and laboratory signs of infection remained absent, and ultrasound scan at 28 weeks showed normal growth of the fetus and an amniotic fluid index of 8.4cm.

Upon readmission, she was recommenced on erythromycin and discharged from the hospital. She was advised instead to visit the antenatal day unit twice a week for regular assessments.

The woman remained stable until she presented again at 31⁺⁴ weeks with lower abdominal pain and recurrent slight vaginal bleeding. It was found that her cervix was dilating and that the baby's presentation was breech. An emergency cesarean section was thus performed under spinal anesthetic. She made a good postoperative recovery and was discharged after 5 days.

The baby boy was born with Apgar scores of 61 and 105 minutes and weighed 1830g (50th percentile). He required some initial resuscitation but was transferred to our special care baby unit with spontaneous respiratory effort in facial oxygen. His white cell count and C reactive protein level were within the normal range (6.3 and <5, respectively) while his blood cultures were negative at birth. The baby was treated with oral nystatin, intravenous benzyl penicillin and gentamicin. Isolation and barrier nursing was also advised.

X-linked SCID (consistent with the mother's carrier type) was confirmed by genetics testing during the neonatal period. He received intravenous therapy of 1g immunoglobulin on Day 3 and was transferred to a specialist paediatric centre on Day 6. The baby underwent an unconditioned CD34-selected mismatched family donor bone marrow transplant (from his father) on Day 46. He continued to receive monthly 2g intravenous immunoglobulin and regular outpatient specialist paediatric immunology reviews. As of this writing, the baby is thriving and still breastfeeding at 1 year of life. He is also showing a good response to his treatment.

Discussion

Fetuses affected by SCID have significantly lower levels of IgM and IgA at birth compared to gestationally age-matched immunocompetent babies. It is thus likely that SCID affected babies will be unable to mount any IgA and IgG immune response in utero in response to ascending infection as a result of SROM. As immunocompetent premature babies produce such a poor response in utero, the question is whether SCID affected babies in a condition of preterm SROM have a higher risk of in utero infection than those who do not have SCID.

Conclusions

This baby was born in good condition and is currently thriving and living a normal life. This unusual case of adverse prognostic factors, including an underlying genetic condition, prelabor preterm SROM and maternal protein C deficiency, demonstrates that the outcome for babies with this condition is not necessarily hopeless.

This baby was born without evidence of in utero infection despite the expected poor prognosis of having premature prelabor SROM from 14+ weeks. Had an infection occurred, the prognosis would have been certainly poor. However, this would not be as a result of the SCID condition, and the baby would have had normal levels of IgG at birth because of transplacental transfer from his mother. Because normal babies have a poor IgA and IgM immune response in utero at 31 weeks, it is very unlikely that the inability to mount any IgA or IgM response because of the SCID condition had any effect on the outcome in this case. It is therefore reasonable to conclude that the in utero management of fetuses with known or suspected primary

congenital immunodeficiency including SCID should not be managed any differently than preterm prelabor SROM in normal pregnancies.

The counselling of parents regarding the possible prognosis following a diagnosis of SROM at extreme prematurity should not be altered if the baby is known or suspected to be affected with SCID. With regard to the antenatal use of antibiotics in babies with SCID, the standard dose and duration of treatment of erythromycin 250mg 4 times daily for 7 days should be prescribed. Measures to discourage ascending infection such as the avoidance of vaginal examinations and sexual intercourse should be advised regardless of an underlying diagnosis of SCID.

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Gestational Age...continued from page 18

Summary

The crux of the matter is whether strict guidelines, reference standards based on the gestational age parameter, and authority rules are necessary. We believe that the right answer to this question is "no." In a decisional sphere burdened by such limited prognostic certainties, an individual approach is infinitely more acceptable than a statistical approach: any decision ought to be based upon the individual circumstances of each newborn rather than on references to guidelines, especially if these are based on gestational age. Physicians do not need rigid rules based on inflexible gestational age and birthweight guidelines but guidance to address the difficult and trying issues associated with infants born at the margins of viability with a realistic assessment of the infant's clinical condition. We firmly think that the principles regarding treatment of low or very low gestational age newborns should be the same as those followed for other patients; there is no need for specific policy statements. Generally, the purposes of guidelines have been to improve knowledge regarding neonatal outcomes, to provide consistency in periviability counseling, and to promote informed, supportive, responsible choices. Flexible guidelines are well accepted and can be used by all neonatologists, obstetricians, and nurses who provide care to pregnant women and infants at extremely early gestational ages, but resuscitation decisions for extremely preterm infants should be approached in the same way as for other patients. They should be individualized with objective and accurate individual prognostication, taking into account all the relevant clinical characteristics.

In conclusion, the physician has the responsibility to make an assessment of the infant's condition at birth and of the baby's response to the clinical intervention provided, and then to render a judgment on whether or not to initiate resuscitation. All subsequent decision are to be jointly made on the basis of the infant's best interests, with clinicians and parents entering into what has been described as a "partnership of care."

Does Hypoglycemia Following a Glucose Challenge Test Identify a High Risk Pregnancy?

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Abstract

Objective: An association between maternal hypoglycemia during pregnancy with fetal growth restriction and overall perinatal mortality has been reported. In a retrospective pilot study we found that hypoglycemia was linked with a greater number of special care/neonatal intensive care unit admissions and approached significance in the number of women who developed preeclampsia. That study was limited by its retrospective design, a narrow patient population and the inability to perform multivariate analysis because of the limitations in the data points collected. This study was undertaken to compare the perinatal outcome in pregnancies with hypoglycemia following a glucose challenge test (GCT) to pregnancies with a normal GCT.

Methods: Obstetric patients (not pre-gestational diabetics or gestational diabetes before 24 weeks) were eligible. Women with a 1 hour glucose ≤ 88 mg/dL (4.8 mmol/L) following a 50-gram oral GCT were matched with the next patient with a 1 hour glucose of 89-139 mg/dL. Pregnancy outcomes were evaluated.

Results: Over 22 months, 436 hypoglycemic patients and 434 normal subjects were identified. Hypoglycemia was increased in women < 25 ($p=0.003$) and with pre-existing medical conditions ($p<0.001$). Hypoglycemia was decreased if pre-pregnancy BMI ≥ 30 ($p=0.008$). Preeclampsia/eclampsia was more common in hypoglycemic women. (OR=3.13, 95% CI 1.51-6.51, $p=0.002$) but not other intrapartum and perinatal outcomes.

Conclusion: Hypoglycemic patients are younger, have reduced pre-pregnancy weight, lower BMIs, and are more likely to develop preeclampsia than normoglycemic women.

An association between maternal hypoglycemia during pregnancy with fetal growth restriction and overall perinatal mortality was reported in 1979.¹ Since that time other investigators have used a variety of screening methods

including both oral and intravenous glucose loading to identify hypoglycemia in pregnancy and relate this finding to pregnancy outcomes.²⁻⁹ One of the most recent studies used the 100-gram oral glucose tolerance test and found a significantly lower incidence of both gestational diabetes and neonatal birth weights.¹⁰ The best test to categorize pregnancies with hypoglycemia is uncertain, but the most widely available and frequently used test in most pregnancies would be the most effective screening test if correlated with pregnancy outcomes.

Previously, we undertook a retrospective pilot study to evaluate hypoglycemia following a 1 hour 50 g glucose challenge test (GCT) to determine if any association could be identified between hypoglycemia and an adverse pregnancy outcome.¹¹ That investigation found that hypoglycemia was linked with a greater number of special care/neonatal intensive care unit admissions and approached significance in the number of women who developed preeclampsia. The study was limited by its retrospective design, a narrow patient population and the inability to perform multivariate analysis because of the limitations in the data points collected. The purpose of this prospective study was to compare the perinatal outcomes of pregnancies with hypoglycemia following a second trimester oral GCT to pregnancies with a normal GCT.

Methods

All pregnant women attending the Obstetric Clinics of the Naval Medical Center Portsmouth, VA, and the Obstetric Clinics at the University of Mississippi Medical Center, Jackson, MS, who had not been diagnosed with pre-gestational diabetes or who had not been screened and identified as having diabetes prior to 24 weeks gestation were eligible for this study. Prospectively, these women routinely had a 1-hour 50-gram oral GCT as a screen for gestational diabetes performed at 24-28 weeks of gestational age. Hypoglycemia on the one hour oral GCT was defined for this investigation as it has been defined by others as a glucose level ≤ 88 mg/dL (4.8 mmol/L).^{1,11} All women with a one hour glucose of ≤ 88 mg/dL (4.8 mmol/L) (hypoglycemic group) were identified and normoglycemic controls the next patient with a one hour glucose following the glucose challenge test of 89-139 mg/dL (4.9-7.7 mmol/L). Women with 1-hour glucose of ≥ 140 mg/dL (7.7 mmol/L) following the 50-gram oral GCT would undergo a 3-hour glucose tolerance test with a 100-gram glucose load. A data sheet was completed and antenatal, intrapartum, and neonatal outcomes of the hypoglycemic group were compared with the normal group. Each patient was assigned a study number, and there were no patient identifiers on the data collection sheet.

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Table 1: Maternal Characteristics

	Groups		
	Hypoglycemic (n = 436)	Controls (n = 434)	P-value
Maternal age ⁽¹⁾	24.7 ± 5.4	25.9 ± 5.5	0.001
Race			
Caucasian	179 (41%)	204 (47%)	
African American	214 (49%)	187 (43%)	
Other	38 (9%)	38 (9%)	0.179
Primigravidas	149 (34%)	149 (34%)	0.941
Nulliparous	190 (44%)	200 (46%)	0.421
Height (in) ⁽²⁾	65 (63 – 67)	64 (63 – 67)	0.931
Pre-pregnancy weight (lb) ⁽²⁾	150 (129 – 180)	157 (135 – 190)	0.003
Pre-pregnancy BMI ⁽²⁾	24.7 (21.8 – 29.5)	26.5 (22.9 – 32.3)	0.002
BMI			
<19	22 (7%)	15 (5%)	
19–30	232 (69%)	209 (63%)	
≥30	82 (24%)	107 (32%)	0.056
Pregnancy weight gain (lb) ⁽²⁾	33.0 (22.0–43.0)	32.0 (20.0 – 43.5)	0.393
History of spontaneous preterm birth	30 (7%)	23 (5%)	0.330
Any pre-existing medical conditions	54 (12%)	23 (5%)	<0.001
Chronic hypertension ⁽³⁾	42 (78%)	19 (83%)	0.442
Other conditions ^(3,4)	12 (22%)	4 (17%)	0.764
Any prenatal complications	79 (18%)	44 (10%)	<0.001
Preeclampsia/eclampsia	35 (8%)	10 (2%)	<0.001
Preterm Labor	19 (4%)	15 (4%)	0.600
Oligohydramnios	11 (3%)	1 (0.2%)	0.006
Unexplained elevation of MSFAP	4 (1%)	7 (2%)	0.384
Other prenatal complications ⁽⁵⁾	19 (4%)	10 (2%)	0.130
Antepartum hospitalization	53 (12%)	26 (6%)	0.002
Duration of stay (days) ^(2,3)	3 (3 – 7)	4 (3 – 4)	0.284

(1) mean ± standard deviation shown; (2) medians and interquartile ranges (1st – 3rd quartile) are shown; (3) percentages for subsets of patients with condition present are shown; (4) other conditions include gestational diabetes (n = 3), sickle cell disease (n = 3), multiple sclerosis (n = 3), PPROM (n = 1), lupus APA syndrome (n = 1), protein C deficiency (n = 1), renal disease (n = 1), seizure disorder (n = 1), ulcerative colitis (n = 1) and FV Leiden (n = 1); (5) GHTN (n = 7), PPROM (n = 4), gestational diabetes (n = 4), placenta praevia (n = 3), pyelonephritis (n = 3), 2 vessel cord (n = 3), DVT (n = 1), PE (n = 1), cholestasis (n = 1), cerclage (n = 1) and gastroschisis (n = 1).

This study was approved by the Chief, Navy Bureau of Medicine and Surgery, Washington, DC, through the local Clinical Investigation Program (Naval Medical Center–Portsmouth). Approval was also obtained through the Investigation Review Board at the University of Mississippi Medical Center, Jackson, MS. The sharing of information between the institutions was approved through the Navy Clinical and Cooperative Research and Development Agreement between the Naval Medical Center–Portsmouth and the University of Mississippi Medical Center.

We recruited 436 women with hypoglycemia and 434 women with normal blood glucose on the GCT to detect odds ratios ≥2.50 with 80% power for association between hypoglycemia and adverse pregnancy outcomes such as IUGR and preeclampsia when using multivariable logistic regression analysis.

Data were summarized using means and standard deviations or medians and interquartile ranges (IQR) for continuous data, depending on data normality. Frequency distributions were used to summarize categorical data. Univariate comparisons between women with hypoglycemia and normal glycemic controls

were based on Mann-Whitney tests for continuous outcomes and Chi-square tests for categorical outcomes. Supplementary analyses utilized logistic regression modeling to investigate factors simultaneously associated with each pregnancy outcome considered such as preeclampsia, preterm delivery and IUGR. Odds ratios (OR) and 95% confidence intervals (CI) were used to summarize the covariate effects on the outcomes of interest. Relative risks have been obtained using the group prevalence of each outcome considered and OR estimates from the logistic regression analysis.¹² Statistical analysis was conducted using SPSS statistical software (SPSS, Inc., Version 11.0, Chicago, Illinois). P-values <0.05 were considered statistically significant.

Results

Eight hundred seventy women were recruited (436 and 434 with GCT ≤88 mg/dL (4.8 mmol) and GCT range 89–139 mg/dL (4.9–7.7 mmol) respectively) into the study between September 2004 and May 2006. Groups were similar in race, gravidity, parity and pregnancy weight gain (Table 1). Compared to women with normal GCT, hypoglycemic women were younger (24.7 vs. 25.9 years of age, $p < 0.001$), had lower pre-pregnancy weight (150 lb

Table 2: Intrapartum Outcomes

	Groups		P-value
	Hypoglycemic (n = 436)	Controls (n = 434)	
Cervical ripening	36 (8%)	38 (9%)	0.792
Induction of labor	129 (30%)	87 (20%)	<0.001
Delivery mode			
Spontaneous vaginal	314 (72%)	295 (68%)	0.364
Assisted vaginal	15 (3%)	14 (3%)	
Cesarean section	107 (25%)	125 (29%)	
Reason for cesarean section ⁽¹⁾			
Fetal distress	26 (24%)	23 (18%)	0.572
Failure to progress	24 (22%)	36 (29%)	
Repeat cesarean section	35 (32%)	46 (37%)	
Breech/transverse lie	11 (10%)	9 (7%)	
Other	11 (10%)	11 (9%)	
Reason for assisted vaginal delivery ⁽¹⁾			
Fetal distress	12 (80%)	10 (71%)	0.682
Other	3 (20%)	4 (29%)	
Fetal distress in labor	38 (9%)	33 (8%)	0.621
Cesarean delivery for fetal distress	26 (6%)	23 (5%)	0.769
Gestational age at delivery (med, min-max)	39 (23–41.5)	39 (28.6–41.6)	0.689
Gestational age distribution			
<37	67 (15%)	43 (10%)	0.024
37–40	242 (56%)	273 (63%)	
>40	127 (29%)	118 (27%)	
Gestational age at delivery <37	67 (15%)	43 (10%)	0.015

(1) Percentages for subsets of patients with condition present are shown.

vs. 157 lb, $p=0.003$) and lower pre-pregnancy BMI (27.0 vs. 26.5, $p=0.002$). Higher rates of pre-existing medical conditions (12% vs. 5%, $p<0.001$), prenatal complications (18% vs. 10%, $p<0.001$) and antepartum hospitalizations (12% vs. 6%, $p=0.002$) were found in hypoglycemic women (Table 1). Higher proportion of hypoglycemic women required induction of labor (30% vs. 20%, $p<0.001$) for a variety of reasons including rupture of the membranes without labor, non-reassuring antenatal testing, oligohydramnios, preeclampsia, intrauterine growth restriction, and preterm premature rupture of the membranes, Table 2). However, no differences in frequency of cervical ripening ($p=0.792$), modes of delivery ($p=0.364$) and reasons for cesarean delivery ($p=0.572$) were found. Although the median gestational ages at delivery did not significantly differ between the groups, preterm deliveries were more frequent in the hypoglycemic group ($p=0.019$).

Neonatal outcomes are shown in Table 3. Neonates born to women with hypoglycemia were of lower birth weight (median 3240 gm vs median 3313 gm, $p=0.008$). Similarly, the distribution of birth weight was different ($p=0.002$), with a higher proportion of neonates with a birth weight less than 2500 gm in women with hypoglycemia. These differences, however, were not reflected in the incidence of IUGR which was similar in both groups (12% and 9% for hypoglycemic and control women, respectively,

$p=0.277$). Incidence of pH<7.1 and Apgar scores <7 at 5 minutes were similar between the groups ($p=0.130$ and $p=0.374$). No differences between admission to the NICU were found ($p=0.149$).

Three perinatal deaths occurred in the study, 2 in the hypoglycemic group and 1 in control women. The perinatal death in the control group was a neonate delivered at 36 weeks after prolonged rupture of the membranes that died in the NICU of sepsis. The first of the 2 deaths in the hypoglycemia group occurred following a 24 week delivery with the infant subsequently dying from complications of prematurity. The second death was a stillborn at 36 weeks secondary to a cord accident.

Multivariable analysis of predictors of hypoglycemia in pregnancy indicated age, pre-existing medical conditions and pre-pregnancy BMI categories (<19, 19–30, ≥ 30) as simultaneously significant risk factors. Age under 25 years (OR=1.61, 95% CI 1.18–2.22, $p=0.003$) and presence of pre-existing medical conditions (OR=4.02, 95% CI 2.22–7.27, $p<0.001$) increased the likelihood of hypoglycemia. Compared to women with pre-pregnancy BMI between 19 and 30, women with BMI ≥ 30 had a lower risk of hypoglycemia (OR=0.60, 95% CI 0.42–0.87, $p=0.008$), while women with BMI <19 had similar likelihood of

Table 3: Neonatal Outcomes

	Group		P-value
	Hypoglycemic (n = 436)	Controls (n = 434)	
Birth weight (gm) (med, Q1-Q3)	3240 (2928–3550)	3313 (2980–3690)	0.008
Birth weight distribution			
<2500	43 (10%)	22 (5%)	
2500–4000	370 (85%)	370 (85%)	
>4000	23 (5%)	42 (10%)	0.002
IUGR	36 (12%)	29 (9%)	0.277
Umbilical artery pH<7.1	14 (3%)	7 (2%)	0.130
5 minutes Apgar score <7	4 (1%)	1 (2%)	0.374
Admission to NICU	36 (8%)	25 (6%)	0.149
Admission reasons ⁽²⁾			
Prematurity	6 (17%)	4 (16%)	
RDS/TTN	26 (72%)	12 (48%)	
Other ⁽²⁾	4 (11%)	9 (36%)	0.054

(1) Medians and interquartile ranges (1st quartile – 3rd quartile) are shown; ⁽²⁾ percentages for subsets of patients with condition present are shown.

hypoglycemia in pregnancy (OR=1.20, 95% CI 0.60-2.37, p=0.608). 1.60-4.81, p<0.001), and gestational age at delivery (p<0.001).

Evaluation of effects of hypoglycemia on pregnancy outcomes in multivariable logistic regression analyses indicated that, compared to women with 1 hour glucose between 89 and 139 mg/dL, women with hypoglycemia were more likely to develop preeclampsia/eclampsia (OR=3.13, 95% CI 1.51-6.51, p=0.002). Another simultaneous predictor of preeclampsia/eclampsia was presence of pre-existing hypertension (OR=7.29, 95% CI 3.61-14.75, p<0.001), while presence of other pre-existing medical conditions did not alter the risk (OR=1.36, 95% CI 0.17-10.81, p=0.769). Sensitivity of hypoglycemia in pregnancy for prediction of preeclampsia had 77.8% sensitivity, 51.4% specificity, 8% positive predictive power and 97.7% negative predictive power.

Hypoglycemia in pregnancy was not related to an indicated induction of labor (OR=1.75, 95% CI 0.83-1.66, p=0.361), once other risk factors were simultaneously considered including age under 25 (OR=2.18, 95% CI 1.53-3.11, p<0.001), presence of preeclampsia/eclampsia (OR=11.63, 95% CI 5.23-25.85, p<0.001), presence of pre-existing medical conditions (OR=2.77, 95% CI

Hypoglycemia in pregnancy appeared not to be related to the likelihood of preterm delivery (OR=1.61, 95% CI 0.92-2.82, p=0.093) when the adjustments for preeclampsia/eclampsia (OR=9.05, 95% CI 4.28-19.16, p<0.001) and preterm labor (OR=39.34, 95% CI 16.31-94.87, p<0.001) were made. No effects of hypoglycemia in pregnancy were associated with fetal distress in labor, cesarean delivery, IUGR, low pH, low Apgar scores at 5 minutes, or admissions to a NICU after adjusting for other risk factors (Table 4). No multivariable assessment of oligohydramnios was performed due to the small number of cases (n=12).

Discussion

Nearly universal screening of pregnant women is undertaken with a one hour GCT between 24 and 28 weeks of gestation except in women who are diabetic prior to the pregnancy or who have risk factors for diabetes and are screened at an earlier gestational age. Elevated blood glucoses on the one hour screen lead to further evaluation with a three hour glucose

Table 4: Adjusted odds ratios (OR) and the equivalent relative risks (RR) with their 95% confidence intervals (CI) that reflect the effects of hypoglycemia on select perinatal outcomes

Outcome	OR	95% CI	RR	95% CI	p-value
Preeclampsia	3.13	1.51–6.51	2.98	1.49–5.78	0.002
Induction of labor	1.75	0.83–1.66	1.52	0.86–1.47	0.361
Preterm delivery	1.61	0.92–2.82	1.52	0.93–2.39	0.093
IUGR	1.24	0.73–2.10	1.21	0.75–1.91	0.425
Macrosomia	0.49	0.28–0.85	0.51	0.30–0.86	0.011
Umbilical artery pH<7.1	2.00	0.76–5.26	1.97	0.77–4.93	0.159
5 min Apgar score <7	1.97	0.20–19.91	1.97	0.20–19.19	0.564
NICU admission	1.27	0.62–2.05	1.12	0.63–1.94	0.965

Preeclampsia: presence of pre-existing hypertension, presence of other medical history, maternal age.

Induction of labor: any pre-existing medical history, gestational age, preeclampsia, maternal age.

Preterm delivery: preeclampsia, antenatal hospitalizations, threatened preterm labor, labor induction.

IUGR: gestational age at delivery, pre-existing medical conditions present.

Macrosomia: maternal age, preeclampsia and gestational age at delivery.

Umbilical artery pH<7.1: gestational age at delivery and mode of delivery.

5 min Apgar < 7: gestational age at delivery and induction of labor.

NICU admission for any reason: gestational age at delivery, fetal distress in labor, cesarean delivery, IUGR, macrosomia.

tolerance test. To date, an association of low blood glucoses to adverse pregnancy outcome remains uncertain. The literature that is present on hypoglycemia and pregnancy outcomes is old and a variety of glucose challenge tests have been used to define hypoglycemia in pregnancy. This study evaluated the predictability of a laboratory result that is widely available on pregnant women and its possible association with an unfavorable pregnancy outcome.

Conditions were identified by multivariate analysis in which the participants would be more likely to have hypoglycemia on the GCT. They include a maternal age <25 years and the presence of preexisting medical conditions (chronic hypertension, chronic renal disease, thrombophilia, lupus, and seizure disorders). However, no difference in the risk of hypoglycemia was observed between women with a pre-pregnancy BMI of 19-30 vs. those with a BMI <19, but as expected, women with a BMI >30 had a significantly reduced incidence of hypoglycemia. This finding is consistent with the observation that women with a pre-pregnancy BMI >30 are more likely to develop gestational diabetes and would therefore more likely have a blood glucose >140 mg/dL (7.7 mmol/L) on GCT.¹³

The pregnancy effects of maternal hypoglycemia were then evaluated. Multivariate analysis revealed that women with hypoglycemia were more likely to develop preeclampsia/eclampsia. This result has not been reported before to our knowledge although in our pilot study the incidence of preeclampsia approached significance in those women with hypoglycemia following the GCT. We do acknowledge that the strength of this association is currently uncertain, as we have no precise information on the time that the glucose challenge test was undertaken and when the preeclampsia was diagnosed in each of the patients. The relationship was assumed based on an implicit close relationship in gestational age of the diagnosis of the hypoglycemia and the development of the preeclampsia. We can speculate that since preeclampsia is present early in pregnancy and alters placental implantation with a failure of vascular remodeling, the maternal/placental function is affected. Rather than an increasing resistance to insulin with the production of HPL by the placenta and other diabetogenic hormones and factors, as is observed in a normal pregnancy, these would be reduced resulting in less insulin resistance and a greater tendency for hypoglycemia following a glucose challenge test. The vasospasm of preeclampsia could also play some unknown role in altering the maternal response to a glucose load. Further investigations are needed to clarify if a relationship does exist between glucose loading and women who subsequently develop preeclampsia, and if so, the pathophysiology of that maternal response.

Indicated inductions of labor for a variety of reasons including rupture of membranes without labor, non-reassuring antenatal testing, oligohydramnios, preeclampsia, intrauterine growth restriction and preterm premature rupture of the membranes were more commonly identified in the hypoglycemic group compared with women with a normal glucose following the GCT. As expected, this would suggest that women develop a variety of problems in the latter part of pregnancy that would result in an indicated induction. Hypoglycemia was also associated with a significant reduction in fetal macrosomia. This is not an unexpected finding as the hyperglycemia of gestational diabetes is linked with a greater risk of fetal macrosomia.

Also notable was the lack of association between hypoglycemia and preterm labor and/or delivery. The women with hypoglycemia were not at increased risk compared to women with a normal GCT for fetal distress in labor, cesarean delivery, low Apgar scores, low cord pH or admission to a neonatal intensive care unit. The lack of correlation between hypoglycemia and intrauterine growth retardation is different from the finding of most other investigators,^{1-7,9} except for 2 of the more recent studies which also evaluated hypoglycemia after the 50 gram oral glucose challenge test.^{8,11} The older studies used a variety of techniques to identify the hypoglycemic pregnancies including higher both oral and IV glucose loading than that achieved with the oral 50-gram load as in our screening protocol. One possible explanation is that pregnancies identified as hypoglycemic by higher pre-test loads identify pregnancies in which the fetuses become growth restricted, but that the lower load with the 50-gram dose does not categorize the same women as hypoglycemic. Different patient demographics and different definitions of intrauterine growth restriction may also have contributed to the lack of significance with hypoglycemia in this study. Intrauterine growth restriction, low Apgar scores, umbilical artery pH and NICU admissions were all seen more frequently in the hypoglycemic group compared to the control group but the findings were not statistically significantly different. Even though this was a large prospective study with 870 women the possibility of a sample size error must be taken into consideration and that with larger number of participants a significant difference may be observed.

One of the weaknesses of this study may be that the glucose load to identify the pregnancies which are linked to an adverse pregnancy outcome may be too low. However, this must be balanced with the availability and ease of administration of the test. Use of the 50-gram load is very appealing to most pregnant women undergoing this test in the second trimester of pregnancy. The strength of this study is the large number of prospectively matched women which was evaluated and the multiple analyses undertaken to accurately determine which women are more likely to become hypoglycemic and the outcomes of those pregnancies.

Future investigations are needed to clearly describe the associations between women who are hypoglycemic following a glucose challenge, women with one abnormal value on a glucose tolerance test, and women with 2 abnormal values (gestational diabetics) with adverse pregnancy outcomes. The use of additional diagnostic tests such as the homeostasis model assessment (HOMA) with both insulin resistance (HOMA-IR) and beta cell function (HOMA-BETA) may well prove to be beneficial in further understanding of the links between maternal glucose and their effects on pregnancies. The observed association between hypoglycemia and oligohydramnios and the known link between hyperglycemia and hydramnios in addition to the witnessed relationship between oligohydramnios and intrauterine growth restriction and hydramnios with macrosomia provide a very fruitful area for further investigations to assist in the understanding of the role of maternal glucose and these connections.

Conclusion

Women with hypoglycemia on GCT are younger and more likely to have a pre-existing medical condition prior to pregnancy. They may be more likely to develop preeclampsia during pregnancy but not intrauterine growth restriction.

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Metabolic Bone Disease in the Preterm Newborn: An Update On Nutritional Issues

Valentina Bozzetti, Paolo Tagliabue

Abstract

Osteopenia, a condition characterized by a reduction in bone mineral content, is a common disease of preterm babies between the tenth and sixteenth week of life. Prematurely born infants are deprived of the intrauterine supply of minerals affecting bone mineralization. The etiology is multifactorial: inadequate nutrients intake (calcium, phosphorus and vitamin D), a prolonged period of total parenteral nutrition, immobilization and the intake of some drugs. The diagnosis of metabolic bone disease is done by biochemical analysis: low serum levels of phosphorus and high levels of alkaline phosphatase are suggestive of metabolic bone disease. The disease can remain clinically silent or presents with symptoms and signs of rickets depending on the severity of bone demineralization.

An early nutritional intervention can reduce both the prevalence and the severity of osteopenia. This article reviews the pathophysiology of fetal and neonatal bone metabolism, focuses on the nutrient requirements of premature babies and on the ways to early detect and treat osteopenia.

Background

The continuous advances in intensive care of preterm newborns have led to a progressive decline of mortality in institutions where facilities and expertise for respiratory resuscitation and respiratory distress syndrome are available. Infant mortality dropped among all races between 1980 and 2000. The survival rate depends on the gestational age of the newborn; actually the survival rates for very low birth weight (VLBW) are the following: for those weighing 501-750 g is 56% and for the ones above 750 is 88%.¹ However, the success in the survival achieved through an aggressive intensive care is not always paralleled by a subsequent fully healthy development of the newborn.

Among the common conditions of morbidity due to prematurity, (cerebral impairment, bronchopulmonary dysplasia, growth failure, retinopathy, etc) a growing interest is focusing now on the metabolic bone disease of the prematurity (MBD), also called osteopenia of prematurity. This condition is characterized by a

reduction in bone mineral content (osteopenia), with or without rachitic changes, and is caused by several nutritional and biomechanical factors.

An inadequate supply of nutrients (vitamin D, calcium and phosphorus), a prolonged period of total parenteral nutrition, immobilization and the intake of some drugs are the main factors involved in the pathogenesis of osteopenia.² The MBD usually occurs between tenth and sixteenth week of life, but it may remain silent until severe demineralization (a reduction of BMD of 20-40%) occurs. The clinical picture is various, ranging from a totally silent condition to a clinical picture of overt rickets, with multiple fractures and other alterations, when the demineralization is severe. The purpose of this review is to focus on the recent advances in the understanding of the bone tissue metabolism and on the nutritional approach to prevent and to treat the MBD.

Magnitude of the Problem: The prevalence of MBD varies depending on gestational age, birthweight and kind of alimentation. It occurs in up to 55% of babies born with weight under 1000 g³ and 23% of infants weighing <1500 g at birth⁴ and it is especially frequent in babies under 28 weeks of gestation. The prevalence is 40% in premature infants who are breastfed, in contrast to 16% of those fed with a formula designed for preterm infants and supplemented with calcium and phosphorus.^{5,6} Preterm infants with a complicated medical course and delayed nutrition are also at high risk for MBD. Actually in western countries there is a trend of decrease of gestational age and birthweight, so the frequency of the MBD is expected to further increase.

Homeostasis of Calcium Phosphorus: The homeostasis of calcium, phosphorus and magnesium is fundamental for structural matrix of the bone. Calcium and phosphate represent the major inorganic constituents of bone. The highest amount of calcium (99%) and of phosphorus (80%) of the whole body is in the bone as microcrystalline apatite.

Only 1% of the total body calcium is within the extracellular fluids and soft tissues. About the 50% of total serum calcium is in the ionized form and represents the biologically active part. A further 8-10% is bounded to organic and inorganic acid and the remaining percentage of calcium is protein-bound (80% to albumin, 20% to globulin).

The formation of the apatite takes place if calcium and

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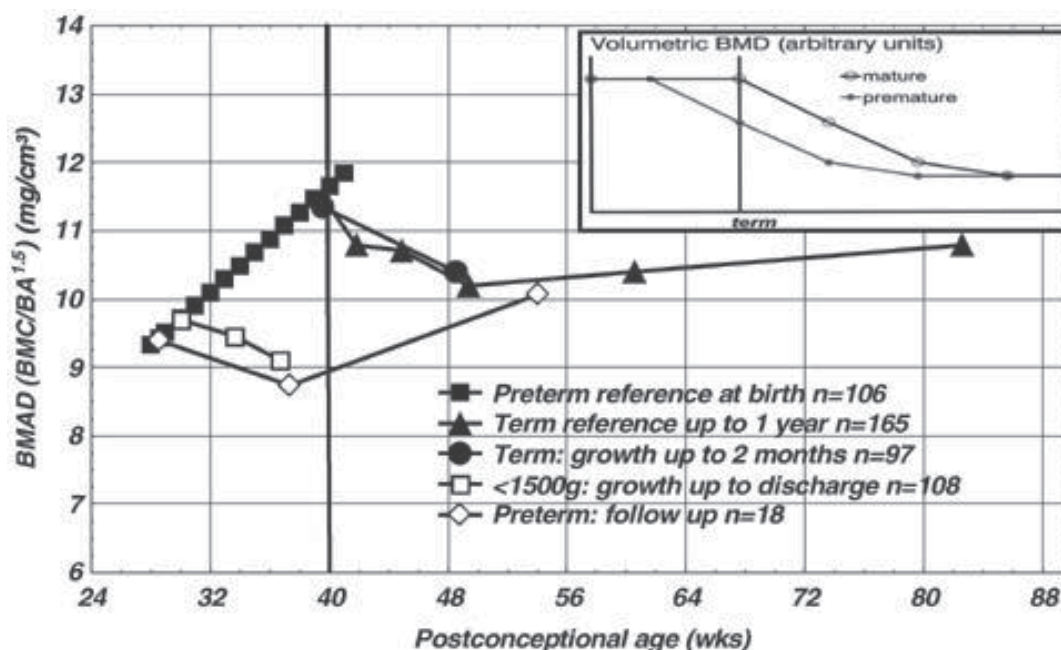


Figure 1
Physiological evolution of DEXA apparent bone mineral density during the last trimester of gestation (filled squares) and during the first year of life in healthy term infants (upper triangles) compared to that observed in preterm infants (open squares and lower triangles). (With permission from Ref [12]).

phosphorus are simultaneously available in optimal proportions. Also magnesium is part of the bone matrix and the 60% of total body magnesium is in the bone. Calcium and phosphorus homeostasis is a function of hormones, vitamin D and dietary intake, and depends on the intestinal absorption, skeletal accretion and reabsorption, and urinary excretion.⁷ Parathyroid hormone (PTH) is synthesized and secreted from the parathyroid glands in response to a reduction of serum level of ionised calcium. PTH regulates mineral metabolism and skeletal homeostasis through its action on target cells in bone and kidneys. It stimulates the reabsorption of calcium and excretion of phosphorus in the kidney and bone reabsorption of calcium. PTH also is able to activate the synthesis of calcitriol via stimulation of renal 25 (OH) D3-1-alpha-hydroxylase activities. In its active form, 1, 25(OH) 2 vitamin D, it stimulates the renal reabsorption of calcium and phosphorus. The synthesis of calcitriol is inhibited by elevated serum levels of calcium and phosphorus. The combined actions of PTH and calcitriol maintain the adequate concentration of calcium in the extracellular fluids. Kidneys contribute to maintain homeostasis of calcium; urinary calcium is one third derived from diet and the remaining from body stores, mostly bone. Diuretics, such as furosemide, increase renal calcium excretion.

Prenatal Bone Physiology: The amounts of minerals required for a correct accretion of the skeleton are widely different depending on the age of the babies. The period of greater skeletal development is during the intrauterine life and specifically during the last trimester. The bone volume increases significantly with gestational age and the high net bone formation activity is mainly due to modelling, with a rapidly increasing trabecular thickness (the trabecular thickening rate being approximately 240 times faster in the fetus than in the children). The mineralization process is determined by synthesis of the organic bone matrix by osteoblasts (osteoid) onto which calcium and phosphate salts are deposited. This process increases exponentially between 24 and 37 weeks of gestation, reaching the 80% of mineral accretion in the third trimester.⁸

During gestation the developing fetus receives supplies of energy, protein and mineral for adequate growth (1.2 cm/week) and bone development. At term the newborn skeleton has a high physical density (expressed as bone mass divided by bone volume). The fetal accretion of calcium and phosphate during the last three months of gestation is about 20 g and 10 g respectively, which represents accretion rates of 100-120 mg/kg/day for calcium and 50-65 mg/kg/day for phosphate.⁹

A very important role in skeletal accretion of the fetus is played by the placenta. In fact the transfer of calcium from the mother to the foetus through the placenta occurs via an active transport done by the calcium pump in the basal membrane.¹⁰ There is a 1:4 maternal to fetal calcium gradient.¹¹ Moreover, the placenta is able to convert vitamin D to 1,25-dihydrocholecalciferol which is fundamental for transferring phosphate to the fetus.¹²

The fetus is maintained hypercalcemic in a high calcitonin and estrogen environment which promotes the modelling/remodelling ratio in favor of modeling and thus increasing the endocortical bone.¹³ As a result, infants born prematurely will be deprived of the intrauterine supply of calcium and phosphorus affecting bone mineralization.

It is well known that a chronic damage to the placenta may alter the phosphate transport; this explains why babies with intrauterine growth restriction may be osteopenic. Demineralization is also observed in infants born from mother with chorioamnionitis and placental infection.¹⁴ Maternal dietary intake of calcium is a factor implied in fetal bone accretion. A supplement of calcium (2 g from before 22 weeks of gestation) to women with a low dietary calcium intake resulted in higher bone mineral content (BMC) of the total body in infants born at term.¹⁵

Post-natal Bone Physiology: After birth the physical density of term newborns bones decreases by 30% in the first 6 months of life.¹³ This is mostly due to an enlargement of the marrow cavity size, which occurs faster than the increase in the cross-sectional

Table 1: Minerals and vitamin D recommended intakes in growing preterm infants.

Requirements	ESPGAN [32] 1987	LSRO [31] 2002	Atkinson [33] 2005	Rigo [34] 2007
Calcium (mg/kg/day)	70–140	150–220	120–200	100–160
Phosphorus (mg/kg/day)	50–90	100–130	60–140	60–90
Vitamin D (I.U./day) (I.U./kg/day)	800–1600	90–225	200–1000 150–400	800–1000

area of the bone cortex.¹⁶ In term infants these postnatal changes are not accompanied by an increase in bone fragility and occur because bone is exposed to different conditions before and after birth.

First, there are important changes of hormonal environment: the reduction of maternal estrogens¹⁷ and a postnatal increase of PTH level mainly due to a reduction of the calcium supply by the placenta.¹⁸

As the serum calcium levels falls in the first day of life, PTH secretion is stimulated. During this transition the response of the parathyroid gland to falling levels of ionized calcium is blunted, as emphasized in a recent review article.¹⁹ This finally results in a physiological nadir in neonatal serum calcium levels within the first 48 hours of life. Of note, PTH level is still within the normal range for term babies or adult, but represents a decrease from foetal levels.

Many factors affect calcium absorption, including the maternal vitamin D status, solubility and bioavailability of calcium salts, quality and quantity of calcium, amount and type of lipids and, obviously, gut function.

Calcium absorption from the intestine occurs both passively and through a vitamin-D dependent active transport mechanism. In a newly born preterm the low mineral content of human milk associated with a poorly efficient absorption of the developing gut determine a net reduction of calcium and phosphorus supply. Absorption of phosphorus takes place in the jejunum and depends on the dietary intake. The phosphorus supply regulates calcium absorption and retention: the higher is the phosphorus content of the diet, the higher is the calcium retention. However, an excessive amount of one decreases the absorption of the other. Moreover, while in utero, the fetus experiments with mechanical stimulation by kicking against the uterine wall, this kind of training is missing during the extrauterine life, since preterm babies usually stay in the incubator.^{20,21} Inactivity due to immobilization stimulates bone reabsorption by osteoclasts and urinary calcium excretion. Furthermore, the reduced muscle activity prevents the addition of new bone tissue.²² *Conditio sine qua non* for the physical activity to be beneficial is that an adequate mineral intake is guaranteed.²³

Figure 1 shows that during the third trimester of gestation, bone mineral apparent density (BMAD) increases at a faster rate in utero (term infants) than ex utero (preterm infants) according to gestational age. BMAD is an estimation of volumetric BMD (g/cm³) calculated as bone mineral content/bone area (BMC/BA). The figure also shows that there is a sharp reduction in BMAD in neonatal age followed by a stabilization that lasts all

the first year of life (“black triangles”). A similar event occurs in preterm babies: from birth to the term, mineral retention sharply diminishes compared with the fetal life, while the skeletal growth remains high. This leads to a reduction of bone density (“white squares”). A catch up mineralization occurs after discharge of VLBWs so BMC spontaneously improves (“white rhombs”). Among the other pathogenic factors are problems related to inadequate supply of calcium to babies, which require parenteral nutrition and interference of several drugs, and may contribute to determine preterm osteopenia with an increasing risk of bones fractures. The drugs mostly implied in pathogenesis of MBD include steroids, methylxanthines and diuretics. They stimulate osteoclasts activation, decrease calcium absorption, reduce osteoblasts proliferation and increase calcium renal excretion and hence increase the risk of poor bone mineralization.^{24–26}

Neonatal Mineral Requirements: The requirements of calcium and phosphorus are based on demands for matching intrauterine bone mineral accretion rates. Supplying calcium and phosphorus in parenteral nutrition is a challenge because of limited solubility of these two minerals. Calcium and phosphorus solubility in nutrition admixtures depends on temperature, type and concentration of aminoacid, glucose concentration, pH, type and concentration of calcium salts, and presence of lipid and so on.

In parenteral nutrition calcium is administered as inorganic salt and phosphorus may be administered as inorganic sodium and potassium phosphate or sodium-glucose phosphate or glycerolphosphate, which are quite soluble in water. The addition of cystein to lower pH of the parenteral admixtures improves the solubility of calcium and phosphorus. For all such reasons it is not possible to supply these minerals according to the physiologic requirements of the preterm to reach an adequate bone mineralization.

In the transition period, most VLBW neonates receive full or partial parenteral nutrition with the goal of maintaining normal levels of calcium and phosphorus. Hypocalcemia, in fact, is a common event during the first days of life because of the sharp decrease of the calcium supply by the placenta and the delayed release of PTH due to the immature response of the parathyroid glands.

Parenteral administration of 50–75 mg of calcium/kg/day can prevent early neonatal hypocalcaemia in preterm infants. Through the parenteral administration of calcium and phosphorus (40–70 mg/kg/day and of 25–45 mg/kg/day respectively) it is possible to achieve 60–70% of intrauterine mineralization.²⁷ The best calcium to phosphorus ratio for bone mineralization is 1.7:1.^{28–30} In preterm babies receiving parenteral

nutrition only limited amounts of vitamin D are required since calcium is given by vein and there is no need of calcitriol to facilitate the intestinal uptake. Moreover only the parent compound needs to be administered since the preterm infant is able to hydroxylate the inactive form to the active one since the 24th week of gestation. It is now generally accepted the daily recommended dose of vitamin D is 400 U.I./day.¹⁸

For the transitional period, when infants are weaned from parenteral nutrition to enteral, the aim is to maintain an adequate serum level of calcium and phosphorus. However the serum level of calcium is not a good marker of adequacy of calcium intake since the level is maintained stable at the expense of the bone. Therefore the clinician should be aware that a normal serum level of both calcium and phosphorus are not a guarantee for an adequate whole body accretion as in intrauterine life.

The enteral administration of calcium is fraught with many problems as regards the calcium bioavailability. Vomiting, large gastric aspirates, constipation and abdominal distension are quite common in preterm babies and the gut absorption capacity is impaired due to the immaturity of the gastrointestinal mucosa. Calcium absorption depends on vitamin D status, solubility of calcium salts, quality and quantity of lipid intake. Moreover, in preterm babies, vitamin D demands are influenced by body contents at birth which depends on the duration of gestation and maternal vitamin status. Current estimates of requirements for calcium, phosphorus and vitamin D in growing premature infants vary among international sources of recommendations (Table 1).³¹⁻³⁴

The human milk content is inadequate for preterm requirements since the content of calcium and phosphorus in preterm human milk is 31 mg/100 kcal and 20 mg/100 kcal¹⁸ while the Life Science Research Office³¹ suggests, for premature formulas, a dose approximately 4-6 times higher (123 to 185 mg Ca/100 kcal and 80 to 110 mg P/100 kcal). Even when VLBW infants are fed at high feeding volumes (180-200 mL/Kg), assuming calcium and phosphorus absorption of 70% and 80% respectively, this would provide only one-third of the in utero level of absorbed calcium and phosphorus.⁶ Formula milk is richer in calcium and phosphorus than human milk, but bioavailability is quite different. In formula-fed infants, calcium absorption is usually less than with human milk, ranging from 35 to 60% of the intake. Hence the human milk intake has to be promoted, but a fortification with mineral and protein fortifier is necessary to achieve adequate nutrient intake.

With the current human milk fortifiers, containing highly soluble calcium glycerolphosphate, calcium retention reaches a level of 90 mg/kg/day (88% of the overall intake). However the new human milk fortifiers available on the market still do not allow intakes of calcium comparable with the values achieved during the last trimester of gestation (100-120 mg/kg/day) which are considered the target mineral accretion for preterm infants. Nevertheless, the use of multinutrient fortification of human milk for premature infants is currently recommended. A Cochrane systematic review and metaanalysis of human milk fortifiers, which however included studies on children who were not extremely preterm (the class at major risk) stated that the effects on bone mineralization were not conclusive.³⁵

Finally, it must be noted that high calcium supplementation of milk is not well tolerated; it is associated with high faecal

calcium, prolonged gastrointestinal transit time and impaired fat absorption. All these effects are potential risk factors for developing necrotizing enterocolitis (see table 1).

Clinical Features and Diagnosis: MBD remains silent until a severe demineralization occurs. The most evident clinical findings of osteopenia are deformity of the skull (diastasis of the suture, enlargement of the sagittal fontanelle and frontal bosses, craniotabe), thickening of the chondrocostal junctions and of the wrists, rib and long bones fractures. Softening and/or fractures of the ribs can cause pulmonary changes and respiratory distress, typically between 5 and 11 weeks of age.³⁶

Diagnosis of osteopenia is mainly done by serum analysis. Biochemically osteopenia is characterized by low serum levels of phosphorus and by an increase in serum levels of alkaline phosphatase that can reach values 5 times higher than the upper reference range used for adults.³⁷ It is useful dosing the isoenzymes of alkaline phosphatase since this enzyme is synthesised also by the liver and by the gut. Backstrom and colleagues suggested that serum alkaline phosphatase levels higher than 900 U.I./l associated with a serum phosphate level lower than 1.8 mmol/l have a diagnostic sensitivity of 100% and specificity of 70%.³⁸ However, the opinions in the literature about the reliability of alkaline phosphatase to predict the status of bone mineralization are still conflicting.^{39,40}

Serum level of calcium is usually within the normal range due to effects of PTH on the bone. Low concentrations of calcium and phosphorus in the urine suggest an inadequate intake. This is mainly due by an increase of the tubular reabsorption of phosphate because of the low dietary intake and by an increase of PTH level that stimulates the reabsorption of calcium. Markers of nutritional status should be assessed at baseline, and then weekly during the initial phase; once the newborn is stable, assessment must be done at the starting of total enteral nutrition and successively every 2-3 weeks. If MBD is diagnosed and nutritional supplementation is started, a periodic assessment of laboratory data is necessary to evaluate the response to treatment also when babies are discharged from hospital. The key clinical goal is to maintain normocalcemia and normophosphatemia and to avoid an excessive calciuria.

Once levels of ALP, calcium and phosphorus normalize, serum analysis can be performed monthly up to 6 months of age and then every 3 months. X-rays examination may show fractures, thin bones and other alterations as reduction of thickness of the cortical, enlargement of the epiphysis, irregular border between growth cartilage and bony metaphysis.⁴¹ Dual energy X-ray absorbitometry (DEXA) is able to determine the bone mass content of neonates and can predict the risk of fractures^{39,42} since it is sensitive in detecting small changes in BMC and BMD. Its use is now validated in neonates both term and preterm ones. DEXA reflects most accurately the state of bone mineralization in preterm infants⁴³ but the examination involves radiations for the baby and the device is not portable. Quantitative ultrasound is simpler than DEXA and is non-invasive; it can be used bedside without moving the baby. Reference values are now available for infants. Quantitative ultrasound gives information about structure of the bone and about bone density.⁴⁴

Osteopenia has a good prognosis since the disease is self-resolving, provided that calcium, phosphates and vitamin D are appropriately administered to the babies. The need for high

calcium and phosphorus intakes in preterm infants after hospital discharge is still controversial. Few data are available about the optimal length, quantity and methods of providing supplemental minerals for preterm infants who are in stable growth. There are studies that show increased bone mineral mass in infants who receive formulas containing more minerals than the traditional ones for up to 9 months.^{45,46} It has been shown, with studies assessing bone mineralization with quantitative ultrasound and DEXA, that preterm infants show a catch-up mineralization for the first year of life. There is no difference in late childhood of bone mineralization between term and ex-preterm infants⁴⁷ even though the biochemical evidence of metabolic bone disease during the neonatal period may have a long-term stunting effect which continues up to 12 years later. A recent study published on *Journal of Perinatology*⁴⁸ stated that children who were born prematurely with birth weights less than 1.5 kg tend to be significantly smaller for age and have lower lumbar spinal bone mineral content and density compared with children born at term gestation. The long duration of this complication provides further rationale for implementing any practice that can prevent this condition.⁴⁹

In the case of BMD of prematurity nutrition is both therapy and prevention. An adequate intake of minerals and of vitamin D, with breast milk fortifier or formula with a content of minerals suitable for preterm infant's requirements, are necessary for a correct bone mineralization. A regular physical stimulation, when the preterm infant is clinically stable and is receiving adequate doses of calcium, phosphate and vitamin D, should also be included in the standard preventive approach.

Conclusion

An adequate nutritional intake of calcium, phosphorus and vitamin D and passive physical exercise may prevent abnormal bone-remodelling activity during first weeks of life and may optimize growth potential of preterm infants. It is important to recognize the biochemical signs of osteopenia in an early stage in order to be able to implement dietary intake and reduce the risk of bones fractures. The determination of alkaline phosphatase and of phosphoremia seems to be useful in assessing the risk of metabolic bone disease and serum analysis need to be performed periodically in order to assess response to nutritional treatment. Through DEXA and quantitative ultrasound it is also possible to determine the state of bone mineralization and therefore to plan a nutritional intervention.

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Prenatal Exposure to Tetrachloroethylene-Contaminated Drinking Water and the Risk of Congenital Anomalies: A Retrospective Cohort Study

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Prior animal and human studies of prenatal exposure to solvents including tetrachloroethylene (PCE) have shown increases in the risk of certain congenital anomalies among exposed offspring. This retrospective cohort study examined whether PCE contamination of public drinking water supplies in Massachusetts influenced the occurrence of congenital anomalies among children whose mothers were exposed around the time of conception. The study included 1,658 children whose mothers were exposed to PCE-contaminated drinking water and a comparable group of 2,999 children of unexposed mothers. Mothers completed a self-administered questionnaire to gather information on all of their prior births, including the presence of anomalies, residential histories and confounding variables. PCE exposure was estimated using EPANET water distribution system modeling software that incorporated a fate and transport model. Children whose mothers had high exposure levels around the time of conception had an increased risk of congenital anomalies. The adjusted odds ratio of all anomalies combined among children with prenatal exposure in the uppermost quartile was 1.5. No meaningful increases in the risk were seen for lower exposure levels. Increases were also observed in the risk of neural tube defects and oral clefts among offspring with any prenatal exposure. The results of this study suggest that the risk of certain congenital anomalies is increased among the offspring of women who were exposed to PCE-contaminated drinking water around the time of conception. Because these results are limited by the small number of children with congenital anomalies that were based on maternal reports, a follow-up investigation should be conducted with a larger number of affected children who are identified by independent records.

In 1980 New England government officials discovered that PCE (perchloroethylene, tetrachloroethylene) was leaching into public drinking water supplies from the inner vinyl lining (VL) of

asbestos cement (AC) water distribution pipes. The vinyl liner had been introduced in the late 1960s to solve taste and odor problems in some sections of the distribution system. The liner had been painted onto the inner surface of the pipe in a slurry of vinyl toluene resin (Piccotex) and PCE. After a 48 hour drying period, the pipes were shipped to the towns for installation. Because PCE is a volatile solvent, the manufacturer assumed that most would evaporate by the time the pipes were installed. However, more than a decade elapsed before officials discovered that high levels of PCE remained in the liner and were slowly discharging into the public drinking water supplies.

An investigation revealed that approximately 660 miles of VL/AC pipes were installed in Massachusetts. A sizeable portion had been installed in the Cape Cod region. Because the lined pipes had been used to replace existing pipes and to extend the water system, the pattern of contamination was quite irregular. Adjacent streets and even adjacent houses had different supply pipes, leading to a "vast natural experiment" reminiscent of John Snow's cholera investigation in 1854 London.

PCE levels in residential areas in the Cape Cod town of Falmouth ranged from undetectable to 80 µg/L in water pipes along main streets with high water flow and from 1,600 to 7,750 µg/L in water pipes along dead end streets with low water flow. Currently, US EPA drinking water regulations set PCE's maximum contaminant level at 5 µg/L. The main exposure routes for PCE-contaminated drinking water are ingestion, as well as inhalation, and dermal exposure during showering and bathing. During this time period, concentrations of other measured drinking water contaminants were low. Because it was too costly to replace the VL/AC pipes, officials instituted a flushing and bleeding program in the most problematic areas to reduce levels below 40 µg/L, the suggested action guide in 1980.

While health concerns regarding PCE have been based mainly on its carcinogenicity, animal experiments also suggest an adverse effect of prenatal exposure to PCE, the closely related solvent trichloroethylene (TCE), and their metabolite trichloroacetic acid (TCA) on the risk of congenital anomalies. In particular, an increased prevalence of several malformations, including cardiovascular, musculoskeletal, central nervous system and ocular anomalies, have been observed among chicks and rats over a wide range of prenatal exposure levels. Several epidemiological studies have also found associations between prenatal exposure to organic solvents and the risk of congenital anomalies. A meta-analysis of studies on maternal

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occupational exposure to solvents found a statistically significant 60% increased risk of major malformations. While studies among female dry cleaners exposed to PCE have found no increased risk of congenital anomalies, small sample sizes limited their statistical power. Studies of women exposed to contaminated drinking water have reported increases in the risk of cardiac and central nervous system anomalies, as well as oral clefts. We undertook a population-based retrospective cohort study to examine the influence of maternal exposure to PCE contaminated drinking water on a variety of pregnancy and developmental outcomes, including low birth weight, prematurity and learning disabilities. The current report focuses on the risk of congenital anomalies, using the reproductive histories reported by mothers in the study.

Women were eligible for the study if they gave birth to a child during 1969-1983 while they were living in a Cape Cod town with some VL/AC water distribution pipes. The extent of VL/AC pipes in these towns ranged from one mile to 50 miles. Two groups of women were selected: mothers who were exposed to PCE-contaminated drinking water and mothers who were unexposed when the child was born. The initial "exposed" group included 1,492 mothers who gave birth to 1,862 singletons and 24 sets of twins. A comparison group of mothers initially designated as unexposed was randomly selected from the remaining resident women who gave birth during this period. The initial "unexposed" group included 1,704 mothers who gave birth to 1,853 singletons and 37 sets of twins or triplets.

Follow-up and enrollment of mothers occurred during 2002-2003.

We conducted analyses comparing birth certificate data on birth weight, gestational duration, and demographic characteristics among children of participants and non-participants. Following receipt of a completed questionnaire, we requested permission to review the prenatal and delivery records of the last-born child from each participating mother. The reproductive histories and related information in these medical records were compared to that reported by mothers in the self-administered questionnaires. We also compared reproductive history data reported in the questionnaires with that on the birth certificates.

All maternal reports of congenital anomalies were reviewed. Anomalies were categorized into major and minor malformations and organ system groups; and, if the numbers were sufficient, into specific diagnostic categories. Anomaly groups included central nervous, cardiovascular, respiratory, gastrointestinal, genitourinary tract, and musculoskeletal systems; eye; ear, face and neck; chromosomal; and other and unspecified anomalies. Children with neural tube defects, oral clefts and hypospadias were also examined separately.

All residential addresses on Cape Cod reported on the questionnaires were geocoded to a latitude and longitude, and where possible, specific address.

We assigned an initial exposure designation to each child after visually inspecting maps of the pipe distribution network in the immediate vicinity of the mother's address when the child was born. To determine the final exposure designation for all index and non-index births, we used a leaching and transport model. Using maps of subject residences and a town's distribution system, we created a schematic depicting the water source locations, pipe characteristics and points along the pipe where

water consumption occurs. We estimated the average monthly PCE exposure during the prenatal period of each birth by dividing the annual mass of PCE that entered an exposed residence during the year of the last menstrual period (LMP) by twelve. The first trimester was completed during the same year as the LMP for 85% of study pregnancies. We estimated PCE exposure levels only for children whose mothers had complete geocoded residential histories.

A total of 4,657 children were included in the final analysis. The analysis compared the occurrence of congenital anomalies among children with and without prenatal exposure. We examined all congenital anomalies combined, all major congenital anomalies combined, organ system groups, and specific diagnostic categories. Children with more than one anomaly diagnosis could contribute to more than one organ system or diagnostic group. The odds ratio was used to estimate the strength of the association between PCE exposure and the occurrence of an anomaly. Odds ratios were calculated only if there were at least three exposed cases. Ninety-five percent confidence intervals were used to assess the precision of the odds ratios.

We used a locally weighted regression smoother and we dichotomized the average monthly prenatal exposure at the level corresponding to an average drinking water concentration of 40 ug/L, the suggested action guide when the pollution was discovered in 1980.

Results

There were 61 children with congenital anomalies among 1,658 children with some prenatal PCE exposure and 95 children with congenital anomalies among 2,999 children with no prenatal PCE exposure. The corresponding prevalence proportions per 1,000 births were 3.7 and 3.2, respectively. Many characteristics of the exposed and unexposed groups were similar. For example, mothers in both groups were predominantly white, and comparable proportions had medical conditions, prenatal multivitamin use, and exposure to non-drinking water sources of solvents. However, there were also many differences between the groups. Due to the timing of the PCE contamination, exposed mothers were more likely to give birth in later calendar years. Exposed mothers and fathers were older than unexposed parents, and exposed mothers were less likely to smoke cigarettes during the first trimester. Exposed children with anomalies were also more likely to be male and have mothers with high educational levels and prior pregnancy losses, and alcoholic beverage consumption during the first trimester.

The proportions who drank bottled water (about 22%), consumed more than four glasses of tap water per day (about 51%), and took long showers (about 23%) were similar across the exposed and unexposed groups. There was a wide distribution of PCE exposure levels encompassing several orders of magnitude in the exposed group. Average monthly PCE exposure levels during the LMP year ranged from 9.6E-05 to 131.8 grams. The 25th, 50th, 75th and 90th percentiles were 0.1, 0.6, 2.3, and 6.4 grams, respectively. The annual mass of PCE entering a home was diluted in an estimated 90,000 gallons of water, the annual usage of average households in Massachusetts, and only a small portion of this water was directly consumed by the subjects. Using this annual estimate of household water use, we converted the PCE mass delivered to a home during pregnancy to average annual point concentrations and estimated that the PCE

concentrations in the water entering the homes ranged from less than 1 ug/L to 5,197 ug/L. These concentrations are consistent with actual water sampling data from the time period.

The crude and unadjusted odds ratios for all congenital anomalies combined were 1.2 and 1.1 respectively, among children with any prenatal PCE exposure. The parental-age adjusted odds ratio for all anomalies was elevated by 40% among children whose average monthly prenatal exposure was greater than 1.136 grams, the cut point corresponding to an average drinking water concentration of 40 ug/L, and elevated by 50% among children whose average monthly prenatal exposure was \geq 75th percentile. The 75th percentile corresponded to an average monthly prenatal exposure of 2.3 grams. No meaningful increases in risk were seen for lower exposure levels. Again, these results were unchanged when only major malformations were included.

When organ system and diagnostic groups were examined, we found large increases in the odds ratios for neural tube defects and oral clefts and modest increases in the odds ratios for gastrointestinal and genitourinary malformations, including hypospadias; and chromosomal malformations among children with any prenatal PCE exposure. No meaningful increases in odds ratios were seen for cardiac and musculoskeletal malformations, and there were too few exposed cases to estimate odds ratios for eye, ear, respiratory, and other malformations.

Among the nine children affected by neural tube defects, there were four exposed cases of anencephaly in three different families vs no unexposed cases; one exposed case of spina bifida vs three unexposed cases and one exposed case of Arnold-Chiari malformation vs no unexposed cases.

We found that odds ratios for all gastrointestinal defects combined and oral clefts were further increased among children whose average monthly prenatal exposure was greater than 1.136 grams. No dose-response relationship was observed for neural tube defects.

While we were able to validate only a small number of questionnaire reports against prenatal and obstetric records, we found excellent agreement between the information provided by the mothers and these records. There was also excellent agreement between the survey and medical record on gestational duration, birth weight, prenatal cigarette smoking, alcohol consumption, and multivitamin use. Furthermore, when we compared questionnaire and birth certificate data from all index children born in Massachusetts ($n=2,490$), we found very good agreement on month and year of birth, mother's and father's age at the birth, birth weight, number of prior live births, and number of prior pregnancy terminations (including spontaneous and induced abortions).

In contrast, when we compared the mother's self-assessed exposure status to that derived from the EPA assessment, we found that only 15% of mothers considered exposed by the EPA assessment thought that their drinking water was contaminated, whereas 28% of these mothers thought that their water was not contaminated and 57% were unsure. Similarly, we found that 37% of mothers considered unexposed thought that their drinking water was not contaminated while 9% thought that their drinking water was contaminated and 53% were unsure.

Discussion

The results of this study suggest that prenatal exposure to PCE increases the risk of certain kinds of congenital anomalies. Prenatal exposure was associated with large increases in the risk of gastrointestinal defects (particularly oral clefts), neural tube defects (particularly anencephaly) and, modest increases in the risk of genitourinary defects (particularly hypospadias). No meaningful increases in risk were seen for cardiac, musculoskeletal and chromosomal anomalies, and there were too few exposed cases to estimate odds ratios for eye; ear, face, and neck; respiratory; and other anomalies. An exposure-response relationship was observed for oral clefts but not for neural tube or genitourinary defects.

Taken together, the results of the present and prior studies provide mounting evidence of an increased risk of oral clefts, and perhaps neural tube defects and other anomalies in relation to prenatal PCE exposure from drinking water.

Conclusions

Prior studies of prenatal exposure to solvents have found increases in the risk of congenital anomalies among exposed offspring, and so we undertook a retrospective cohort study to examine whether prenatal exposure to PCE-contaminated public drinking water influenced the occurrence of congenital anomalies in the Cape Cod region of Massachusetts. We found that children with prenatal exposure had increased risks of oral clefts and neural tube defects; however, an exposure-response relationship was observed for oral clefts but not for neural tube defects. These findings were limited by the small number of children with anomalies that were based on maternal reports. Therefore, we recommend that a follow-up investigation be conducted with a larger number of affected children who are identified by independent records.

Characteristics and Outcome of Infants with Candiduria in Neonatal Intensive Care—A Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) Study

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Background: There is limited information in the literature on the presentation and prognosis of candidal urinary tract infection (UTI) in infants in the neonatal intensive care unit (NICU).

Methods: This was a prospective cohort study performed in 13 Canadian NICUs. Infants with candidal UTI without extra-renal candidal infection at presentation were enrolled.

Results: Thirty infants fit the study criteria. Median birth weight and gestational age were 2595 grams (range 575-4255) and 35 weeks (range 24-41) with 10 infants being <30 weeks gestation. The most common primary underlying diagnosis was congenital heart disease (n=10). The median age at initial diagnosis was 16 days (range 6-84 days). Renal ultrasonography findings were compatible with possible fungal disease in 15 of the 26 infants (58%) in whom it was performed. Treatment was variable, but fluconazole and either amphotericin B deoxycholate or lipid-based amphotericin B in combination or sequentially were used most frequently. Extra-renal candidiasis subsequently developed in 4 infants. In 2 of these 4 infants, dissemination happened during prolonged courses of anti-fungal therapy. Three of 9 deaths were considered to be related to candidal infection. No recurrences of candiduria or episodes of invasive candidiasis following treatment were documented.

Conclusion: Candidal UTI in the NICU population occurs both in term infants with congenital abnormalities and in preterm infants, and is associated with renal parenchymal disease and extra-renal dissemination. A wide variation in clinical approach was documented in this multicenter study. The overall mortality rate in these infants was significant (30%). In one third of the deaths, Candida infection was deemed to be a contributing factor, suggesting the need for antifungal therapy with repeat evaluation for dissemination in infants who are slow to respond to therapy.

Background

Isolation of *Candida* from the urine of newborns can be indicative of contamination or of urinary tract infection. Although bacteremia is a complication of less than 3% of pediatric nosocomial bacterial urinary tract infections (UTIs),¹ it is not clear how often candidal UTI is a precursor to candidemia or to candidal infection at other sites. The primary purpose of this multi-center study was to describe the presentation, therapy, and prognosis of candidal UTIs in infants in the neonatal intensive care unit (NICU) in the absence of documented extra-renal infection at presentation.

Methods

This prospective study was performed in 13 tertiary level NICUs in 9 cities in Canada by members of the Paediatric Investigators Collaborative Network on Infections in Canada (PICNIC). The study protocol was approved by the institutional ethics review board at each center. As part of a larger study,² infants ≤90 days of age were prospectively enrolled between February 1, 2001 and July 31, 2003 if they met one of three criteria: 1) *Candida* was isolated from any sterile body site, 2) there was histologic or ophthalmologic evidence of *Candida* infection, or 3) they had candidal UTI, defined as growth of *Candida* from urine at >10⁶ CFU/L from a suprapubic aspirate or >10⁷ CFU/L from a bladder catheter specimen (2). In this report we describe those infants who fulfilled the third criterion without documented evidence of extra-renal infection at the time of enrolment. Infants with *Candida* isolated only from a bag urine were excluded. Institutions were instructed to follow their usual protocols for the diagnosis and treatment of candidal infection during the study.

Demographic and clinical data were collected on a standard case report form and entered into an Access (Microsoft Access 2002) database. Data were analyzed using SAS (version 9.1, SAS Institute Inc, Cary, NC, USA.). The day the first positive urine culture with significant growth of *Candida* was submitted

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Table 1: Characteristics and outcome of 30 infants with candiduria from 13 Canadian neonatal intensive care units

Case	GA	BW	Primary Diagnoses	Corticosteroids prior to candiduria	Day of life candiduria detected (Source)	Species	Sites of extra-renal dissemination	Outcome
1	24	780	Trisomy 21, Prematurity	yes	19 (catheter)	<i>C. albicans</i>	None	deceased
2	24	752	RDS, Prematurity	yes	16 (catheter)	<i>C. glabrata</i>	None	
3	33	2435	Renal Disease	no	13 (catheter)	<i>C. albicans</i>	None	
4	35	3320	Sepsis	no	17 (catheter)	<i>C. parapsilosis</i>	None	
5	41	3385	RDS, Renal Disease	yes	6 (catheter)	<i>C. albicans</i>	None	
6	35	2570	Renal Disease	no	15 (SPA)	<i>C. albicans</i>	None	
7	38	3000	Omphalocele	yes	11 (catheter)	<i>C. albicans</i>	None	
8	26	635	CHD, Prematurity	no	29 (catheter)	<i>C. parapsilosis</i>	None	deceased
9	34	1875	Sepsis	no	15 (SPA)	<i>C. parapsilosis</i>	None	
10	40	2800	CHD	no	15 (catheter)	<i>C. lusitanae</i>	None	
11	27	1025	RDS, Prematurity	yes	22 (SPA)	<i>C. albicans</i>	None	
12	40	3024	CHD	yes	39 (catheter)	<i>C. parapsilosis</i>	None	
13	37	3090	Renal Disease	no	15 (catheter)	<i>C. albicans</i>	None	
14	39	3400	CHD	no	16 (catheter)	<i>C. tropicalis</i>	None	deceased
15	38	4255	GI Disease	no	14 (catheter)	<i>C. albicans</i>	None	
16	35	2620	Renal Disease	yes	21 (SPA)	<i>C. albicans</i>	None	
17	40	3630	CHD	yes	11 (catheter)	<i>C. albicans</i>	None	
18	38	2750	Trisomy 21	yes	35 (catheter)	<i>C. albicans</i>	None	deceased
19	40	3500	CHD	yes	15 (catheter)	<i>C. tropicalis</i>	None	deceased*
20	39	3930	CHD	no	84 (catheter)	<i>C. albicans</i>	None	deceased
21	40	3030	Renal Disease	no	11 (SPA)	<i>C. albicans</i>	None	
22	30	1445	Sepsis	no	7 (catheter)	<i>C. albicans</i>	None	
23	25	815	RDS, Prematurity	yes	48 (catheter)	<i>C. lusitanae</i>	None	
24	24	650	RDS, Prematurity	no	9 (SPA)	<i>C. albicans</i>	None	
25	25	725	RDS, Prematurity	no	35 (catheter)	<i>C. albicans</i>	None	
26	24	575	RDS, Prematurity	yes	56 (catheter)	<i>C. albicans</i>	None	
27	26	830	Prematurity, NEC	no	6 (SPA)	<i>C. albicans</i>	Blood	
28	28	1170	CHD	no	58 (catheter)	<i>C. albicans</i>	Brain	deceased*
29	33	2200	CHD	no	77 (SPA)	<i>C. parapsilosis</i>	Blood	deceased
30	37	3225	CHD	yes	50 (catheter)	<i>C. albicans</i>	Blood	deceased*

BW - birthweight; CHD - congenital heart disease; GA - gestational age; NEC - necrotizing enterocolitis; RDS - respiratory distress syndrome; SPA - suprapubic aspirate

* Death was thought to be related to candidal infection

was considered to be the day of identification of candiduria, recognizing that the onset of candiduria may have been earlier in some cases. The local investigator was asked to determine if *Candida* infection contributed to death.

Results

Thirty infants (16 males, 14 females, 23 singletons and 7 twins) met the study inclusion criteria (Table 1). The median birth weight was 2595 grams (range 575-4255 grams) and the median

gestational age (GA) was 35 weeks (range 24-41 weeks). Ten infants (33%) were born prior to 30 weeks. Delivery was vaginal (n=13), via elective cesarean section (n=6) or via emergency cesarean section (n=11). The primary reason for NICU admission was congenital heart disease (n=10, of which 7 had a GA=37 weeks), respiratory distress (n=8), renal disease (n=5), sepsis (n=3), gastrointestinal disease (n=2), and trisomy 21 (n=2). None of the infants received prophylactic topical or systemic antifungal therapy. Thirteen infants (43%) received systemic corticosteroids for 1 to 31 days (median 3 days) prior to the candidal UTI. These consisted of a wide range of doses of intravenous methylprednisolone, hydrocortisone, or dexamethasone.

Three of the 30 infants developed candidemia 2 to 41 days following the candidal UTI and a fourth infant had evidence of central nervous system candidal infection first detected at autopsy (Table 1).

Candidal UTI was diagnosed at a median of 16 days of age (range 6 to 84 days). Three infants of GA 26, 30, and 41 weeks had possible congenital candidal infection with diagnosis on days 6, 7, and 6 of life, respectively. The placenta was examined for these 3 infants. The one from the infant born at 41 weeks GA was normal while the 2 preterm infants showed chorioamnionitis and funisitis.

Clinical findings on the day of diagnosis included fever of 38.0°Celsius or higher (n=7, 23%), feeding intolerance (n=2, 7%), and respiratory deterioration (n=5, 17%). Rash occurred on the day of diagnosis in all 3 infants with possible congenital candidiasis (diaper dermatitis in the preterm infants and a generalized excoriating rash in the term infant). Three other

infants born at 25, 27, and 35 weeks GA had diaper dermatitis when they presented on days 48, 22, and 21 of life.

Positive urine cultures were obtained via suprapubic aspirate (n=8) or bladder catheter (n=22). Seventy percent were *C. albicans* (Table 3). Urinalysis was obtained within 24 hours of diagnosis of candidal UTI for only 10 infants. Two infants had no pyuria, 2 had an occasional WBC/HPF, 2 had 1-10 WBCs/HPF, and 4 had >10 WBCs/HPF. Hematologic abnormalities included a peripheral leukocyte count of $<5 \times 10^9/L$ in 1 infant and $>25 \times 10^9/L$ in 2 infants, an absolute granulocyte count of $>10 \times 10^9/L$ in 10 infants, and platelets $<100 \times 10^9/L$ in 6 infants. Serum creatinine at diagnosis was $<60 \mu\text{mol/L}$ in 16 infants, 61-100 $\mu\text{mol/L}$ in 5 infants, 101-150 $\mu\text{mol/L}$ in 3 infants, $>150 \mu\text{mol/L}$ in 4 infants and not recorded in 2 infants.

Blood culture was performed and was negative for fungi in 24 of the 30 infants on the day of diagnosis of candidal UTI and in another 2 infants prior to initiation of antifungals. Of the four infants who did not have blood cultures prior to antifungals, three subsequently had no clinical or laboratory evidence of invasive candidal infection but one had a positive blood culture 41 days later (Table 1). Lumbar puncture was performed in only 5 infants within 2 days of the diagnosis of candidal UTI. A cell count was available in 3 of these infants, of whom 2 had pleocytosis (WBC $44 \times 10^6/L$ (100% monocytes) with RBC $62 \times 10^6/L$, and WBC $315 \times 10^6/L$ (45% polymorphonuclear cells) with RBC $12,720 \times 10^6/L$) and all 5 CSF cultures were sterile. Four other infants had CSF obtained more than 2 days after the diagnosis of UTI but prior to laboratory documentation of clearance of candiduria. All CSF cultures were sterile, and there was no pleocytosis in the 2 cases where a cell count was available.

Table 2: Infants who developed extra-renal dissemination of candidal infection from a cohort of 30 infants diagnosed with candiduria

Patient number	GA	Primary diagnosis	Extra-renal site	Species	Days between positive urine culture and positive culture at extra-renal site	Cultures performed between date of positive urine and date of positive culture at extra-renal site ¹	Therapy between candiduria and positive culture at extra-renal site	Outcome of candidal infection	Treatment after diagnosis of extra-renal candidal infection
1	26 weeks	Prematurity	Blood	<i>C. albicans</i>	2	1 urine culture positive for <i>C. albicans</i>	None	Survived	32 days AMP, FCZ and 5FC in various combinations
2	28 weeks	Congenital heart disease	CNS (at autopsy) ²	<i>C. albicans</i>	11	4 negative blood cultures	7 days AMP	Died	None
3	33 weeks	Congenital heart disease	Blood	<i>C. parapsilosis</i>	41	5 negative urine cultures ³	13 days AMP	Survived ⁴	28 days AMP and L-AMP
4	37 weeks	Congenital heart disease	Blood	<i>C. albicans</i>	32	5 urine cultures positive for <i>C. albicans</i> and 4 negative blood cultures	26 days AMP, FCZ or both ⁵	Died	4 days L-AMP and FCZ

AMP - amphotericin B deoxycholate; CNS - central nervous system; FCZ - fluconazole; GA - gestational age; L-AMP - lipid-based amphotericin B; 5FC - 5 flucytosine

¹All had a negative blood culture on the day of diagnosis of candiduria

²Prior to the positive urine culture, had 7 negative blood cultures and 2 negative CSF cultures. Between the onset of candiduria and death had 4 negative blood cultures but cerebrospinal fluid not obtained

³Blood culture was not performed initially or until 41 days after the date of the positive urine culture

⁴Ultimately died of congenital heart disease

⁵There was a 5-day gap after the first 5 days of therapy.

Table 3: Species of *Candida* in 30 infants in neonatal intensive care units with candiduria

Species	Number of cases of candiduria (%) - current study; n = 30 ¹	Number of cases of candiduria (%) (3) n = 25	Number of cases of candiduria (%) (4) n = 36 ²
Years of study	2001-2003	1989-1995	1982-1993
<i>Candida albicans</i>	21 (70%)	15 (60%)	26 (72%)
<i>Candida parapsilosis</i>	4 (13%)	8 (32%)	7 (19%)
<i>Candida tropicalis</i>	2 (7%)	2 (8%)	1 (3%)
<i>Candida lusitanae</i>	2 (7%)	0	0
<i>Candida glabrata</i>	1 (3%)	0	2 (6%)

¹Two of the infants with *C. albicans* and one with *C. parapsilosis* were fungemic.

²Study reports 41 infants but microbiologic data only provided for 36 infants

Radiographic findings: Renal ultrasonography revealed abnormalities compatible with fungal disease in 15 of the 26 infants (58%) in whom it was performed. Twenty-four of the 26 scans were performed within 4 days of the onset of candiduria. These abnormalities included diffuse parenchymal echogenicity (n=5), focal parenchymal echogenicity (n=1), unspecified echogenicity (n=1), dilatation of the collecting ducts (n=3) and both parenchymal echogenicity and dilatation of the collecting ducts (n=5). Almost all abnormalities were bilateral. The radiologic appearance was consistent with “fungal balls” in 3 of these 15 infants—a term infant with diffuse parenchymal disease and 2 infants born at 25 and 35 weeks GA with dilated collecting ducts, none of whom developed candidemia. Follow-up imaging was not performed in these 3 infants.

Ultrasonography of the liver and spleen was abnormal in 6 of the 16 infants (37.5%) in whom it was performed, revealing hepatomegaly (n=2), a solitary hepatic hemangioma, a calcified hepatic thrombosis, a splenic hematoma, and diffusely abnormal splenic echogenicity of uncertain significance. None of the findings were considered to be suggestive of hepatosplenic candidiasis. None of the 12 infants who had fundoscopic examinations had evidence of fungal retinitis.

Therapy: Two infants did not receive antifungal therapy—a term infant with renal failure who was treated for a *Pseudomonas* UTI and had no follow-up urine cultures prior to discharge (patient 13 in Table 1) and an infant with trisomy 21 who had candidal UTI 3 days prior to death with no evidence of *Candida* infection at autopsy (patient 18 in Table 1). Therapy for the remaining infants consisted of fluconazole (FCZ), amphotericin B deoxycholate (AMP), lipid-based amphotericin B (L-AMP) and 5-flucytosine (5-FC) in various combinations (Figure 1). For the 22 infants who survived to the end of therapy and did not develop extra-renal candidal infection, 4 infants received AMP or L-AMP alone, 6 infants received FCZ alone, 10 infants received a combination of AMP or L-AMP and FCZ and 2 infants received AMP or L-AMP with FCZ and 5-FC. The median total duration of antifungals in these 22 infants was 16.5 days (range 5-75 days). For the 3 infants with suspected renal fungal balls, one of the term infants received just two days of L-AMP prior to death (Table 1) while the 2 survivors were treated for 14 and 75 days with sequential AMP and FCZ.

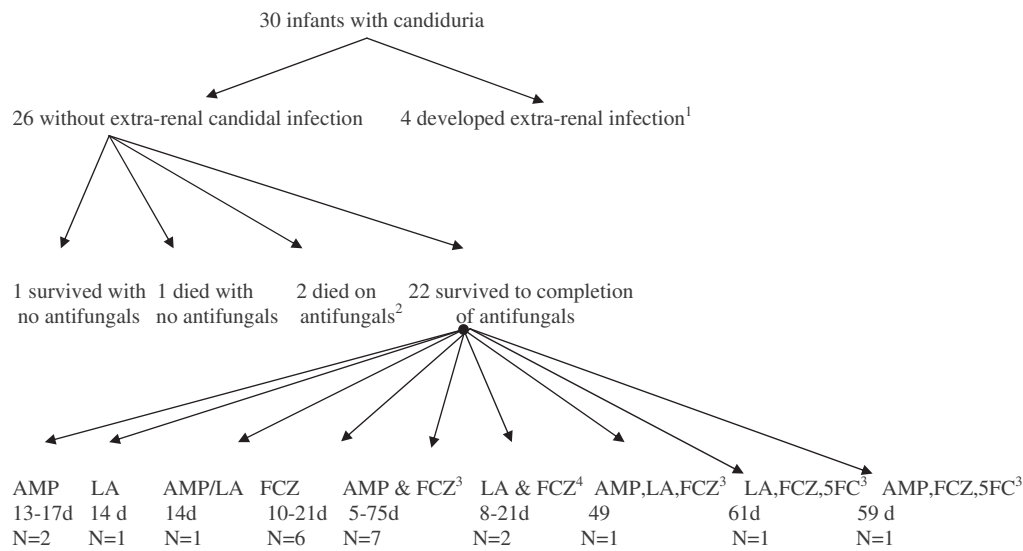
Complications of Therapy: A clinically significant rise in creatinine (defined as an increase of $\geq 20\%$ to a level ≥ 60 $\mu\text{mol/L}$)

was documented in 5 infants while on therapy (a rise from 142 to 178 $\mu\text{mol/L}$ on day 3 of AMP, a rise from 171 to 310 $\mu\text{mol/L}$ on day 9 of L-AMP following a 3 day course of AMP, a rise from 104 to 137 and from 36 to 87 $\mu\text{mol/L}$ on days 2 and 5 of L-AMP respectively and a rise from 32 to 98 $\mu\text{mol/L}$ on day 5 of FCZ). For the 3 infants with suspected fungal balls, the highest serum creatinine levels were 66, 91, and 97 $\mu\text{mol/L}$ respectively. Hypokalemia (defined as serum potassium < 3.3 mEq/L) was documented in 10 infants (33%) of whom 4 were born prior to 30 weeks GA. Attributing hypokalemia to specific antifungals was not possible as 9 of these infants were treated with sequential or combination drugs. New-onset thrombocytopenia (platelets $< 100 \times 10^9/\text{L}$) was documented after commencing antifungals in 5 infants (17%). Four infants developed hypotension while on antifungal therapy (two on FCZ and one on each of AMP and L-AMP).

Outcome: There were 9 deaths among the 30 infants in the study (30%), all in infants with significant underlying conditions (7 with congenital heart disease and 2 with trisomy 21). In three of these deaths, *Candida* infection was thought to be a contributing factor. Two of the deaths were in infants who developed disseminated disease (patients 2 and 4 in Table 1), and one occurred in an infant without evidence of extra-renal candidal infection. The latter infant was born at 40 weeks GA with congenital heart disease and died following 2 days of therapy for candidal UTI, with suspected renal fungal balls on renal ultrasonography. No autopsy was performed. Five of the 6 other infants who died had autopsies, none of which revealed evidence of candidal infection. No recurrences of candiduria or isolation of *Candida* from a sterile site were documented prior to hospital discharge among the 21 survivors, but 5 infants did not have follow-up urine cultures obtained.

Discussion

Multiple previous studies outline the epidemiology and clinical course of invasive candidiasis in the NICU, but there have been limited studies of candidal UTI in the absence of extra-renal disease as detected by routine investigations. This report describes 30 such cases presenting to 13 Canadian NICUs over a 30-month period, many in term or near-term infants with major congenital abnormalities of the heart or kidneys. In addition our results suggest a lack of distinguishing clinical or laboratory features at diagnosis, a high rate of abnormalities on renal ultrasonography ($> 50\%$), and a significant proportion (one third) of the total mortality related to *Candida* infection.



¹ See Table 1 for details of their therapy and outcome.

² Death occurred on day 2 of L-AMP and day 5 of FCZ

³ Given sequentially or in combination

⁴ Given sequentially

Figure 1

Antifungal therapy offered to 30 infants with candiduria in neonatal intensive care units. AMP - amphotericin B deoxycholate; d-days; FCZ - fluconazole; L-AMP- lipid-based amphotericin B; 5FC - 5 flucytosine.

Our finding of candidal UTI in term infants with congenital anomalies differs from two previously published studies of candidal UTIs in NICUs. Philips et al used an identical definition for candidal UTI to the current study but only enrolled infants 7 days of age or older (n=25).³ The second study by Bryant et al enrolled infants from birth (n=41) but accepted any growth of *Candida* from a catheterized urine as being indicative of a UTI.⁴ These previous studies described candidal UTIs mainly in very low birth weight infants (median gestational age 26 weeks³ and 27 weeks⁴ versus 35 weeks in the current study). This discrepancy is likely due to our exclusion of infants who had candidemia on the day of diagnosis of candidal UTI. In the cohort of 66 infants with systemic candidiasis that were part of our larger study who met the first inclusion criteria but are not included in the current report, 8 infants had both blood and urine cultures positive for *Candida* and their median gestational age was 25.5 weeks (unpublished data), consistent with these previously published studies. Differences in NICU populations between the studies may also be a factor with the current multicenter study including a higher proportion of term infants with congenital heart disease than many studies of single NICUs. Although there are no previous studies looking at candidal UTI in term or near-term infants in NICU, a study that looked at invasive candidiasis in infants with a birth weight over 2500 grams described 13 of 17 infants (76%) with serious congenital anomalies.⁵ This pattern fits with the current study where two-thirds of the infants were born after 29 weeks gestation and over half had serious congenital anomalies. In a study from the United Kingdom of infants with fungal infections and a birthweight <1500 grams, 26 of 94 cases had funguria with 6 having isolated funguria.⁶ The species of *Candida* were comparable in all NICU candidal UTI studies to date (Table 2).

On renal ultrasonography, parenchymal changes predominated in the current study, suggesting the possibility of unrecognized

hematogenous spread of *Candida* in infants who are suspected to have candidal infection limited to the urinary tract. Ascending infection would be expected to result in isolated pelvicalyceal disease, with only 3 of the 15 abnormal renal ultrasounds fitting this pattern. However, the terminology for renal ultrasonography reporting in neonates is not uniform. Renal fungal balls or abscesses were suspected in 35%³ and 42%⁴ of the 55 infants with renal imaging or autopsy diagnoses in the previous studies. In the current study, only 12% of the 26 infants with renal imaging had a fungal ball mentioned in the report, but many had changes that appeared to be consistent with those reported as fungal balls in a previous study.⁴ Renal fungal balls can be confused with fibrin, blood clots, necrotic papillae, nephrocalcinosis, or tumors on renal ultrasonography⁷ so that the interpretation may be influenced by the information provided to the radiologist about the possibility of candidal infection. In one study, about half of the suspected fungal balls were apparent only on follow-up ultrasounds⁴ which were not routinely performed in the current study.

Although surgical intervention for renal fungal disease in the collecting system has been described in numerous case reports,⁷ it was not required for infants with fungal balls in our study. For the 66 infants with candidal UTI described in the two previous case series,^{3,4} 22 infants had suspected fungal balls with 2 having partial obstruction but surgery was required for only one infant with a renal abscess.⁴ In another recent study of 9 infants with suspected renal fungal balls, surgical management was not required.⁸ This suggests that medical management can be anticipated to be successful in the majority of cases, even in the presence of documented fungal balls on imaging, unless there is concomitant total obstruction.

The need for, choice and duration of antifungal treatment for candidal UTI in the absence of extra-renal disease has not been

studied and there are no widely-accepted guidelines, explaining the marked variation in therapy in the current study. Two of the 3 deaths that were thought to be related to candidal infection were a result of dissemination of disease, indicating that cases with "apparent isolated candiduria" may later disseminate or may have undetected foci of infection at non-renal distant sites. The significant rate of extra-renal dissemination (13.3%) supports the use of systemic antifungal therapy when candiduria occurs with a significant colony count in the NICU.

Most infants with candidal UTI in previous reports were successfully treated with AMP or FCZ, typically given for a minimum of 7 days after urine cultures became sterile.⁷ Much longer courses have often been given if changes are noted on renal ultrasonography, but it appears that there is no need to document resolution of these changes prior to stopping therapy.⁷ There were only 2 cases of suspected treatment failure in the current study where death was attributable to candidal infection despite 7 or more days of appropriate therapy, both in infants with extra-renal dissemination (Table 1). There were no recurrences of candiduria, suggesting that any of the multiple regimes used by clinicians for candidal UTI are likely to be successful if extra-renal invasive candidal infection has been excluded. Two of the three cases of candidemia occurred after long courses of antifungals, suggesting that extra-renal candidal infection should be sought even in infants on treatment with a slow response to therapy. The role of parenteral prophylactic antifungals for candiduria could not be addressed in the current study as they were not used in any of the NICUs.

The primary limitation in drawing conclusion from this study is that although the patients were enrolled prospectively, investigations for dissemination were at the discretion of the attending physician. This resulted in not all patients being consistently evaluated for meningitis, retinitis, renal parenchymal disease, recurrent candiduria, or even candidemia. However, we recognize that false-negative blood and CSF cultures occur frequently in neonatal candidiasis so associated morbidity is not always recognized even when infants are fully evaluated for disseminated disease. Nonetheless, even though it is widely accepted that all infants with candidemia should be investigated for end-organ damage,⁷ the need for full investigation of infants with candiduria in the absence of candidemia is less clear from the previous literature. The role of fundoscopy in infants with candiduria alone is not clear although a study has shown a higher incidence of candidal retinitis with candidaemia of greater gestational age,⁹ suggesting that fundoscopy is indicated even in term infants with extra-renal candidiasis.

Further limitations are that it would have been ideal to have all renal ultrasounds interpreted by a single radiologist, and that changes in management of infants will have occurred since this study was performed. For example, fewer infants would be exposed to post-natal corticosteroids and echinocandins are now used as antifungal therapy in some centers.

One of the limitations of all studies to date is that definitions devised for the diagnosis of bacterial UTIs have been extrapolated to fungal UTIs, without validation of these definitions in any age group.¹ There are no standard definitions for colony counts defining UTIs in children with indwelling bladder catheters¹ which would include a small number of infants in the current study. The fact that over half of the renal

ultrasounds in our study demonstrated abnormalities consistent with fungal infection of the renal parenchyma or collecting system suggests that the specificity of the definitions used is reasonable. It is however possible that clinically significant fungal UTIs can occur at lower colony counts than those applied in this study, as has been described in infants with suspected fungal balls.¹⁰ In addition, infants with fungal UTI may have been missed if only a bag urine had been submitted or if antifungals had been started prior to obtaining the urine specimen.

Conclusion

In this study of Canadian neonates, we were able to show that neonates presenting as candidal UTI without dissemination, within the NICU population of low birth weight infants and older gestational age infants with underlying illness, is associated with significant morbidity and mortality. It is difficult to separate out the effect of candiduria on outcome versus the tendency of infants with a poor prognosis to develop candiduria. There is significant variation in the diagnosis and management of candiduria in academic tertiary level NICUs in Canada. The cases of extra-renal invasive candidal disease suggest that investigation for *Candida* in the blood, cerebrospinal fluid, renal parenchyma and retina may be indicated along with systemic antifungal therapy. Evidence of extra-renal spread in the face of appropriate systemic therapy may be a poor prognostic sign, and is not restricted to extremely premature infants. Multi-center randomized trials are needed to determine the optimal therapy and duration of treatment for this relatively rare entity.

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Multifocal Multi-organ Ischemia and Infarction in a Preterm Baby Due to Maternal Intravenous Cocaine Use

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Abstract

Introduction: Although the adverse effects of cocaine use in pregnancy are well recognized, we believe this case highlights the importance of considering the route of administration, and suggests the possibility of multifocal damage relating to intravenous use.

Case presentation: A Caucasian female baby of 29-weeks' gestation was spontaneously delivered and subsequently developed multi-organ failure considered unrelated to simple prematurity. Intensive care was re-orientated following the development of massive intraventricular hemorrhage.

Conclusion: This case illustrates the need for regular cranial ultrasound in babies of pregnancies at risk due to intravenous cocaine use and also the necessity of counselling women who misuse cocaine in the antenatal period. As such, this article will be of most interest to pediatric and obstetric staff.

Introduction

Cocaine use in pregnancy has been associated with adverse fetal outcomes including congenital malformations. We report a female baby of 29 weeks' gestation whose mother had extensive polydrug misuse throughout her pregnancy, including the use of intravenous cocaine. Following spontaneous delivery, the baby died after three days of intensive support. A postmortem examination revealed widespread ischemic change throughout multiple organs. We hypothesize that the unusual extent of this damage is related to the route of administration and dosage of cocaine during the pregnancy.

Case presentation

A 29-year-old Caucasian primigravida presented at 29+0 weeks' gestation with abdominal pain and fever. A presumptive diagnosis of urinary tract infection was made with laboratory investigations demonstrating a raised C-reactive protein and peripheral leukocytosis, and treatment with intravenous cefuroxime was commenced. The expectant mother reported regular use of heroin, diazepam, "street" methadone and

cocaine. Heroin and cocaine were both smoked and injected intravenously. Frequency of use was difficult to clarify.

Abdominal pain continued intermittently and antenatal betamethasone was administered. A cardiotocograph (CTG) trace was non-reassuring and necessitated an emergency cesarean section approximately five hours after the initial dose of betamethasone. A female was delivered alive and in good condition, weighing 1,530 g (75th centile). Apgar scores were 71 and 85. There were no external dysmorphic features, organomegaly, rash or bleeding. An initial cranial ultrasound scan was normal with no evidence of hemorrhage. Mean blood pressure (BP) was normal. Laboratory investigations demonstrated marked coagulopathy and abnormal liver function tests (Table 1). Aspartate transaminase (AST) was disproportionately elevated in comparison with other liver enzymes, a pattern suggesting extensive tissue injury due to the nonspecificity of AST.

Fresh frozen plasma (FFP) and cryoprecipitate were administered without improvement in the coagulopathy. Urine was noted to be pink in color, but microscopy did not demonstrate red cells. At 16 hours of age, there was generalized seizure activity confirmed on amplitude integrated EEG (Cerebral Function Monitoring—CFM). The infant was loaded with phenobarbitone and received a half correction of sodium

Table 1. Temporal evolution of laboratory parameters

Laboratory parameter		Age		
Parameter	Reference Range	1 hour	12 hours	36 hours
PT	10.6-16.2 secs	54	29	
APTT	27.5-79.4 secs	60	41	
TCT	19.2-30.4 secs	23	19	
Fibrinogen	1.5-3.73 g	0.5	1.2	
Urea	2.5-7.5 mmol/l		6.4	9.5
Creatinine	35-100 µmol/l		78	136
Bicarbonate	21-28 mmol/l	22.0	15.6	13.1
AST	<40 U/l		1891	2168
ALT	<50 U/l		200	203
Gamma-GT	<55 U/l		259	227
Albumin	g/l		21	17

Stated coagulation reference ranges are applicable to 30-week gestation healthy controls on the first day of life. ALT, alanine transaminase; APTT, activated partial thromboplastin time; AST, aspartate transaminase; Gamma GT, gamma glutamyl transferase; PT, prothrombin time; TCT, thrombin clotting time.

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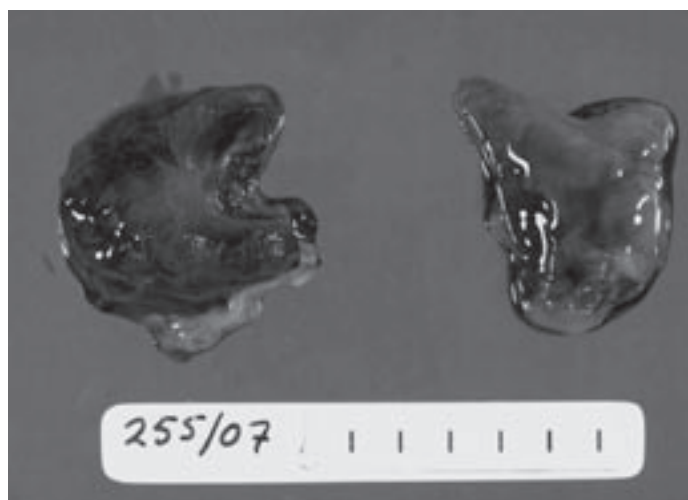


Figure 1. Bilateral blood casts of cerebral ventricles. Post-mortem pathological specimen demonstrating 'cast' formed by cerebral ventricles entirely filled with blood following massive intraventricular haemorrhage.

bicarbonate for a progressive metabolic acidosis. Morphine was infused at 10 micrograms/ kg/hour.

Urine output was <0.5ml/kg/day by 24 hours of age and she was passing extremely liquid stools. Coagulopathy persisted and liver function deteriorated further on sequential monitoring (Table 1). Repeat ultrasound at 36 hours of age showed bilateral intraventricular blood with evidence of marked midline shift. It was decided that continuing care aimed at the baby's survival was inappropriate and care was re-orientated following discussion with the baby's mother. The infant was extubated one hour following baptism, and died shortly afterwards.

A postmortem examination was performed and it demonstrated intraventricular haemorrhage (IVH) (Figure 1) expanding all four ventricles and extending around the brain stem and cerebellum (grade 3). Histology showed recent subarachnoid hemorrhage and cortical vascular congestion consistent with multiple small focal interstitial hemorrhages distinct from the IVH. There was hepatic necrosis (Figure 2) and evidence of colonic mucosal ischemic injury with multiple punctate erythematous areas. The kidneys showed zonal interstitial hemorrhage involving the medullary pyramids. The bladder also contained an area of large submucosal hemorrhage. These urogenital changes probably explain the pink-colored urine. The absence of red cells was possibly attributable to hemolysis within the urinary tract. In addition, there was ischemia and necrosis of the islets of Langerhans with sparing of the exocrine pancreas. Thymus, heart and adrenals appeared normal. Examination of the placenta showed acute decidual hemorrhage and chronic intervillitis. Microbiological and metabolic investigations did not demonstrate any further cause for deterioration or death.

Discussion

Cocaine has been used for recreational purposes for over 5,000 years.¹ The drug can be ingested, smoked, injected or inhaled intranasally. Smoking and snorting cocaine are the most common methods of cocaine use. Intravenous use is infrequent and accounts for less than 10% of cocaine use in the USA.² Comparative figures for the UK are unavailable and comprehensive Department of Health public information only briefly mentions injection as a route of administration.³

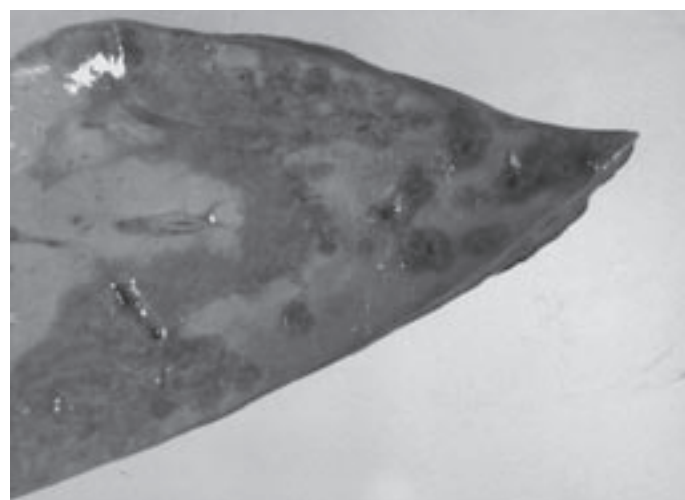


Figure 2. A clear demarcation of healthy liver on the left, ischaemic liver centrally, and necrotic areas to the right. Postmortem pathological specimen of liver demonstrating zonal multifocal necrosis, with marked macroscopic necrosis visible on right side of specimen, healthy liver on left and a 'border' of ischaemic tissue between.

Adverse effects of cocaine on the adult user are well recognized.¹ Vasoconstrictive effects are mediated via blockage of catecholamine uptake and beta-adrenergic stimulation. Cocaine use during pregnancy and its teratogenic effects on the fetus are less well defined. Early observational reports suggested "crack babies" could have a variety of congenital abnormalities, including gastroschisis, intraventricular hemorrhage, growth restriction, and genitourinary and renal anomalies.⁴ While evidence has increased, meta-analyses⁴ and larger scale studies⁴ have not confirmed any of the anatomical sequelae, although behavioral effects appear true. The mode of cocaine use is rarely considered or controlled for, nor is the cumulative dose of cocaine. Polydrug use and the chaotic lifestyle associated with substance misuse are variably considered as confounding within studies. Maturity at birth is also often omitted though it is suggested that preterm babies are affected differently.⁶

The role of cocaine in intraventricular hemorrhage is still unclear. A prospective study⁷ comparing light and heavy cocaine users with controls demonstrated an increased incidence of subependymal hemorrhage within term babies in the heavy cocaine user group only. A subsequent retrospective review⁸ found a similar finding in preterm babies. Although, the review did not stratify according to cocaine usage, it suggested that this effect may have been even more pronounced in mothers who used large quantities. A small prospective study⁹ of very low birth weight (VLBW) babies showed a higher incidence of grade I to II hemorrhage, but not more severe bleeds. A further larger prospective study of VLBW babies¹⁰ did not find any increased risk of grade III or IV intraventricular haemorrhage though it did not consider dosage for confounding or consider smaller bleeds.

Widespread focal ischemia and infarction affecting multiple organs have not previously been reported in an infant as a result of maternal cocaine use. We hypothesise that the postmortem findings are related to the vasoconstrictive effects of cocaine use. The occurrence or extent of intraventricular hemorrhage within cocaine-exposed babies may be related to dosage. Intravenous usage may aggravate this effect. This case is of particular interest due to the widespread nature of the ischaemic infarcts affecting multiple organ systems. The focal nature of the infarcts affecting multiple organs makes them highly

unlikely to be attributable to either complications of prematurity or the other illicit substances taken during this pregnancy. Due to the mixed nature, another substance or a cumulative effect cannot be excluded. However, similar infarcts have not, to our knowledge, been reported with heroin, methadone, or benzodiazepine use.

Conclusions

We advocate early and regular coagulation screening and cranial ultrasound scans for pregnant women with significant cocaine use, particularly if taken intravenously. The risk of significant morbidity and mortality should be considered during antenatal counselling of women who use cocaine. We also suggest that there is a need for further prospective research in this area with dosage and mode of administration being considered as confounding factors.

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Determinants in Early Life for Asthma Development

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Abstract

A reliable screening test in newborns for the subsequent development of bronchial asthma (BA) has not been found yet. This is mainly due to the complexity of BA, being made up by different types and underlying mechanisms. In different studies, a number of risk factors for BA have been identified. These include a positive family history of BA, passive smoking (also during pregnancy), and prematurity (including pulmonary infections, RDS and BPD), early viral respiratory infections (such as RSV-bronchiolitis), male gender, early lung function abnormalities and atopic constitution. Therefore, early symptoms and markers of allergy (ie The Allergic March) and a positive family history for allergy should be considered as important risk factors for the development of BA.

Background

What is asthma? Bronchial asthma (BA) is more than just one disease of the lower airways, and is now considered to be a syndrome, the asthma syndrome, made by a spectrum of different conditions that are manifested by recurrent symptoms of bronchial obstruction, ie recurrent symptoms of wheezing and/or cough, and having as a major feature the existence of bronchial hyperreactivity, as a consequence of chronic bronchial inflammation. A number of classifications of BA have been proposed, based on severity, etiology or age of the patient. In one classification two major subtypes of BA are distinguished: primary and secondary BA. Furthermore, it is recognized that BA can also be a consequence of an underlying specific airway disease.¹

Primary asthma can be considered as a type of asthma of which the etiology can be situated in the bronchi itself, ie bronchial hyperresponsiveness to a number of triggers, such as allergens, viruses and pollution. Secondary asthma is a type of asthma of which the etiology is situated outside the bronchi, such as in asthma maintained by chronic rhino-sinusitis or gastro-oesophageal reflux. In this latter type, bronchial hyperresponsiveness is a secondary phenomenon, indicating that treatment should be focused on pathologies outside the lower airways. Asthma with specific airway diseases is the existence of asthmatic symptoms (ie recurrent wheeze and/or cough)

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in specific airway diseases such as cystic fibrosis, structural bronchial malformations, immune deficiencies, ciliar dyskinesia and others.

This classification of BA not only refers to the different causes of asthma, but also to a different prognosis, suggesting that specific treatment regimens should be used. This is clearly illustrated by looking at asthma in children younger than 3 years of age. The evidence suggests that recurrent obstructive symptoms (ie recurrent wheezing) remit in a large number of these children who develop these symptoms during the first 3 years of life. In these children, recurrent wheezing is usually evoked by viral infections and low lung function parameters seem to be the main risk factor for these transient episodes. On the other hand, children who will go on to develop persistent wheezing beyond infancy and early childhood usually have a family history of asthma and allergies and present with allergic symptoms very early in life.^{2,3}

Determinants in early life for asthma development : Since asthma (ie recurrent wheezing) constitutes different types, it is very difficult to predict its occurrence, especially in newborns. Furthermore, a severe lower airway infection with RSV or with another respiratory virus is able to induce BA in a previously complete healthy baby with a complete negative family history for BA or allergy.⁴ Therefore, there are few truly justified recommendations for the prevention of asthma.⁵ The GINA guidelines (2006, chapter 4) mention "...few measures can be recommended for prevention of asthma because the development of the disease is complex and incompletely understood."

However, in different studies, a number of risk factors for BA have been described.¹ These include: 1. A positive family history of BA, 2. A passive smoking (prenatally and postnatally), 3. Prematurity (including pulmonary infections, RDS and BPD), 4. Early viral respiratory infections (such as RSV-bronchiolitis), 5. Male gender, 6. Early lung function abnormalities and 7. An atopic constitution.

1. Family history of BA: In a large number of studies it was demonstrated that a positive family history for BA and for atopy (see below) are important risk factors for BA. In a recent study from the South Bronx it was shown that the most important risk factors for BA are Hispanic ethnicity, family history of asthma, and exposure to tobacco smoke.⁶ In other studies the effect of early-life environmental exposures on genetic factors has been

Table 1. A clinical index to define asthma risk (from Castro-Rodriguez et al, 2000)

Major Criteria	Minor Criteria
1. Parental asthma*	1. allergic rhinitis*
2. eczema*	2. Wheezing apart from colds
	3. Eosinophilia (>4 %)

*Physician diagnosis of asthma, eczema or allergic rhinitis.

shown. In a study by Kuiper et al, a modification of the effect of family history of BA on respiratory morbidity by environmental exposures in early life was demonstrated. Postnatal parental smoking and high indoor dust mite allergen levels accentuated the increased risk of wheeze associated with a positive family history, whereas breast-feeding attenuated the increased risk of upper airway pathologies.⁷

2. Passive smoking: Although passive exposure to cigarette smoke in young children is a risk factor for respiratory symptoms, childhood asthma, airway hyperresponsiveness and diminished pulmonary function status, no definitive study has implicated passive smoking as a risk factor for the persistence of recurrent wheezing.¹ On the other hand, it seems very acceptable that passive smoking worsens prognosis of BA in young children, based on the observation that lung growth is diminished in children from smoking pregnant women.⁸

3. Prematurity: Prematurity with respiratory morbidity, such as RDS, can result in longterm lung damage (bronchopulmonary dysplasia) and bronchial hyperreactivity, which is predisposing situation for severe viral-induced wheezing during years.⁹

4. Viral respiratory infections: RSV lower respiratory tract illnesses in early life are an independent risk factor for the subsequent development of wheezing up to age 11 years. Severe RSV infections, requiring hospitalization, can induce persistent IgE-mediated hypersensitivity reactions up to the age of 7 years.^{10,11} The exact mechanisms are fairly unknown, but a RSV-induced switch from Th1 to Th2 features has been shown.¹² However, the relation between RSV infection and subsequent BA is still very much debated. It seems that pre-existing atopy may be a marker for more severe bronchiolitis and atopy itself predisposes to BA.¹³

5. Male gender: Male gender has been demonstrated to be a risk factor for BA in children before the age of 14 years, while female gender to be a risk factor for asthma in adults. In one study it was shown that boys had a higher incidence rate of BA, while girls had a greater deficit in pulmonary function, suggesting a worse long term prognosis in female patients.¹⁴ An explanation for this could be that boys have a higher prevalence of allergic sensitization than girls, while in adults the gender difference is reversed.¹⁵

6. Early lung function abnormalities: Early lung function abnormalities have been associated with an increased risk of recurrent wheezing. In a recent study it was found that poor airway function shortly after birth should be recognized as a risk factor for airflow obstruction in young adults and that prevention of chronic obstructive pulmonary disease might need to start in fetal life.¹⁶

7. Allergy as a major risk factor to develop persistent asthma: The causes of allergy are multi-factorial and the

development of an allergic disease is the result of complex interactions between genetic constitution and environmental factors. Genetic constitution is important, as it is in genetically predisposed individuals that the environment is able to trigger symptoms of allergy. At birth allergic symptoms usually are not present, although it was demonstrated that allergic immune responses already can start during fetal life and that the fetus is able to respond to allergens from week 20 of pregnancy.¹⁷ In young children, eczema and food allergy (diarrhea, vomiting, failure to thrive) are usually the first manifestations of allergy, while in older subjects allergy manifests itself more often as a chronic or recurrent asthma and/or allergic rhinitis. This phenomenon of switching from one expression of allergy to another is called the "Allergic March."

Among risk factors to develop BA, from a substantial number of studies it was concluded that atopy is one of the most important risk factors.¹⁸ Early allergen exposure seems to be a major trigger, but attempts at prevention by allergen avoidance have produced conflicting results.¹⁹ Moreover, from recent studies it seems that there is no linear relationship between early allergen contacts and the development of BA, as both exposure to high doses and low doses of allergens might have a protective effect, suggesting the existence of a bellshaped relationship.²⁰

It is generally accepted that atopy is associated with a poorer prognosis of asthma during childhood.¹ Atopy was associated with a poorer prognosis of asthma during childhood.¹ Atopy was associated with persistent wheezing in a cohort of babies at high risk for allergic diseases and was associated with an increased risk for both early and later childhood onset of wheezing.²¹ In a follow-up of a 1958 birth cohort, subjects who had asthma or wheezy bronchitis by age 16 years were twice as likely to have a report of wheezing during the preceding year if they had hay fever, allergic rhinitis, or eczema.²² Furthermore, children experiencing persistent asthma beyond early life have increased serum IgE levels during the first year of life and are more likely than other children to be sensitized to foods.^{23,24} In one study a clinical index, based on family history and atopic features, was proposed (Table 1).²⁵ In that study it was found that 95% of young wheezy children with a negative index never developed asthma between the ages 6-13 years. In another study from Finland, food allergy during the first three years of life was also a risk factor to develop persistence of wheezing until school age.²⁶

Taken together, it is clear that allergy is a risk factor to develop persistent asthma in infants and young children. Once asthma has itself established in the child, allergy appears not to be an independent determinant of prognosis into adulthood, suggesting that inflammatory processes in the airways run their own courses irrespective of the subject's atopic status.¹

Determinants in early life of atopy: Early prevention of allergic diseases, including BA, has been regarded as an important corner stone in the management of atopic diseases. Therefore, the identification of reliable screening markers detecting individuals (newborns) at risk has been an area of intense research during the past thirty years. Many efforts have been made to find reliable predictors of atopy which might identify children at risk and allow the initiation of primary preventive strategies at an early stage. As a consequence, various studies have been performed in which markers of atopy in cord blood were assessed.¹⁸ These include genetic markers of allergy, IgE levels, levels of soluble mediators of atopy (cytokines,

receptors), determination of receptors connected to bacterial immune defense (linked to the so-called "Hygiene Hypothesis"), determination of polyunsaturated fatty acids, cytokine profiles of mononuclear cells and markers of antigen presenting cells.

From a number of studies it seems that interferon-gamma (IFN- γ) might be one of the appropriate candidate-markers for the prediction of BA and allergy. Production of IFN- γ has been used as a potential marker for the postnatal immune maturation processes that are associated with the subsequent risk for development of BA or allergic diseases. Studies on cord blood mononuclear cells have shown that subjects who will develop allergic symptoms have a characteristic pattern of response that includes decreased production of IFN- γ , suggesting a Th2-type predominance.^{27,28} Stern et al found that low IFN- γ production by mitogen-stimulated mononuclear cells at the age of 9 months was associated with an increased risk of wheezing between 2 and 13 years.²⁹ Guerra et al reported that low IFN- γ production at 3 months of age was associated with recurrent wheeze in the first year of life.³⁰

Björkstén et al showed that interleukin-4 (IL-4) production by peripheral blood mononuclear cells in early life may be predictive of the subsequent development of allergic symptoms.³¹ In another cross-sectional study, no major differences in dendritic cell features were found between children from allergic and nonallergic studies. However, no follow-up for wheezing was performed.³² In a more recent study from Germany, a strong interaction of cord blood adiponectin and history of atopic disease in the mother with respect to the risk of physician reported asthma or obstructive bronchitis was found ($p=0.006$). The authors concluded that in children of mothers with a history of atopy concentrations of adiponectin in cord blood could play an important role in determining risk of wheezing disorders in early childhood.³³

Although the findings of these studies have improved current knowledge on the initial mechanisms and evolution of atopy (eg the prenatal events of atopy), most of these parameters that were studied did not show any reliable association or predictive value, and studies showed conflicting results. The main reasons for screening difficulties in atopic diseases include: 1/ allergic manifestations are usually not present at birth, but usually start during the first years of life, as a consequence of interactions between genetic constitution and environment. 2/ features of allergy can be present in healthy persons (eg positive skin prick tests were found in >10% of healthy children). 3/ so-called symptoms of allergy (asthma, rhinitis, eczema) can be present without the presence of allergy (=patients have negative skin prick tests). 4/ allergy is multi-factorial (a large number of genes involved in allergy have been described), dynamic, unpredictable, and certainly not a constant disease.

Nowadays we still have no reliable predictive marker(s) of allergy, although, in theory, because of its large burden of allergic diseases to society, it would be of value to identify newborns at risk. Furthermore, the effectiveness of specific primary preventive measures is very limited for the newborn at risk (apart from breast feeding and avoidance of passive smoking). Nowadays, the best screening for allergy still is an extensive family history (including questions on childhood of the parents), in combination with an objective assessment of allergy in the parents or siblings using skin prick testing or determination of specific serum IgE.

Conclusion

A reliable screening test in newborns for the subsequent development of BA has not been found yet. This is mainly due to the complexity of BA, which is made up by different types and underlying mechanisms (ie The Asthma Syndrome). However, in different studies, a number of risk factors for BA have been identified, such as: a positive family history of BA, passive smoking (also during pregnancy), prematurity (including pulmonary infections, RDS and BPD), early viral respiratory infections (such as RSV-bronchiolitis), male gender, early lung function abnormalities and atopic constitution. The major risk factor for persistent BA is an underlying allergic constitution. Early symptoms and markers of allergy (ie The Allergic March) and a positive family history for allergy should be considered as important risk factors for the development of asthma. As such, the profile of the newborn at risk to develop BA can be summarized as follows: it is a male, prematurely born infant whose parents suffer from asthma and/or allergy and who smoke. The baby has a dry skin with eczematous patches and develops a severe bronchiolitis early in life for which he had to be admitted to PICU for 1 week.

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