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Vol. 21 No. 3  
May-June 2008

The Journal of Perinatology-Neonatology

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## neonatal INTENSIVE CARE

**Vol. 21 No. 3**  
**May-June 2008**

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## Editorial

### Personal and Political

Politics has been on our collective minds lately, as evidenced by any media you care to look at. Indeed, perhaps at no time in recent memory has politics been so personal. It's true, as someone once said, (either C. Wright Mills or Margaret Sanger), the personal is the political. As such, I invite you to take a look at two news items in this issue, "Rights Unlimited" and "Painful Truth." These news stories could easily disabuse anyone with a notion that politics and politico-ethical issues are somehow beyond the domain of healthcare practitioners involved with neonatology-perinatology.

The first story tackles the outsourcing of wombs, and highlights the underlying assumptions that are used to validate this baby-making tactic. According to Judith Warner of The New York Times, what were once "dystopic fantasies" are now reality, as globalization reaches its furthest consequences with "industrial outsourcing pushed to a nightmarish extreme," whereby the process of childbirth is reduced to making some women "incubators on legs" and "baby-making machines." The article also discusses how modern reproductive technology has aided and abetted the foregoing, laying the groundwork for the notion that every potential parent can get what they want, and that giving birth, like receiving every benefit of lifesaving technology, has become an entitlement, a right – if it can be paid for. As one respondent to Warner's piece noted, "mixed up in this is the advances made by modern medicine," and another noted that the first world was simply "outsourcing the pain" of not being able to have a child.

And pain is what leads into our second item, the politicized battle over fetal pain. The subject of the pain fetuses feel (or don't feel) has also been hijacked by politicians with particular agendas. As Annie Murphy Paul writes in The New York Times, "Over the past four years, anti-abortion groups have turned fetal pain into a new front in their battle to restrict or ban abortion. Anti-abortion politicians have drafted laws requiring doctors to tell patients seeking abortions that a fetus can feel pain and to offer the fetus anesthesia; such legislation has already passed in five states."

Research on fetal pain has been used to pass recent laws forbidding intact dilation and extraction. Testimony by expert neonatologists, Annie Murphy Paul writes, "has helped clear the way for legislation aimed specifically at fetal pain," with the repeated introduction of the Unborn Child Pain Awareness Act, which "requires doctors to tell women seeking abortions at 20 weeks or later that their fetuses can feel pain and to offer anesthesia." Similar bills have been introduced in 25 states, and have become law in five. As a joke, a website has put up an editorial purporting to promote an addenda to the aforementioned act, which urged lawmakers to provide legal protection to fetuses "subjected to repeated, violent maternal uterine contraction and then forced through the unimaginably narrow vaginal canal." And the joke was taken seriously by some.

What does this have to do with neonatal/perinatal caregivers? Both wombs for sale and the arguments about fetal pain have to do with political incursions on the personal, the former on the global level, the latter on the national. Both issues have to do with so-called "rights" and governmental approaches to these rights. How long is it until political agendas drive basic NICU decision-making? In fact, aren't neonatal/perinatal care decisions already driven to a great extent by economic considerations that are part and parcel of a global super-capitalism that apportions care on the basis of profit and loss? Of course they are. In fact, the de-facto politicization of neonatal care has already arrived.

Les Plesko, Editor



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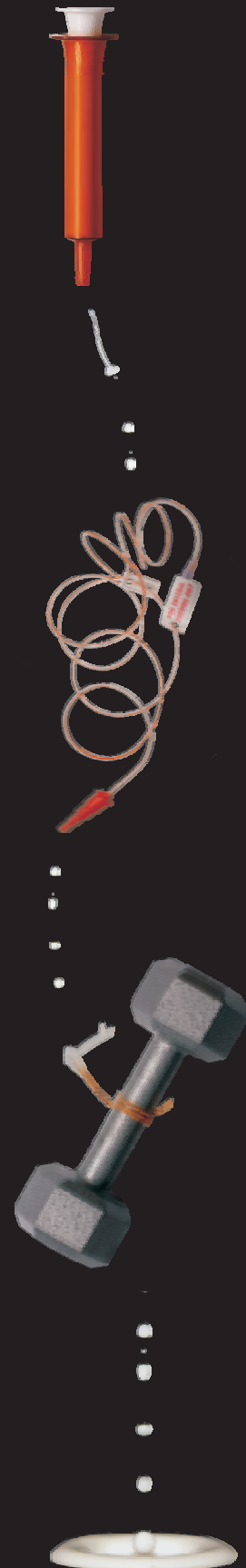
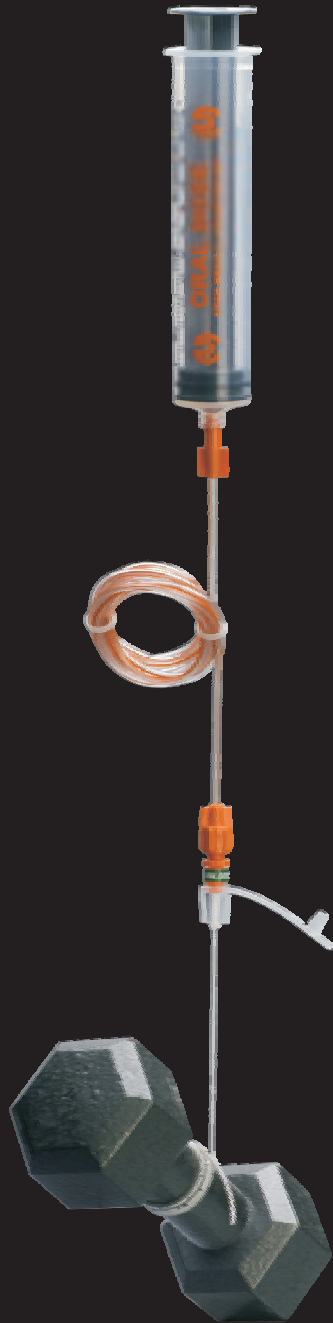
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# News

□ May-June 2008

## LETTER

I couldn't agree more with your observations. [See our editorial in the March/April Issue, A Message to a Multiple Birth Mother.] As an old NICU nurse, I used to frequently pose the question, "Are we *really* doing these families any favors?" These babies may be able to get home, but what happens on their first day of school? Are they able to perform at the same level as their peers? Thank you for saying what so many think but are afraid to say.

*Shelley Buchanan, RN, BSN, Director, Physician Relations, Mercy Hospital  
Clermont, Ohio*

## SHORT PEOPLE HAVE NO REASON...

The BBC reports that boys who are short at birth have double the risk of attempting suicide as adults even if their growth catches up in childhood, a study suggests. Those under 18.5 inches were found to be at highest risk. Swedish researchers at the Karolinska Institute noted that poor fetal growth may have long-term effects on brain chemistry and said more should be done to help pregnant women and babies who were at risk. The researchers looked at national data on male births between 1973 and 1980 and at suicide attempts up until 1999. The shortest babies were compared to those with an average length of 20 inches. There were 759 violent suicide attempts—defined as hanging, using a gun or a knife jumping from heights or in front of a vehicle or drowning, among the whole group. The link between birth length and suicide risk was strongest, but a birthweight of under 2,500 g was also linked to an increasing risk of suicide attempts. The study also found men who were normal length babies, but who were short in adult life, were 56% more likely than tall men to attempt to take their own lives. Low levels of the brain chemical serotonin, which have been linked to aggression and suicidal behavior could be the key, the researchers say, or perhaps maternal drug and alcohol use. But really, who knows?

## KEEP YOUR PANTS ON

The BBC reports that babies fathered by teenagers are more likely to be unhealthy at birth, a study suggests. The age of the mother has been linked to birth problems, but the researchers do not know why a younger dad might have an impact. Specialists from the UK said that teenage fathers were generally less affluent, and might offer less emotional support to their partner. The study comprised 2.6 million mothers, aged between 20 and 29 when they gave birth, and fathers divided into age groups, so that the babies of teenage dads could be compared with those fathered by older men. Men aged 20 and upwards did not show any abnormal risk of fathering a child with birth problems. However, the teenagers had a 13% increased chance of a low birthweight baby, a 17% chance of a small baby and a 15% increased chance of having a baby born prematurely. The chances of a baby dying within the first year also increased by 41%. Researchers said they could not rule out a biological difference in younger men which might be contributing, but said there were more obvious societal reasons. One explanation was that older men are simply better able to provide for their pregnant partners than younger fathers.

## THREE FOR ONE

Identical boy triplets were born recently at North Shore University Hospital on Long Island, an event so rare that an obstetrician estimated it might happen just once in 200 million births. The triplets' mother, Allison Penn, was impregnated with just one embryo through in-vitro fertilization. The embryo split in half, and then one half of that split again, he said. It was said to be the first instance in the US in which only

one embryo was used and the woman gave birth to triplets. To help tell them apart, the boys have a dot of maroon nail polish on different fingers. The babies weighed 4 lbs 12 oz, 4 lbs, and 4 lbs, 11 oz. Reported by the Associated Press via CNN. One of the kids had a non-functioning kidney at the time of birth.

## ROCK A BYE

Doctors in Colombia are using hammocks to help care for premature babies. The specially-designed hammocks measure just 50cms in length and are placed in the incubator for the baby to lie on. The team at the hospital in Cartagena, a port on the northern coast of the South American country, first started using the technique two years ago. Pediatricians wanted to find a way of keeping the babies on their backs, which makes it easier for them to breathe. The babies sleep longer which helps their growing and development. The hammocks are also said to help reduce the risk of apnea. Reported by the BBC.

## KICK AND SAVE

BBC News reports that a mother who found she had a tumor while pregnant was saved by her unborn twins' kicking. She developed a tumor but was only diagnosed with cervical cancer when she was taken to hospital with a suspected miscarriage. Doctors found her twins' kicking had dislodged the tumor. The mom, from Cheam, south-west London, refused to undergo chemotherapy and a hysterectomy which would have meant the termination of her twins. She also had a five-year-old son, and said she opted to have her life-saving operation after the twins were born. Doctors at the Royal Marsden Hospital gave Mrs Stepney limited chemotherapy. The twins were delivered by cesarean section 33 weeks into the pregnancy. They were healthy but born without hair because of the cancer treatment. The mother had a hysterectomy four weeks later, and has been given the all-clear. She has been nominated for a Woman of Courage Award by Cancer Research UK.

## SENSITIVE RATS

The BBC reports that premature babies who receive morphine may grow up to be more sensitive to pain, a study on rats suggests. US researchers found rodents given the drug just after birth later needed higher doses of morphine to kill pain than counterparts in a placebo group. Researchers at the University of South Carolina treated newborn rats with morphine injections for the first nine days of life and tested their pain responses a few weeks later. Rats are born so immature that their early development is comparable with that of a premature baby. After nearly six weeks, broadly equivalent to a human becoming a teenager, the morphine rat appeared to be more sensitive to be pain than the rat given the placebo. For instance it withdrew its paws more readily when these were heated with a lamp, and when pain was induced appeared to need more morphine to quell it. Other studies have produced contradictory findings about children and pain. For instance, a Canadian study found that infants who were circumcised without anesthetic appeared more sensitive to pain when given their immunization injections later on than children who had not been circumcised.

## OLDE ENGLISH

The BBC reports that the number of English and Welsh women aged over 40 becoming pregnant is at a record level. The conception rate for the over 40s in England and Wales rose by 6% between 2005 and 2006, and now stands at 12.2 pregnancies per 1,000 women. The overall pregnancy rate rose by 3% over the same period. Teenagers, though, are having fewer babies,

with a slight fall in pregnancies among 13 to 15-year-olds. There were 866,800 conceptions in 2006, a rise of 25,000 from the previous year. The most likely age for motherhood was 25 to 29, with a rate of 129 pregnancies for every 1,000 women in this group. Four out of five women who became pregnant went on to give birth. More than half of the pregnancies happened outside marriage, although the figures only cover those where the parents were unmarried at the time of the birth, and both appeared on the birth certificate. More women are putting off motherhood until their 40s, partly due to advances in fertility techniques.

## TOO MANY

The New York Times reports on the unintended consequences of IVF: too many twins. The rate of twin births has climbed 70% since 1980, to 3.2% of US births. Fertility centers are trying to lower that rate, according to Laurie Tarkan of the Times. Clinics are focusing on transferring fewer embryos and on developing more sophisticated ways to identify the healthiest embryos with the greatest chance of success. The number of IVF cycles in which four or more embryos were transferred has dropped sharply, to 21% in 2004 from 62% in 1996. However, this hasn't made a dent in the twin rate, because docs and patients don't want to go for SET, single embryo transfer, which still accounts for only 8% of transfers. The American Society of Reproductive Medicine is urging women under 35, who make up 44% of IVF cycles, to go for SET. In women older than 37, three to five embryos are still recommended, depending on the woman's age. The obstacle to single embryo transfer is its lower success rate. Since clinics are aiming to transfer one or two embryos, they're looking for the best ones. Previous selection was based on

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visual examination, but now doctors are starting to go beyond using just microscopes. One method now being employed is to leave the embryos sitting for five days, to allow time for chromosomal abnormalities to show up. Meanwhile, researchers are also looking at factors that might make some women more likely to have multiples. Still others are trying preimplant genetic screenings to select healthy embryos. However, this process may damage the embryos. Genomic hybridization is yet another screening method, which provides a 60% chance of a live birth, by assessing all 23 pairs of chromosomes. However, this method also results in a 60% twin rate. Meanwhile, many women don't care and don't mind having twins, according to anecdotal evidence, even given a more risky pregnancy and delivery. The Times article says that women are trusting improvements to take care of problems associated with twins. As Tarkan notes, "Many people just see the adorable twins cooing in the double strollers crisscrossing Central Park—not the ones that do not make it out of neonatal intensive care." Finally, Tarkan adds that the biggest obstacle to reducing twins due to IVF treatments are not medical, but lack of insurance coverage, and pressure from patients.

## OF TWO MINDS

Women who endure severe stress early in pregnancy may be more likely to have children who go on to develop schizophrenia, according to research by the University of Manchester, which looked at data from 1.38 million Danish births occurring between 1973 and 1995. The risk of schizophrenia and related disorders was around 67% greater among the offspring of women who lost a relative during their first trimester. The findings appear to confirm the theory that a mother's psychological state can have a profound influence on her unborn baby. Previous research has linked stress in pregnancy to a raised risk of low birth weight and prematurity. Some studies have also suggested that the abnormalities in brain structure and function that are associated with schizophrenia may begin to form in the earliest stages of development. However, the researchers found no evidence that a loss of a relative at any other time during the pregnancy, or in the six months leading up to a pregnancy, had any effect on the unborn baby. In addition, the association between bereavement and schizophrenia risk only appeared significant for people without a family history of mental illness. The researchers suggest that chemicals released by the mother's brain in response to stress may have a direct impact on the fetus's developing brain. These effects may be strongest in early pregnancy, when protective barriers between the mother and fetus are not fully constructed. They add that the risk of schizophrenia is likely to be influenced by other factors, such as genes.

## RIGHTS UNLIMITED?

Judith Warner, writing in the New York Times, quotes a woman who has enlisted the use of a surrogate mother from India to bear her child: "The legal issues in the United States are complicated, having to do with that the surrogate mother still has legal rights to that child until they sign over their parental rights at the time of the delivery. Of course, and there's the factor of costs. For some couples in the United States surrogacy can reach up to \$80,000... You have no idea if your surrogate mother is smoking, drinking alcohol, doing drugs. You don't know what she's doing. You have a third-party agency as a mediator between the two of you, but there's no one policing her in the sense that you don't know what's going on." A surrogate said, "From the money I earn as a surrogate mother, I

can buy a house... It's not possible for my husband to earn more as he's not educated and only earns \$50 a month." Surrogacy, or "wombs for rent," is a \$445-million-a-year business right out of "Brave New World," Warner writes, or "Handmaid's Tale." But Warner notes that the topic, and the act, banned in many countries, is "murky, ambiguous and confused... perhaps as it should be... The confusion, at least, acknowledges that there is more to the process of carrying a baby and giving birth to it than being an incubator on legs. It acknowledges that there are physiological and psychological factors that bind a mother and baby together at birth and a violence — perhaps temporary, perhaps not—that is done to each of them if you sever that unique bond." While it is a caveat (at least in France, where surrogacy is outlawed), that the human body "is not lent out, is not rented out, is not sold," Warner notes that "our rules of decency seem to differ when the women in question are living in abject poverty, half a world away. Then, selling one's body for money is not degrading but empowering. And the transaction is not outsourcing of the basest nature—not modern-day wet-nursing taken to the nth degree—but a good deal for everyone concerned." Warner goes on to say, "Being infertile when you deeply desire a baby is one of those heartbreaking, life-altering trials that an outsider to the experience cannot begin to appreciate... What is not being questioned here is the assumption held in the western world that a woman has *the right* to have a child. This supposedly god-given or "natural" biological destiny then renders rational debate on the lengths some women (and their partners) will go to obtain their child, invalid." But, she says, this so-called right doesn't speak to the "rights" of the child, or the surrogate. Warner says, "It is always difficult to come to terms with the fact that you may not be able to have something you really want, and believe you have the right to have." One respondent to Warner's article noted, "if the surrogate develops preeclampsia, gestational diabetes or other life threatening condition, or is to be discovered carrying a child with birth defects, what assurance can she have that her needs and the needs of the child will be met? What's to keep the waiting "parents" from abandoning the situation and leaving her in a far worse position than when she began?" Another respondent wrote, "A woman who has to pay someone to have her child because they are so desperate to be a "mother" needs a therapist. If a woman cannot physically give birth to a child she does one of two things. Accept it and move on with her life, or adopt a child." Of course the foregoing has implications for the limits of neonatal care, and the "right" to the latest technologies that attempt to sustain life at the limits of viability. See our editorial in this issue. (Quotes and information in this article are from The New York Times, "Outsourced Wombs," by Judith Warner, January 3, 2008.)

## GERM-FRIENDLY

New research commissioned by the National Institute for Health Research's Health Technology Assessment program is investigating whether giving premature babies so-called "friendly bacteria" (probiotics) decreases the risk of bacterial infections. There is evidence that probiotics may reduce the incidence of necrotising enterocolitis. They are also thought to reduce the chance of infection, but there is limited evidence to support this. The research team, from Queen Mary, University of London, is assessing the effectiveness of giving 1,300 preterm babies a few drops of liquid containing probiotics daily. This multi-center trial will measure the number of infections, growth rate, use of antibiotics and length of stay of the babies given probiotics, compared with a placebo group; it will also confirm



whether or not their use is associated with a reduction of NEC. The study is among the first funded by the HTA program as a result of a special call for research proposals in the area of medicines for children.

## TOO CHEWY

HIV can be transmitted to infants through food that is pre-chewed by an HIV-positive parent or caregiver, according to the CDC. According to the New York Times, pre-chewing food most often occurs in developing countries, where commercially prepared infant food and blenders are not available and caregivers need to soften food before giving it to an infant. The practice is rare in the US. The virus is transmitted in blood in the saliva of HIV-positive people who have inflammations or sores in their mouths through cuts associated with teething in the infants' mouths. Previous studies have linked pre-chewing to the spread of other infections such as *Helicobacter pylori*, which causes stomach ailments, and streptococcal pharyngitis, which causes sore throats. Three cases of HIV transmitted through pre-chewing have been identified in the US since 1993. In at least two, the infants' mothers were HIV-positive and had bleeding gums or mouth sores while they were pre-chewing food for their children. The researchers ruled out other possible transmission modes, such as blood transfusions or breastfeeding, in all three cases. In two of the cases, genetic studies of the infants' viruses matched those of their mothers, according to the Times.

## PAINFUL TRUTH

The New York Times Magazine recently examined different views about fetal pain among medical experts, lawmakers and advocates, as well as how such views have affected abortion policy. The Times reported that recent research suggests fetuses can feel pain beginning at about 20 weeks' gestation. However, a 2005 review of 2,000 medical journal articles that involved fetal pain studies found that fetuses do not have the capacity to feel pain until about 29 to 30 weeks' gestation. Some researchers believe that fetal responses interpreted as pain are just reflexes to the fetus' environment. Still other researchers believe that pain is not inherent at birth but is learned during an infant's first year. Antiabortion groups have cited fetal pain in their efforts to restrict or ban abortion. Based on medical testimony, courts have ruled that it is impossible to determine whether a fetus suffers pain "as humans suffer pain." However, based on some studies, legislation has been introduced that would require physicians to tell women seeking abortions at 20 weeks' gestation or later that their fetuses could feel pain and offer to deliver anesthesia directly to the "pain-capable unborn child." Abortion-rights opponents note that the research backing up claims to fetal pain is dubious, and anesthesia researchers have added that abortion clinics do not have the necessary equipment to administer anesthesia to fetuses. Doctors have noted that providing fetal anesthesia during abortions would be an experimental procedure that could carry health risks for the woman, including infection and bleeding. The article in the New York Times, by Annie Murphy Paul, is called, "The First Ache," and was published in the February 10 issue. Here are some highlights from the article: Even as some research suggests that fetuses can feel pain as preterm babies do, other evidence indicates that they are anatomically, biochemically and psychologically distinct from babies in ways that make the experience of pain unlikely. However, research showed that fetuses as young as 18 weeks react to an invasive procedure with a spike in stress hormones and a shunting of blood flow

toward the brain—a strategy, also seen in infants and adults, to protect a vital organ from threat. The most invasive procedure is open fetal surgery, in which the uterus is cut open and the fetus exposed. [In one case, when] the surgeon lowered his scalpel to the 25-week-old fetus, [he] saw the tiny figure recoil in what looked like pain. The doctor said he tremendously upped the dose of anesthetic to make sure that wouldn't happen again. In the more than 200 operations he assisted in since then, not a single fetus has drawn back from the knife. "I don't care how primitive the reaction is, it's still a human reaction," he said. But whether pain is being felt is open to question. An anesthesiologist who participated at the first open fetal transplantation in 1981 said he doesn't believe that fetal pain exists. Research persuaded him that before a point relatively late in pregnancy, the fetus is unable to perceive pain: "I have every reason to want to believe that the fetus feels pain, that I've been treating pain all these years... but if you look at the evidence, it's hard to conclude that that's true." This claim was based on collecting more than 2,000 articles from medical journals, with evidence for and against fetal pain. He concluded that pain perception probably does not function before the third trimester, because the fetus's higher pain pathways are not yet fully developed and functional before that time. But what about a fetus that draws back at the touch of a scalpel? He says it's a reflex movement, like a leg that jerks when tapped by a doc's rubber mallet. He added that the release of stress hormones doesn't necessarily indicate the experience of pain and that such a release occurs even for brain-dead patients during organ harvesting: in order for pain to be felt, the pain signal must be able to travel from receptors located all over the body, to the spinal cord, up through the brain's thalamus and finally into the cerebral cortex. Naturally, others disagreed, and said that the subplate zone may process pain signals instead. The zone is a "holding station" for developing nerve cells. Researchers have noted that babies with hydranencephaly are clearly cognizant and conscious, with all the attendant physiologic responses. In any event, in the fetus, some say, we can't deduce the presence or absence of consciousness from its anatomical development alone; we must also consider the peculiar environment in which fetuses live. For instance, biochemicals produced by the placenta and fetus have a sedating and even an anesthetizing effect on the fetus. Even the starts and kicks felt by a pregnant woman may well be reflex movements that go on in a fetus's sleep. While it's not known if the intense stimulation of surgery would wake it up, when faced with other potential threats, like an acute shortage of oxygen, the fetus does not rouse itself but rather shuts down more completely in an attempt to conserve energy and promote survival. In that sense, these doctors note, a fetus is not a baby who just hasn't been born yet. Finally, the article in the Times notes that the arguments about fetal pain or lack thereof, while certainly not new, are now being applied to arguments about abortion, and thus politicized, as has the opinion of pro-pain researchers. (The summary of the article appeared in a different form in Medical News Today. The highlights from the article appeared in a different form in The New York Times and has been extensively edited by Neonatal Intensive Care.)

## CLAMPING DOWN

A team at the University of Leeds has discovered a way of diagnosing preeclampsia and say they are within five years of developing a user-friendly diagnostic kit which could be used in hospitals to safely and speedily test all pregnant women. The team distinguished between pregnant women who are healthy

and those with preeclampsia by studying samples of their blood plasma taken at the same time as routine blood samples. Researchers used a technique which is based on the same science as MRI scans but which operates on fluids taken from the body, to identify chemicals in the blood plasma of pregnant women. The concentration of certain chemicals such as amino acids and fat in the body has been found to vary in a way which is dependent on the health of the woman. Some of these chemicals increase in concentration when the woman is suffering from preeclampsia, while others decrease. If an early prognostic tool was to become available, doctors and midwives could focus their attention and resources on caring for those more likely to develop the condition and instigate methods of prevention.

## **BIGGER AND FATTER**

A copyrighted article in Medical News Today by Anna Sophia McKenney, revealed that mothers given multiple micronutrient supplementation tend to give birth to children who are bigger and heavier, in contrast to mothers given just iron and folic acid supplementation, according to researchers at the Institute of Child Health, London. A randomized controlled trial compared 1,200 women given either IFA (a control) or MMN, a supplement with the recommended daily value of 15 vitamins and minerals, during the second and third trimesters of pregnancy. A previous study showed that the birth weight of children born to mothers given MMN was on average 77g heavier than those born to mothers given only IFA. The latest study focused on the follow up of 917 of the children born in the first study. At an average age of 2.5 years, 455 of these children had been born of mothers in the IFA group, while 462 children were in the MMN group. A comparison of the sizes and weights of these children found that children of MMN mothers still weighed more, an average of 10.9 kg, while those of IFA mothers had a mean 10.7 kg. This indicates 204 g discrepancy between the two. The children of MMN were generally bigger, with a mean head circumference of 2.4 mm larger, a mean chest circumference 3.2 mm larger, a mean mid-upper arm circumference of 2.4 mm larger, and mean triceps skinfold thickness 2.0 mm larger than those born of IFA mothers. MMN children had a mean systolic blood pressure that was 2.5 mmHg lower than the IFA children.

## **NOT SO FAST**

The UK's Daily Mail recently reported that men over 60 have healthier babies than teen fathers, and the news was quickly picked up by other media sources (including us). Not so fast! Analysis of the study on which the stories were based revealed that older fathers were not compared directly with their teenage counterparts, but that all groups, young and old, were compared to an age group 20 to 29 years of age. This age group was used as a reference point, since it's been shown to have the lowest risk of adverse birth outcomes. This was also the age group of all the mothers and therefore contained most of the pregnancies where the moms and dads were of the similar ages. When the comparison between teenage fathers and the reference group was made, the researchers found a small difference in birth outcomes, some perhaps biological, others possibly socioeconomic or lifestyle-related. When all's said and done, it's likely these factors, not necessarily the father's age, that account for the differences noted in the popular press, especially insofar as none of the differences in adverse birth outcomes between older fathers and the 20 to 29-year-old reference group were statistically significant.

## **AND STOP BREATHING, TOO**

Pregnant women should avoid caffeine, according to researchers who found that even moderate consumption in early pregnancy raises the miscarriage risk. A study in the American Journal of Obstetrics and Gynecology study found that more than 200 mg of caffeine a day doubled the risk. The study noted that it was unclear if pregnant women needed to avoid caffeine in later pregnancy. For the latest research, Kaiser studied 1,063 recently-pregnant women and asked them to provide a detailed diary about their caffeine intake up to their 20th week of pregnancy. They compared this information with how many of the women had miscarried by 20 weeks gestation. Compared with non-drinkers, women who consumed up to 200 mg of caffeine a day had an increased risk of miscarriage of 15% versus 12%. For women who drank more than 200mg, the risk increased to 25%. The increased risk appeared to be related to the caffeine itself, rather than other coffee ingredients because other caffeinated beverages such as tea and hot chocolate showed a similar trend to coffee. Caffeine is able to cross the placenta to the fetus.

## **DRUNK MONKEYS**

A new study on monkeys has found that moderate exposure to alcohol and stress during pregnancy can lead to sensitivity to touch in the monkeys' babies. In human children, sensitivity to touch is one of a number of characteristics of the approximately 5% of children who over-respond to sensory information. The study, conducted by researchers at the University of Wisconsin-Madison, involved 38 5 to 7 year old rhesus monkeys born to mothers who either drank a moderate dose of alcohol every day during their pregnancies, were exposed to a mild 10-minute stressor during their pregnancies, drank a moderate amount of alcohol and were exposed to the stressor during their pregnancies, or were unstressed teetotalers. A moderate dose of alcohol for the monkeys was defined as the equivalent of two drinks a day for a human. Researchers rated the monkeys' offspring according to how they responded to repeated touch with a feather, a cotton ball, and a stiff brush. They found that monkeys whose mothers had not been stressed or consumed alcohol got used to touch over time, while monkeys whose mothers had been stressed grew more disturbed. Monkeys who had been exposed to alcohol prenatally were disturbed by touch more than monkeys who had not been. Using PET, the researchers found that the monkeys' sensitivities to touch were related to changes in dopamine in the striatum.

## **FEAR OF BIRTH**

BJOG reports on the social and psychological indications which lead to a fear of childbirth among first-time mothers. Denmark researchers studied 30,480 healthy women expecting a single child between 1997 and 2003, with interviews conducted at the 16th and 32nd week of pregnancy. At both interviews, women were asked if they feared the impending childbirth. Researchers found that the fear of childbirth in women is relatively consistent throughout. The overall frequency of fear was experienced in 7.6% of women at interview one and 7.4% at interview two, while 3.2% reported fear at both interviews. The social factors contributing to this fear were: the lack of a social network, having an unskilled job, being a smoker, young age and unemployment. Women were five times more likely to fear childbirth if they reported experiencing feelings of anxiety and twice more likely to fear childbirth if they had symptoms of depression. Researchers noted that the fear of childbirth should not be mistaken for the fear of the pain during childbirth since

the former is a psychological fear. Therefore, the fear of childbirth cannot be resolved through the offer of an epidural. To reference the full study, see Fear of childbirth: predictors and temporal changes among nulliparous women in the Danish National Birth Cohort, Laursen M, Hedegaard M, Johansen C., BJOG 2008;115:354-360.

## THEY'RE AGAINST IT

ACOG has reiterated its long-standing opposition to home births. The group says that while childbirth is a normal physiologic process that most women experience without problems, monitoring of both the woman and the fetus during labor and delivery in a hospital or accredited birthing center is essential because complications can arise with little or no warning even among women with low-risk pregnancies. ACOG acknowledges a woman's right to make informed decisions regarding her delivery and to have a choice in choosing her healthcare provider, but it doesn't support programs that advocate for, or individuals who provide, home births. Nor does ACOG support the provision of care by midwives who are not certified by the American College of Nurse-Midwives (ACNM) or the American Midwifery Certification Board (AMCB). The organization noted, "Childbirth decisions should not be dictated or influenced by what's fashionable, trendy, or the latest cause célèbre. Despite the rosy picture painted by home birth advocates, a seemingly normal labor and delivery can quickly become life-threatening for both the mother and baby. Attempting a vaginal birth after cesarean at home is especially dangerous because if the uterus ruptures during labor, both the mother and baby face an emergency situation with potentially catastrophic consequences, including death. Unless a woman is in a hospital, an accredited freestanding birthing center, or a birthing center within a hospital complex, with physicians ready to intervene quickly if necessary, she puts herself and her baby's health and life at unnecessary risk." The organization also claimed that there was no such thing as an "ideal" national cesarean rate.

## KEEPING IT SAFE

Minerva Ginecol published a study investigating the effect of variation of the incision-to-delivery interval on neonatal wellbeing during cesarean delivery. In the prospective study, 71 women, hemodynamically stable and without severe comorbidities, underwent an antepartum cesarean delivery. Acid-base status, umbilical arterial oxygen content and Apgar score were used as indicators of neonatal wellbeing. Umbilical cord blood gas, the Apgar score of each neonate, the interval between skin incision and delivery and the interval between hysterotomy and fetal extraction of 71 cesarean deliveries were assessed in a level III University Hospital. Neither variation of skin incision-to-delivery interval nor variation of the interval between hysterotomy and delivery of the fetus was associated with a variation of indicators of neonatal wellbeing. The study concluded: A longer skin incision-to-delivery interval in cesarean birth does not compromise neonatal acid-base balance. Similarly, a longer interval between hysterotomy and delivery of the fetus is not associated with a variation of indicators of neonatal wellbeing. Awareness of this fact could give the surgeon more tranquility and help to prevent part of the iatrogenic complications associated with cesarean delivery. Information is available in abstract form on Pubmed. The study is from Minerva Ginecol. 2008, 2008 Feb;60(1):23-27. Incision-to-delivery interval and neonatal wellbeing during cesarean section. M. Fontanarosa, N. Fontanarosa, Department of

Gynecology, Perinatology and Human Reproduction, University of Florence, Italy.

## PEE-P

Phthalates can be detected in the urine, according to a study of exposure to the chemicals, found in baby care products like shampoo, talc and lotion. The study was carried out by researchers at the University of Washington in Seattle, the CDC and the University of Rochester School of Medicine and Dentistry in New York. The researchers tested the urine of 163 babies born between 2000 and 2005 for 9 phthalate metabolites and correlated the results with information given by their mothers on products that the infants had been exposed to in the 24 hours leading up to the urine sampling. The products included anything applied to the babies' skin such as baby shampoos and lotions. The analysis revealed that: 81 per cent of infants had detectable levels of 7 or more phthalate metabolites in their urine. Exposure to baby lotion was significantly linked to detectable levels of monoethyl phthalate and monomethyl phthalate. Exposure to baby powder was significantly linked to detectable levels of monoisobutyl phthalate. Exposure to baby shampoo was significantly linked to detectable levels of monomethyl phthalate. The more products a baby was exposed to, the more links there were to different phthalates. Most of the links were stronger in babies under 8 months. US manufacturers are not required to show the phthalate content of personal care products on the package or label.

## IVH UPDATE

Pediatr Dev Pathol published findings on Histological Inflammatory Responses in the Placenta and Early Neonatal Brain Injury. The study investigated the relationship between the severity of histological inflammatory responses in the placenta, chorionic plate, and umbilical cord in conjunction with the intra ventricular hemorrhage (IVH) risk in premature infants. Clinical data were prospectively collected for 287 consecutive premature neonates born before 32 completed weeks of gestation, admitted to level III NICU of Pediatric Department of Padua University from January 1999 to December 2004. Placental histology for HCA was graded and scored according to Redline et al. The diagnosis of IVH (grade I to IV) was graded according to Volpe's classification. Among the placentas of the 287 preterm examined infants, 68 (23.6%) were diagnosed with acute HCA. Overall incidence of IVH was 11.8%. Of 68 preterm neonates with HCA, 11 developed IVH (16.1%). Maternal HCA at the higher grades and stages increased the risk of IVH: 7 (64%) of the 11 preterm infant with maternal HCA grade 3 developed IVH (RR; 95% CI 2.05; 1.1-3.6) and 8 (73%) of the 11 preterm neonates with stage 3 developed IVH (RR; 95% CI 1.59; 1.0-2.5), respectively. Conversely, fetal inflammation was not associated with an increased risk of IVH. In conclusion, the IVH risk in preterm infants <32 gestation weeks was found to be significantly associated with severe grade and stage maternal HCA inflammatory scores. The full abstract is available from Pubmed, Pediatr Dev Pathol 2008 Feb 14;1, Histological Inflammatory Responses in the Placenta and Early Neonatal Brain Injury, Zanardo V, Vedovato S, Suppiej A, Trevisanuto D, Migliore M, Chiarelli S.

## BARELY ALIVE

The Journal of Perinatology recently published the study: Infants born at the threshold of viability in relation to neonatal mortality: Colorado, 1991 to 2003. The objective was to determine the contribution of infants born at the threshold of

viability (defined as <750 g birth weight) and the role of regionalization of perinatal care on the neonatal mortality rate in Colorado. Study Researchers performed a retrospective cohort study, evaluating all live births in Colorado from 1991 to 2003, and compared the periods 1991 to 1996 versus 1997 to 2003. The overall unadjusted NMR of the two time periods was 4.3 and 4.4 per 1,000 live births, respectively. The contribution of infants with birth weights <750 g to the overall NMR increased from 45.0 to 54.5%. The odds of death for infants <750 g increased between time periods. However, NMR decreased between time periods for all birth weight categories, until infants <600 g. With respect to regionalization, the number of infants <750 g born in a level III care center increased slightly between the two time periods (69.6 versus 73.3%); however, adjusted analysis showed no difference in the practice of regionalization between time periods. Regardless of time period, infants who weighed <750 g born in a level III center had 60% lower mortality risk when compared to <750 g infants born in a non-level III center. The authors concluded that despite advances in neonatal medicine, the overall NMR in the state of Colorado remained unchanged between the time periods of 1991 to 1996 and 1997 to 2003. The authors stated that “infants at the threshold of viability continue to have a large impact on the Colorado NMR, making up a larger proportion of overall neonatal deaths. While the results demonstrate that the risk of mortality is significantly reduced for <750 g infants born in a level III center, the practice of regionalization has not changed between the two time periods. Improved efforts to standardize the referral practices to ensure delivery of <750 g infants in level III centers could potentially reduce the impact of these infants on the NMR. While the overall NMR in Colorado has not changed between the two time periods, the NMR for infants >600 g has significantly decreased, suggesting that the boundary delineating the threshold of viability needs reevaluation, as it may have been pushed lower than previously defined.” Information is from Pubmed, J Perinatol 2008 Feb 14, Infants born at the threshold of viability in relation to neonatal mortality: Colorado, 1991 to 2003, Kamath BD, Box TL, Simpson M, Hernandez JA, Department of Pediatrics, Section of Neonatology, University of Colorado at Denver and Health Sciences Center, Denver, CO.

## TAKE YOUR PICK

Justin Tse of Hamilton Medical writes, in the Hamilton newsletter item, “Oxygen Versus Room Air: A neonatal perspective”—Oxygen has been used throughout history as a means of rescue for thousands of infants after delivery. Francoise Chaussier first used oxygen for newborn infants who failed to breathe at birth in 1780. He also described mouth to mouth resuscitation of infants as well as laryngo-intubation in 1806 (Newborn’s apparent death (1781-1806) through Francois Chaussier’s Work. Stofft, H. Hist Sci Med. 1997 October—December; 31 (3-4): 341-9). Neonatal resuscitation and oxygen use have come a long way since then. Oxygen therapy during neonatal resuscitation has been a source of controversy in regards to the AAP/AHA Neonatal Resuscitation Guidelines. The topic of discussion is focused on what is considered an appropriate initial concentration of oxygen to use during resuscitation of full-term and preterm infants. The latest recommendation from Neonatal Resuscitation Program (NRP) is to provide 100% oxygen for all term infants who require positive pressure ventilation. Even though NRP cannot address all questions regarding the use of oxygen during resuscitation, some options may be considered as alternatives to 100% oxygen:

An initial oxygen concentration at a concentration between 21% and 100% may be used in infants born at term who are cyanotic or require positive pressure ventilation. If the infant doesn’t respond to the initial concentration of oxygen within 90 seconds, use of higher concentrations of oxygen, up to 100% may be considered. If free-flow oxygen fails to produce improvement in an infant with cardiorespiratory depression, positive pressure may be used. By using a self-inflating bag in a situation in which an oxygen blender is not available, the team has three choices: provide room air; provide 90-100% oxygen by attaching a reservoir to the bag; or provide a concentration of approximately 40% oxygen by using the bag without a reservoir. If supplemental oxygen is unavailable, room air can be used to deliver positive-pressure ventilation. Oxygen blenders and pulse oximeters are being utilized more in the delivery room. Jay Goldsmith MD, FAAP, Co chair of the NRP Steering Committee states, “Hospitals that have medical teams equipped to handle preterm deliveries should now have the ability to blend oxygen in the delivery room.” Research on when oxygen should be utilized and at what concentration is ongoing and will continue to bring controversy to clinicians administering oxygen in the delivery room. “The fact that we’re so motivated by the Apgar score to make babies pink that we probably overuse oxygen, which is in reality a drug with significant side effects” Dr. Goldsmith said (NRP Instructor Update. Vol 16 No 2 Fall/Winter 2007).

## PRODUCTS

### KEEPING ABREAST

Medela has launched a new global website featuring more breastfeeding information and better tools, that caters to the individual. With a presence in more than 90 countries, Medela’s global landing page, medela.com, offers visitors a map of five different regions around the world, which will help them find the Medela website for their home country. Visitors from the US should click on the icon over the Americas, which will take them to medela.us. There, they can choose between the company’s “breastfeeding” segment, which focuses on solutions for breastfeeding moms and lactation professionals, or the “healthcare” segment, which focuses on suction equipment. Once visitors click “breastfeeding,” they’ll have the option to set this as their landing page for future visits. Medela’s breastfeeding site, medelabreastfeedingus.com, has an easy-to-use design, with audience-specific navigation for expectant mothers, nursing moms, professionals, and sales accounts. Each section’s content is customized. For instance, a childbirth educator or lactation consultant can access tools, research, legislation and event information to provide a higher quality of care, while a salesperson can print instruction manuals for clients. The site’s product selector tool helps moms find information and products to breastfeed successfully, and allows moms and professionals to compare pumps, their characteristics, and accessories. The site showcases new online discussion communities, as well. Contact medela.com.

### CLINICAL CASE STUDIES

Masimo, the inventor of Pulse CO-Oximetry and Measure-Through Motion and Low Perfusion pulse oximetry, reported that multiple clinical studies demonstrating the accuracy and clinical effectiveness of the Masimo Rainbow SET platform were highlighted to over 8,000 anesthesiologists at the 14th World Congress of Anesthesiology (WCA) in Cape Town, South



Africa. In addition, WCA attendees were able to preview noninvasive total hemoglobin (SpHb) and oxygen content (SpOC) as part of the Rainbow SET platform (pending FDA clearance). **Continuous Noninvasive Measurement of Hemoglobin via Pulse CO-Oximetry**, presented a study that compared an engineering prototype of Masimo Rainbow SET noninvasive total hemoglobin (SpHb) to invasive laboratory hemoglobin measurements. **New Pulse Oximetry Sensors with Low Saturation Accuracy Claims**, performed by Dr Peter Cox at the Hospital for Sick Children in Toronto, Canada, evaluated 12 patients with congenital cyanotic cardiac lesions (CCCL) to compare noninvasive oxyhemoglobin (SpO<sub>2</sub>) measurements from the Masimo Rainbow SET Radical 7 device with Blue Sensor and the Covidien N-600 device (OxiMax with Lo-Sat) to invasive oxyhemoglobin levels from laboratory CO-Oximetry. Study results demonstrate that the Masimo Blue sensor, which was “designed for use specifically in this patient population, is more accurate,” according to the presenter. **Severe Methemoglobinemia Detected by Pulse CO-Oximetry in the Operating Room**, a case report by Dr Steven J. Barker and Dr E. H. Annabi at the University of Arizona in Tucson, Arizona, documented the use of Masimo noninvasive methemoglobin (SpMet) to accurately diagnose a severe case of drug-induced methemoglobinemia and subsequently monitor and guide the patient’s treatment and recovery. Masimo also previewed, for the first time, continuous noninvasive total hemoglobin (SpHb) and oxygen content (SpOC) as part of the Rainbow SET platform during WCA’s commercial exhibition. Contact [masimo.com](http://masimo.com).

## FASTER

The neonatal ICU at St Michael’s Hospital, Bristol (part of the United Bristol Healthcare NHS Trust) has recently purchased a RapidLab1265 Blood Gas analyser from Siemens Healthcare Diagnostics to provide comprehensive critical care testing parameters in an accurate and timely manner. The RapidLab 1265 is a high volume, low-maintenance whole blood analyser that offers blood gas, electrolyte, metabolite and full co-oximetry analyses from a single sample. It delivers accurate results in 60 seconds or less, allowing medical staff to make critical decisions at the earliest opportunity.

## PATENTED

Vapotherm announced today that US patent rights have been validated for an apparatus used in the delivery tube technology for respiratory tract therapy. Reinforcing Vapotherm’s principal role in the industry, the US Patent No. 7,314,046 B2 has been granted through 2022 and provides Vapotherm the right to prevent or exclude other companies from making, using, selling, or offering to sell or import the invention. The triple lumen design is the vital component for Vapotherm products as it helps deliver humidified air to the respiratory tract of patients. Used throughout all Vapotherm products, including the 2000i and the recently introduced Precision Flow, the apparatus allows Vapotherm to maintain the conditioned breathing gases to the patient and thus aid with respiratory tract therapy and treatment. The company’s patient delivery circuit design is unique in the field in that it provides for the delivery of optimally conditioned breathing gases all the way to the patient, whereas conventional approaches can result in significant temperature and humidity loss. Contact [vtherm.com](http://vtherm.com).

## SOUND MONITORING

Sonicu announced the first fully networked and integrated

sound monitoring and advisory system for the NICU and other environments where excessive noise levels are a problem. The Sonicu system has its roots in the hospital industry, and was designed in response to evolving standards for noise monitoring and control in NICUs. Studies have shown that babies in the NICU experience physical and developmental stresses when exposed to excessive noise. Implementing the Sonicu system allows NICU staff to monitor and control noise levels; consequently, babies get more rest which enhances their development and recovery timelines. The most visible component of the system is a three-tiered “Sound Level Indicator” device, which can be mounted in a variety of positions. The device displays red, yellow or green signals to provide a visual representation of measured sound levels. A green illumination indicates measured sound level is within acceptable parameters. The yellow cautionary light notifies that sound is approaching an excessive decibel level. If the sound level exceeds the programmable excessive decibel limit, the red signal illuminates. The new Sound Level Indicators are graduated in height to assure excessive noise (red zone) indication is given greater visual emphasis. One available option even enables overhead lighting in the noisy area to automatically dim, warning parents, family and hospital staff of excessive noise levels. System graphics indicating sound levels and alarm status changes can be viewed by any hospital networked PC having authorized access to the system. The same graphical interface enables parameter changing through the network, as well as real time trending graphs and printouts for unbiased feedback to those causing programmed levels to be exceeded. Contact [sonicu.net](http://sonicu.net).

## READY FOR TAKEOFF

eVent Medical received FDA 510K clearance for its Heliox gas delivery by its Inspiration ventilator system. Heliox administration has been available on the Inspiration ventilator outside the US since 2006, and now the therapy will be provided to US customers. There have been a number of peer-reviewed medical publications demonstrating the utility of eVent’s Heliox delivery system on the Inspiration ventilator. Researchers have found the Inspiration ventilator—with its patented, compact block design—greatly reduces the consumption of Heliox when compared to other currently marketed older ventilator designs. The Inspiration does not have a bleed system that can waste large amounts of the gas even before it is delivered to the patient. Other studies have noted that the volume accuracy was maintained while using the sensor at the wye. With its expanding US and Canadian sales force, eVent Medical will begin marketing the Inspiration throughout the US with a focus on the pediatric areas that have the highest need for Heliox with asthmatic patients, and this will complement eVent’s dedicated Infant platform for the neonatal population of low birth weight babies. This new capability allows eVent Medical, a division of Kobayashi Medical America LLC, to further its mission of providing innovation and value to the clinical community. eVent Medical markets the Inspiration line of adult through neonatal ventilators with the most aggressive warranty and preventative maintenance programs in the industry—the Inspiration is truly recognized for its lowest cost of maintenance. Contact [event-medical.com](http://event-medical.com).

## SET FOR SAN FRAN

Masimo announced the completion of UCSF Medical Center’s system-wide implementation of Masimo SET pulse oximetry and the Masimo Rainbow SET technology platform, establishing

UCSF Medical Center as the first hospital to implement Masimo Rainbow SET capabilities system-wide. Initially, UCSF Medical Center performed an extensive pulse oximetry comparison and found that Masimo SET obtained accurate and reliable oxygen saturation measurements under difficult conditions. UCSF clinicians also utilized new Masimo Rainbow SET technology to noninvasively and continuously measure physiologic and hemodynamic components that were previously only available by invasive tests. As a result, UCSF decided to expand the adoption of Masimo technologies beyond pulse oximetry to include the noninvasive patient monitoring capabilities of the Masimo Rainbow SET technology platform. Masimo SET provides continuous, accurate oxygen saturation measurements that reflect a patient's true status, even during low perfusion and motion. The new noninvasive measurement capabilities allow for more precise and timely diagnosis and treatment. From becoming the first in the world to successfully perform surgery on a baby still in the womb to developing life-saving treatments for premature infants whose lungs aren't fully developed, UCSF is now pioneering the application of new noninvasive measurements enabled by the Masimo Rainbow SET technology platform to help advance the care they deliver.

## BLOOD TEST

Masimo announced the debut of its breakthrough technology for noninvasive and continuous total hemoglobin (SpHb) and oxygen content (SpOC) monitoring at the World Congress of Anesthesiology in Cape Town, South Africa. The advent of noninvasive total hemoglobin within the Masimo Rainbow SET platform will make hemoglobin testing more convenient and broadly available to medical personnel in both the acute and outpatient settings—the measurement is instantaneous and pain-free. Prior to Masimo Rainbow SET, invasive and time-consuming lab tests were the only methods available to determine total hemoglobin levels which provided delayed and intermittent data. Masimo expects to make SpHb and SpOC shipments to select customers for clinical use in the second half of 2008, pending regulatory clearances. There is a 510(k) pending for SpHb and SpOC in the US. The Masimo Rainbow SET technology platform will provide clinicians with access to real-time trending and tracking of a patient's total hemoglobin status enabling quick identifications of anemia, or blood loss. A simple upgrade to most Masimo Radical pulse oximeters is all that will be necessary to transform an existing monitor to Masimo Rainbow SET performance—enabling integration of noninvasive total hemoglobin monitoring into any clinical setting. Contact [masimo.com](http://masimo.com).

## INTO INFINITY

Draeger recently unveiled the newly improved Infinity Omega solution, now with a widescreen. This integrated two-screen patient monitoring solution, consisting of a full-function patient monitor, is also capable of supporting patient transport. Its 20" medical-grade touchscreen bedside computer brings IT applications to the point of care. Infinity Omega displays real-time monitoring and ventilation data together with networked data—such as lab results, DICOM/X-ray images, and patient/anesthesia data management system information—and allows control of monitoring functions from either screen. The Infinity Omega solution integrates an Infinity Delta series patient monitor and docking station with an Infinity C700 for IT workstation and Infinity Explorer software. The Infinity Delta monitor provides continuous monitoring at the bedside and on transport, while the patented Infinity Docking Station provides

power, network connectivity and departmental screen configuration data. The Infinity C700 displays integrated patient data at the bedside on a 20" wide touchscreen display. Infinity Explorer software enables two-way communication between the Delta and the Infinity C700, bridging the gap between patient monitors and the IT infrastructure of the hospital. Through the Infinity Network, patient information gathered at the bedside can be viewed simultaneously at the Infinity CentralStation, which gathers and displays information from Infinity bedside and telemetry monitors for up to 32 patients. This data includes alarms, real-time waveforms and parameters, laboratory values, and respiratory and ventilator information. Clinical applications in the Infinity CentralStation—such as Full and Event Disclosure, ST Segment Analysis, and 12-Lead Rest ECG Analysis and Trend Display—enhance patient care management by providing rapid assessment, decision support and clinical reporting. In addition, information from the Infinity CentralStation can be viewed remotely via the hospital network through Draeger's innovative remote viewing applications. Contact [draeger.com](http://draeger.com).

## GOOD STOREY

Vapotherm announced that its President & CEO, Robert Storey earned Maryland's 2008 International Business Leadership Award from the World Trade Center Institute (WTICI). Storey was one of seven winners selected by the WTICI for exceptional business leadership, determination, and creative strategy in international business. Established in 1989, WTICI is the region's premier private sector international business partner. Vapotherm, Inc is a privately held manufacturer of respiratory care devices for hospitals and homecare, based in Stevensville, MD. The company is dedicated to the development of innovative, noninvasive technologies for respiratory therapy, especially for the treatment of chronic lung and acute breathing disorders. For more information, visit [vtherm.com](http://vtherm.com).

## GET SMART

Draeger Medical, Inc announced its SmartCare/PS option for the EvitaXL ventilator has received market clearance for additional product claims from the FDA.<sup>1</sup> Introduced in November 2005, SmartCare is a knowledge-based ventilation system developed to improve the efficiency and effectiveness of the weaning process for hemodynamically and neurologically stable patients without severe COPD. SmartCare can help reduce patient intensive care days as well as ventilator days by integrating protocolized care into automated ventilation weaning. The newly cleared claims for SmartCare address clinical and efficiency benefits in ventilator therapy, including time reduction: reduced overall ventilation time by 33%; decreases ICU length of stay by up to 20%, reduced weaning duration by up to 40%.<sup>2</sup> By reducing weaning time and potential associated complications and infections, SmartCare may lead to reductions in the cost of care, improved resource utilization, and decreased incidence of ventilator morbidity. This includes potential medical results such as: increased efficiency and improved therapy; reduced ventilator induced injuries and complications; decreased potential for infections; avoiding re-intubation; increasing quality of outcomes; 100% weaning protocol compliance. SmartCare automates the weaning process, based on the user's input, using continuously measured parameters and patient respiratory profiles. As the level of ventilator support is adjusted automatically, the patient's response and ability to adapt to each change in support is evaluated. Traditional methods of weaning vary greatly, do not

always progress with the patient's ability to wean, and are labor-intensive for hospital staff. Unlike these intermittent processes, SmartCare continuously monitors the patient, interprets the data, and adjusts the level of ventilator in two- or five-minute intervals. "Literature suggests that a significant amount of clinicians' time is spent in attempts to wean patients off ventilator support," said Ed Coombs, RRT, Critical Care and Ventilation, Draeger Medical, Inc.<sup>3</sup> "SmartCare is a reengineering of the weaning process through automation of accepted clinical protocols. It is a tool that extends the clinician's ability to make necessary adjustments required to progress care of the weaning patient. By simply observing, adapting and maintaining the patient, SmartCare provides the potential to improve outcome while decreasing cost." References: 1. Lellouche F. et al, A Multicenter Randomized Trial of Computer-driven Protocolized Weaning from Mechanical Ventilation. American Journal of Respiratory Critical Care Med, Vol. 174. pp 894-900, 2006. 2. These results are based on a European Multi-center Randomized Trial with 144 patients demonstrating improved respiratory condition, with stable hemodynamic and neurologic status, and no ARDS prior to initiating weaning. 3. Esteban A, Alia I, Ibanez J, et al. Modes of mechanical ventilation and weaning. Chest 1994; 106:1188-1193. Contact draeger.com.

## THUMBSUCKER

Children's Medical Ventures, a subsidiary of Respironics, Inc, has announced the introduction of a newly designed version of its Wee Thumbie preemie pacifier which is used by healthcare professionals for VLBW babies in the NICU. The new, more economical design, which incorporates a soft silicone nipple and a rigid guard, makes the pacifier less obtrusive and allows space for oral and nasal tubing. It meets all of the Consumer Product Safety Commission's requirements for pacifiers and is the only pacifier available for newborns under 30 weeks gestation. The Wee Thumbie is modeled after the size and shape of a preemie's thumb and facilitates the important sucking behaviors normally learned in utero. Its uniquely-shaped nipple helps to keep the pacifier in the baby's mouth and its smaller-sized perioral guard keeps the pacifier centered. Wee Thumbie is available in purple and aqua, and is part of the Calming, Soothing and Feeding line of products from Children's Medical Ventures that includes Sweet-Ease and the NICU Soothie, Super Soothie, Wee Soothie and WubbaNub pacifiers. Contact childmed.com.

## EXECUTIVE PROFILE

### SECHRIST

#### **Describe your product(s) and its unique features.**

The Sechrist Millennium is a very easy to use, reliable, infant/pediatric ventilator that is offered at a very affordable price.

#### **How does your product directly affect patient care?**

Sechrist ventilators have been providing neonatal life support for 30 years.

#### **What sets your product apart from others in the field?**

Sechrist ventilators are known for their ease of use, reliability and cost effectiveness.

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

Sechrist ventilators have always been very intuitive and easy to use, and educational information is available on our website along with 24 hour technical support is also available. Technical and Clinical Specialist are available along with CD tutorials, manuals and service training at the factory.

#### **Discuss the international scope of your testing/marketing/development efforts.**

We have a network of international distributors and users who we regularly speak with and visit to gather feedback on current products and future needs.

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

Our attendance at conferences and seminars provides opportunities to demonstrate our products as well as gather input for product development.

# Enhancing the Safety of Medical Suction

Patricia Carroll, RN, BC, CEN, RRT, MS

## Abstract

Medical suctioning is essential for patient care. However, few clinicians receive training on the principles of physics that govern the safe use of medical suction. While all eight manufacturers of vacuum regulators sold in North America require occlusion of the tube before setting or changing vacuum levels, anecdotal evidence reveals that clinicians are not aware of this requirement or skip this step when pressed for time. This white paper summarizes the physics relating to medical suction, the consequences of damaged mucosa, the risks to patient safety when suction levels are not properly set and regulated, and technology advances that enhance patient safety.

Medical suction is an essential part of clinical practice. Since the 1920s, it has been used to empty the stomach, and in the 1950s, airway suction levels were first regulated for safety. Today, medical suction is used for newly born babies and seniors, and in patients weighing between 500 grams and 500 pounds. Medical suction clears the airway, empties the stomach, decompresses the chest, and keeps the operative field clear. It is essential that clinicians have reliable equipment that is accurate and easy to use.

## Why a safety mindset is important

The current focus on patient safety extends to suction procedures and routines. When suction pressures are too high, mucosal damage occurs, both in the airway<sup>1</sup> and in the stomach. If too much negative pressure is applied through a chest tube, lung tissue can be drawn into the eyelets of a thoracic catheter.<sup>2</sup> Researchers are examining the connection between airway mucosal damage and ventilator-associated pneumonia. In pediatrics, airway suction catheters are inserted to a pre-measured length that avoids letting the suction catheter come in contact with the tracheal mucosa distal to the endotracheal tube.<sup>3</sup> Mucosal damage can also be mitigated with appropriate suction techniques, and every effort should be made to reduce this insult to the immune system of patients who are already compromised. Damaged airway mucosa releases nutrients that support bacterial growth,<sup>4</sup> and *P. aeruginosa* and other organisms are drawn to damaged epithelium.<sup>5,6</sup> Mucosal damage

in the stomach can result in bleeding and anemia as well as formation of scar tissue.

## Physics of suction

Flow rate is the term used to describe how fast air, fluid, or secretions are removed from the patient. Ideally, clinicians need the best flow rate out of a vacuum system at the lowest negative pressure. Three main factors affect the flow rate of a suction system:

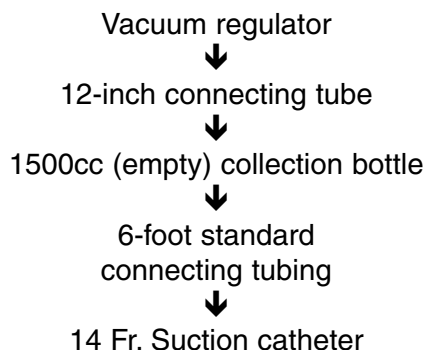
- The amount of negative pressure (vacuum)
- The resistance of the suction system
- The viscosity of the matter being removed

The negative pressure used establishes the pressure gradient that will move air, fluid, or secretions. Materials will move from an area of higher pressure in the patient to an area of lower pressure in the suction apparatus. The resistance of the system is determined primarily by the most narrow part of the system—typically, a tubing connector—but the length of tubing in the system can increase resistance as well. Watery fluid such as blood will move through the suction system much more quickly than thick substances such as sputum. At one time, it was thought that instilling normal saline into an artificial airway would thin secretions, enhancing the flow of secretions out of the airway. However, research shows no thinning occurs and the patients' oxygenation drops with saline installation. Thus, the practice should be abandoned.<sup>7,8</sup>

Increasing the internal diameter of suction tubing or catheters will increase flow better than increasing the negative pressure or shortening the length of the tube. However, in most clinical applications the size of the patient will be the key factor determining the size of the catheter that can be safely used. Researchers at the Madigan Army Medical Center explored factors affecting evacuation of the oral pharynx for emergency airway management. They tested three substances—90 mL of water, activated charcoal, and Progresso vegetable soup—with the three different suction systems, progressing from a standard 0.25-inch internal diameter to a 0.625-inch internal diameter at its most restrictive point. All systems evacuated water in three seconds. The larger diameter tubing removed the soup 10 seconds faster and the charcoal mixture 40 seconds faster than the traditional systems. The researchers note that this advantage in removing particulate material can speed airway



## Suction System Set-Up



Box 1. Suction System Set-up.

A nurse passing the bedside of an infant in the ICU saw blood inside the tube used for airway suction. After checking the child's condition, it was evident that bleeding was not expected. Further investigation determined the maximum level of negative pressure set on the wall regulator was -200mmHg; far more than recommended suction levels for infants. The nurse performing the suctioning did not occlude the tubing to set a safe maximum level of negative pressure. *(personal communication to Ohio Medical Corporation)*

Box 2. Case study.

management and reduce the risk or minimize the complications from aspiration.<sup>9,10,11</sup>

### Occlude to set for safety

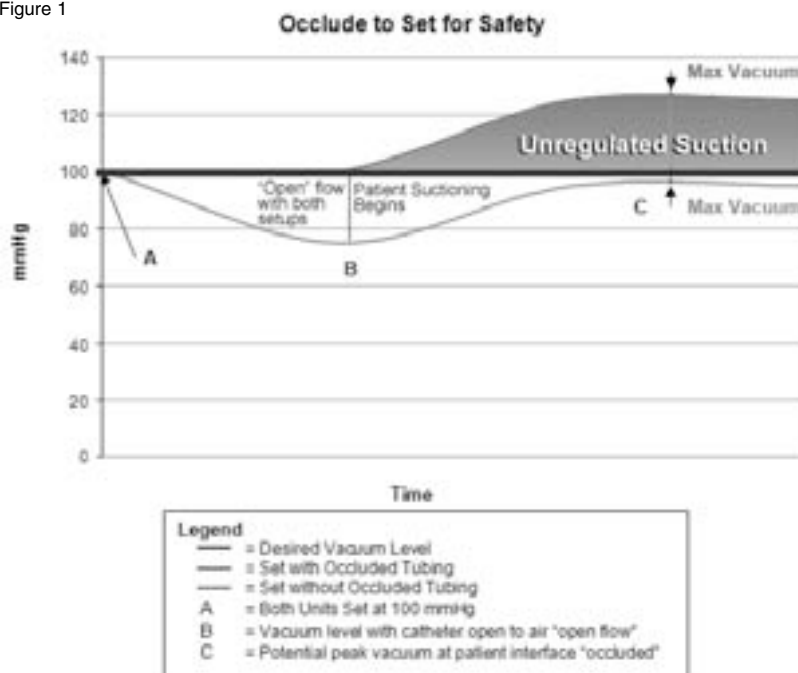
Vacuum regulators are ever-present in the hospital setting. Clinicians use them daily and may not be as attentive to this equipment with the demands of monitors and devices alarming and competing for the clinician's attention and time. Few clinicians learn the finer points of setting up suction systems. A nursing fundamentals text published in 2007<sup>12</sup> does not specify critical elements except to tell the nurse to follow manufacturers' instructions. The text leaves out the critical, universal "occlude to set" step that is recommended by all eight manufacturers of vacuum regulators used in North America.

While a number of organizations have published guidelines, ultimately the clinicians must determine the maximum allowable level of negative pressure that can be applied to the

patient. This is determined by a number of factors: where the suction pressure is applied (airway, stomach, oral pharynx, pleural space, operative field), the age and size of the patient, the susceptibility for mucosal or other tissue damage, and the risks associated with removing air during the suction procedure.

Once the maximum level has been determined, the vacuum regulator must be adjusted so that the maximum pressure is locked in; that is, the regulator must be set correctly so it will not permit a higher pressure to be transmitted to the patient. With traditional technology, the clinicians must actively occlude the system by either pinching the suction tubing closed, or occluding the nipple adaptor (where the tubing is attached) with the finger. Once the system is occluded, the regulator is set to the maximum desired pressure; then the occlusion is released. If the system is not occluded during set-up, the maximum pressure is then unregulated and can spike to harmful levels (see Figure 1 and Box 2).

Figure 1



Suctioning is a dynamic process. As catheters are used to remove substances from the body, the degree of open flow continually changes based on the fill of the catheter and the viscosity of the substance being removed. Under these dynamic conditions, the regulator continually compensates by adjusting flow rate within the device and the tubing to maintain the desired negative pressure. Periodically, mucus plugs or particulate matter will occlude the patient tube. If the system was not occluded to establish the maximum safe pressure at set-up, pressure will spike to clear the occlusion, and once the occlusion passes, the patient will be subjected to potentially dangerous, unregulated vacuum pressures (see Figure 1).

Figure 1 illustrates results of a bench test of two suction systems. The systems were set-up identically as noted in Box 1. The desired maximum level of suction is 100 mmHg (A). One system was set at 100 mmHg with the system open to flow (red line); the other was set by occluding the system to set 100 mmHg (green line). During open flow, the “occlude to set” system will have a lower pressure than the desired maximum pressure because there are no occlusions in the system (B). Once suctioning begins, a dynamic flow condition occurs with varying levels of obstruction, and pressure rises within both systems. The point of maximum suction is key. In the “occlude to set” system, the pressure never rises above the desired maximum pressure of 100 mmHg. In the other system, pressure in this bench test spiked to 125 mmHg of unregulated suction. Without “occlude to set,” the pressure can rise to 25% higher than the desired maximum level or more, exposing the patient to a safety hazard when regulated suction is needed.

Higher negative pressure is a particular hazard for patients with friable mucosa in the airway or stomach, making it more susceptible to traumatic tears. It is also a hazard for infants who have small lung volumes. When all other variables are stable, a 25% increase in negative pressure will increase the amount of air pulled through the system by 25%. That increase could result in a significant loss of lung volume in intubated neonates and infants.<sup>13</sup>

### Breakthrough technologies enhance safety

An ideal patient safety device removes clinician variables as much as possible by providing the added safety passively while the clinician carries out the procedure. Traditionally, the optimal safety of regulated vacuum pressure has depended on the clinicians’ action to occlude the system to set maximum pressure. Now a breakthrough technology from Ohio Medical Corporation in its new Intermittent Suction Unit (ISU), occludes the system automatically when the clinician adjusts the pressure level. This creates a highly effective, passive safety system that removes the clinician variable and protects the patient from unintended, unregulated pressure spikes during suction procedures. The “push to set” innovation assures the clinician that the patient will not be subjected to pressure higher than that set on the regulator.

Another key safety aspect of any vacuum regulator is the ability to quickly adjust to full vacuum mode when emergency strikes and rapid evacuation is essential. An additionally unique concept introduced by Ohio Medical is the dual-spring design of the regulating module contained within the vacuum regulator. This feature provides the clinician with the ability to control vacuum levels more precisely in the clinical range of 0-200 mmHg as well as the ability to achieve full vacuum when

needed with only 2 turns of the knob on the regulator. In other regulators, six or more knob turns are needed to achieve “full vacuum,” and “full vacuum” capability may be limited to the clinical range, not the full system vacuum provided by the Ohio Medical ISU. Since full vacuum is needed in emergency conditions, this enhanced responsiveness saves time when seconds are critical.

While vacuum regulators are often considered basic equipment in the hospital, research and innovation from Ohio Medical Corporation has shown vacuum regulators do have a role in enhancing patient safety in clinical settings. Clinicians should advocate for technology that provides passive safety protection, enhanced control of vacuum pressures, rapid response and ease of use – all of which contribute to a culture of safety around the patient.

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# DuoPAP: Advantages in Neonatal Ventilation

Melissa Turner, BA, RRT; Paul Garbarini, MS, RRT

To say the least, mechanical ventilation in neonates is a very delicate art. Pressure ventilation is the standard most commonly employed mode for neonates. Among the different pressure modes, PC-SIMV is now the most common modality of pressure ventilation in neonates (as opposed to pressure limited/time cycled modes on older generation infant ventilators).

Another mode of ventilation available to this patient population is DuoPAP. DuoPAP is a form of pressure ventilation that is designed to support spontaneous breathing on two alternating levels of CPAP (note, other manufacturers call this mode “Bilevel,” or “APRV”). The higher CPAP level is referred to as  $P_{\text{high}}$  (pressure high), and the lower level is the PEEP/CPAP level (may also be referred to as  $P_{\text{low}}$ -pressure low). This mode allows both mandatory and spontaneous breaths. The spontaneous breaths can occur during any phase of the respiratory cycle. DuoPAP may be set to mimic PC-SIMV: The clinician sets a  $P_{\text{high}}$  setting, which would be the same as setting the pressure control level in PC-SIMV, except the  $P_{\text{high}}$  setting is in relation to atmospheric pressure, and is not PEEP compensated. Next, the clinician would set a  $T_{\text{high}}$  (time high) setting, which should be adjusted to the amount of time that is desired for  $P_{\text{high}}$  to be maintained. This is comparable to setting an I-time in conventional modes. Rate should be set to the number of mandatory breaths desired. PEEP/CPAP should be set to maintain adequate functional residual capacity (FRC), oxygenation and minimize work of breathing (WOB). Pressure support (PS) should be set to desired level for any triggered breaths above the set rate. The pressure support target is set in relation to PEEP, not atmospheric pressure, and therefore is PEEP compensated.

So DuoPAP is very similar to PC-SIMV, but has added advantages. One advantage is the use of an active exhalation valve. The use of an active exhalation valve allows spontaneous breathing at any time during the breath cycle. Allowing the patient to breathe spontaneously at any time during the breath cycle can potentially minimize any dyssynchrony that may occur. For example, I-time is set by the clinician, therefore fixed. However, patient I-time may be variable. In PC-SIMV, when the ventilator's I-time and patient's I-time are not the same, dyssynchrony occurs, accompanied by an increase in WOB. With

DuoPAP, if  $T_{\text{high}}$  and the patient's I-time are not the same, the patient may exhale at any time due to use of the active exhalation valve. Therefore, the patient remains more comfortable and WOB is minimized. Conversely, because DuoPAP is a pressure mode of ventilation, the neonate can demand more flow at anytime during inspiration (as with all pressure modes of ventilation).

Using DuoPAP for neonatal ventilation achieves the same goals as PC-SIMV with the potential added benefits of increased patient comfort and synchrony, and decreased WOB. Since DuoPAP promotes synchrony, there is less fighting at the patient-ventilator interface, and caloric expenditure may be less. Plateau pressures can be maintained within a safe range, since setting a  $P_{\text{high}}$  bleeds off any pressure higher than the set pressure. Clinicians may also find that there are fewer peak pressure alarms when using this mode.

Weaning using DuoPAP is done in the same fashion as PC-SIMV, but can go one step farther. Once the set rate is down to a minimal level (it can be set as low as 1 in the DuoPAP mode), and  $P_{\text{high}}$  and PEEP/CPAP are set to the same level, the patient is essentially on CPAP without the clinician having to change modes.

DuoPAP can be an attractive alternative to PC-SIMV for ventilating neonates. The same goals can be achieved as in PC-SIMV, while the benefits are potentially greater. DuoPAP allows for the maintenance of safe plateau pressures. An active exhalation valve allows for better patient-ventilator synchrony, greater patient comfort, and decreased WOB. And DuoPAP allows the neonate to transition easily from fully supported ventilation through weaning and extubation.

*Editorial note from the authors: Alas, more mode confusion. Let's look at this according to Chatburn's classification of ventilator modes. APRV, DuoPAP and BILEVEL are all simply PC-IMV with the addition of an “active” exhalation valve. The only difference is the timing variables in that the clinician can choose (depending on ventilator manufacturer). Inspiratory time is constant (set) whereas expiratory time is constant (set) or a rate is set, in which case expiratory time will change as the rate setting changes. Another way of saying this is that the clinician can choose to set a fixed I:E ratio for mandatory breaths or let the I:E ratio vary depending on the clinical goals.*

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The authors are with Hamilton Medical; reprinted from Hamilton's newsletter.

# Munchausen Syndrome in Pregnancy

Michael Eshaghian, MD; Boris M. Petrikovsky, MD, PhD; Amir Ansari, MD

Uterine contraction monitoring, in spite of controversy, is widely used to detect pre-term labor.<sup>1-3</sup> Detecting regular uterine contractions often leads to such medical interventions as the tocolytic agents, IV hydration, etc.<sup>4</sup> We report a series of three cases where the external tachodynamometer was manipulated by the patients to have the appearance of regular uterine contractions.

## Case 1

An 18 year old unmarried G2P1 was admitted to the labor and delivery unit complaining of regular uterine contractions and frequent urination. History disclosed that the patient's two-year-old son had been physically abused by her boyfriend, requiring hospitalization until two days prior to her admission to the hospital because of alleged uterine contractions. At the time of her admission, she was living in a home for battered women under an assumed name, and her son had been placed under foster care. She also had a court appearance date against her partner for both physical abuse and paternity testing on her unborn baby as well as her two-year-old son. She admitted smoking three to four cigarettes per day during this pregnancy but denied alcohol or drug abuse. While on external monitor, tracing appeared suspicious and it was observed that the patient was tensing her abdomen pretending to have uterine contractions. (Fig 1) Further repeated pelvic examination detected no changes in the cervix, remaining long, non-effaced and closed. Therefore, monitoring was discontinued and patient was informed that she was not in true labor.

Counseling was provided by social service and she was discharged. The remainder of her pregnancy was uneventful and a healthy baby was born at full term.

## Case 2

A 33 year old G2P1 at 31 weeks of pregnancy was seen in the emergency room complaining of leakage of amniotic fluid and uterine contractions. Upon examination, her cervix was long

and closed and testing for nitrozone and fern were negative. She was placed on uterine monitoring.

Tracing appeared suspicious (Fig2) and it was observed that the patient performed valsalva maneuvers every two to three minutes to imitate regular uterine contractions. Patient social history was unremarkable. Patient was discharged but was readmitted twice with similar findings. She was eventually delivered uneventfully at term.

## Case 3

A 28 year old G3PO admitted to labor and delivery unit at 26 weeks of gestation complained of uterine "tightening." Evidently, she was admitted at 24 and 25 weeks of gestations at two different hospitals with similar symptom. She was given assurance of no impending delivery and was discharged only to be readmitted at 31 weeks of pregnancy complaining of leaking amniotic fluid and a negative fern and nitrozone test. Alpha-fetoprotein test was negative as well. Tachodynamometer monitoring gave the appearance of persistent uterine contractions. However, upon observation, voluntarily tightening of the abdomen was noted. She was discharged but readmitted one more time with presumed diagnosis of pre-term labor requiring discharge soon after. She finally had full term delivery per vagina.

## Discussion

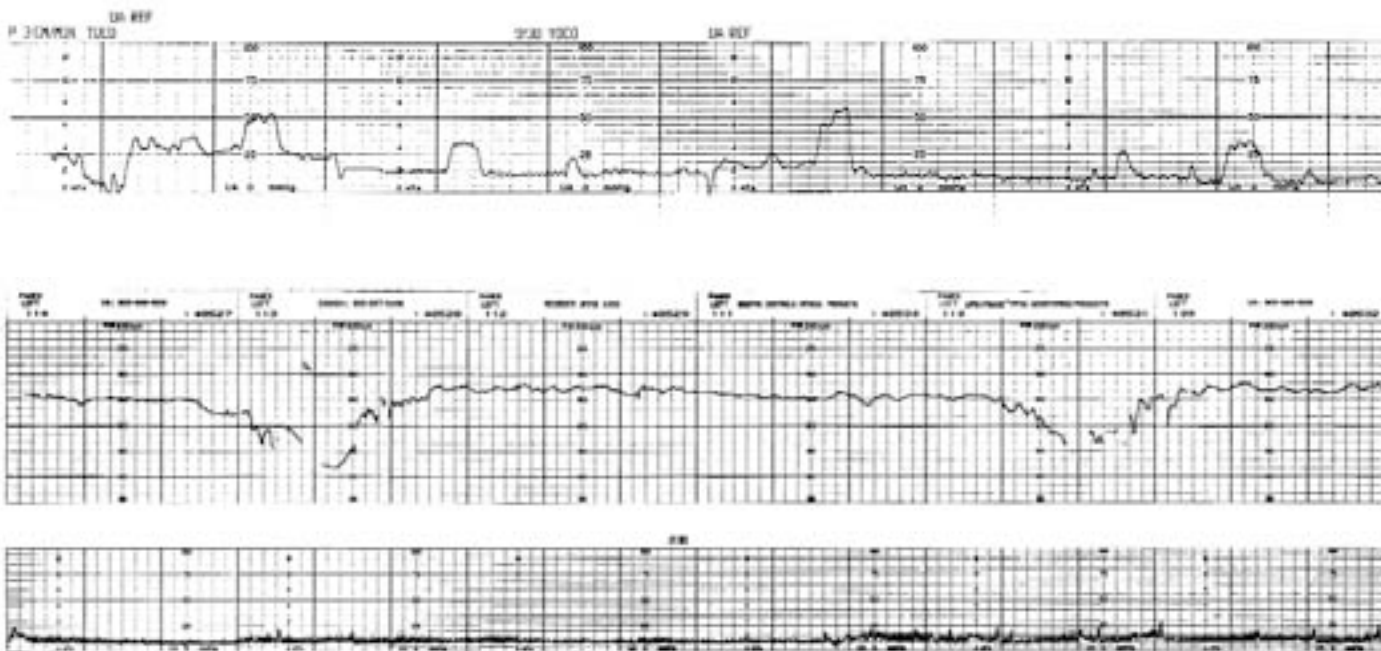
From the first descriptions of Munchausen's syndrome by Asher,<sup>5</sup> the following features have been included in the clinical manifestation; (a) presentation of somatic organic or psychiatric symptoms backed by dramatic (albeit plausible) past history but not substantiated by testing; (b) evidence of surreptitious interference with diagnostic procedures and /or self-inflicted wounds; (c) willingness to undergo extensive physical examination and such invasive procedures as major surgery; (d) concealment of prior admissions to other hospitals, in some or other cities, states, or provinces, using alias's name; (e) evasiveness and truculence when confronted and abusive when faced with hospital discharge; and (f) apparent absence of motive.

Our case series had some of the descriptive symptoms of Munchausen syndrome. Reported by majority of cases of

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Munchausen syndrome are female patients who visit the emergency room, complaining of acute episodes of vaginal bleeding, severe hyperemesis, factitious contractions, and seizures. Lee & Lau<sup>8</sup> described a case similar to ours, where the patient was able to produce contraction-like patterns by increasing abdominal pressure. On the basis of clinical picture (abdominal rigidity) uterine contractions as recorded by external tachodynamometer, an emergency cesarean section was performed with a presumptive diagnosis of abrupt placenta. A premature baby boy weighing 1380 grams was delivered who did well subsequently. In reevaluating the symptoms and tachodynamometer recording, these authors concluded that cesarean section could have been avoided by a more careful evaluation.

In our series of cases, diagnosis of fictitious labor was based on close patient monitoring and findings on vaginal examinations. Accordingly, in the future, suspected cases need to be carefully monitored with a final decision based on the result of cervical examination and detailed abdominal examination assessing to true uterine contractions.

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# Conditions for Parents' Participation in the Care of Their Child in Neonatal Intensive Care – A Field Study

Helena Wiger, Anna-Lena Hellström, Marie Berg

## Abstract

**Background:** To promote participation by parents in the care of their child in neonatal intensive care units (NICU), health professionals need better understanding of what facilitates and what obstructs participation. The aim was to elucidate conditions for parents' participation in the care of their child in NICUs.

**Methods:** A field study with a hermeneutic lifeworld approach was used and data were collected at two NICUs through participative observations and interviews with representatives of management, staff and parents.

**Results:** The results point to a number of contradictions in the way parents were offered the opportunity to participate in neonatal intensive care. Management and staff both had good ambitions to develop ideal care that promoted parent participation. However, the care including the conditions for parental participation was driven by the terms of the staff, routines focusing on the medical-technical care and environment, and budgetary constraints.

**Conclusions:** The result shows that tangible strategies need to be developed in NICUs aimed at optimising conditions for parents to be present and involved in the care of their child.

## Background

It is a major challenge for health care professionals, such as nurses and physicians, to support participation by parents in the care of their child in neonatal intensive care units (NICU), and it raises the central question of how parents are invited to participate in this environment. Parents who have a child in a NICU are vulnerable, they have not yet established a relationship with their child, and their treatment by health care professionals is significant.<sup>1</sup> The mother-child relationship is central to the development of the child,<sup>2-6</sup> but mothers of

children treated in a NICU have been found to feel left out, neither belonging to the maternity ward nor the neonatal unit, a feeling that is still present years afterwards.<sup>7</sup> Research shows that parents who are kept informed and are supported to take an active part in the care of their child in a NICU may gain a feeling of control of the situation, strengthening their parental identity.<sup>1,8,9</sup> The parents appreciate and trust medical competence and have a need to communicate with the staff concerning the care of their child.<sup>10</sup>

Modern care in NICUs is based on parental care of the child when the child is an inpatient. To support this, Swedish mothers and fathers can receive economic compensation for loss of earnings, allowing them to stay in the hospital with their child.<sup>11</sup> A previous study, however, has shown that they have not been offered the right conditions to participate in the care of their child at the NICU. The staff was ambivalent, set limits and dictated conditions for parental participation.<sup>12</sup> The conditions have thus not been in place to meet the standards of the United Nations Children's Convention<sup>13</sup> and the Nordic Association for Sick Children in Hospital,<sup>14</sup> which stress that staff should encourage presence and active participation by parents in the care of their child both day and night. In family-centred care the focus is on parental participation, which means that the parents should follow their child's care and that there should be a partnership between staff and parents.<sup>15-17</sup> Although family-centered and integrated care of the mother and child is more frequent today; it is not common.<sup>18</sup>

In order to promote participation by parents in their child's care, it is therefore necessary to improve understanding of what facilitates and what obstructs this participation. The aim of this study was to elucidate conditions for parents' participation in the care of their child in a NICU. Here, participation includes physical presence as well as active partaking in the child's care.

## Methods

This was a participative, observational study that included interviews with staff and parents. It adopted a hermeneutic lifeworld approach, which offered the researcher a basis from which to analyse the world as experienced and communicated by people. The lifeworld is the everyday world in which we live

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our lives and take all our activities for granted. The research begins with tangible descriptions of lived everyday life experiences:<sup>19</sup> in this study the conditions for parents' participation in the care of their child in neonatal intensive care. The hermeneutic philosophy highlights that being in the world, and its interpretation is the basis of understanding, and language is an essential tool as it gives us access to other people's experiences.<sup>20</sup> hermeneutic lifeworld research requires the researcher to have an open and sensitive attitude to the phenomenon being focus on, and it bridles pre-understanding through a distancing and reflective attitude to new experiences.<sup>19</sup>

**The context:** The study was conducted at two specially selected NICUs: one at a university hospital and one at a regional hospital in a smaller city. Both hospitals were located in the same Swedish region, implying similar political and financial management systems. The NICU at the university hospital admitted seriously ill children from other regional hospitals and had a high throughput of patients, often leading to a high workload. Once a child was in a more stable medical condition, he/she was transferred to another unit. The staff consisted of paediatric nurse assistants, nurses, physicians and administrators. The NICU at the university hospital had 22 beds and a staff of 120, and the local NICU had 15 beds and 60 staff. Common reasons for treating children were prematurity, breath dysfunction and infection. The durations of hospital stays at these two units varied from a few hours to several months, with a mean period of 13 and 8.2 days respectively.

**Ethics:** Permission to perform the study was requested from the heads of the ward, and ethical approval and permission to undertake the study was requested from the Research Ethics Committee. The staff at the two selected NICUs was given verbal and written information about the study, and the interviewed staff and parents were personally informed. All interviewees were assured that participation was voluntary, that all information would be treated confidentially and that the tape-recorded and transcribed interviews would be locked securely in a fireproof place.

**Data collection:** Data were collected over eight months in 2006 through participative observations (O) and interviews with staff and parents. The observations were directed at the phenomenon, i.e., conditions for parents' participation in the care of their child in NICUs, and were included to identify both facilitating and obstructing factors. The observations gave access to interpersonal interaction, and the combination of observations and interviews provided an insider's perspective on the phenomenon in its natural setting.<sup>c.f.19</sup> The data collector (HW) was a paediatric nurse with work experience from NICUs and, together with the results of previous studies,<sup>7,12</sup> this influenced her pre-understanding. The intention, however, was to keep an open mind and to be ready to see, interpret and understanding something new in a new way,<sup>20</sup> and to be aware of the self in relation to the phenomenon being studied<sup>19</sup> through reflection on personal pre-understanding.

The fieldwork was carried out over 64 hours during 22 different working shifts. During the observations, the focus was on the staff's invitation or lack thereof to parents to participate in their child's care. The data collector's role was to become a member of the ward's working team, while at the same time allowing for reduced participation in activities when observations were being made. The data collector did not participate in the

conversations between parent and staff, unless the parents or staff posed direct questions. The observations were carefully described in field notes, and where possible transcribed during the actual observation or directly after it. The next step consisted of reading the field notes, playing back the scenes in the mind and summarising the content as it appeared in its complexity, including personal reflections.

Sometimes observations were supplemented with interviews in order to deepen understanding. A total of thirty-nine interviews were performed: ten with parents (P), six with paediatric nurse assistants (PNA), eight with nurses (N) and fifteen with staff in management positions in the units (M). The management staff consisted of two operational managers, three units managers, two assistant unit managers, two medical officers and six section managers, with between 0.5 and 19 years management experience (Md=6). The participants were asked to reflect as openly as possible on their personal experiences of parental participation. After a situation had been observed, the parents, paediatric nurse assistants and nurses were asked an open question: What was your experience of the situation in the case room? The initial open question in the interviews with the management staff was: Which strategies did you use to facilitate parents' participation in the care of their child in this unit? Attendant questions posed were: Could you explain what you mean? Could you describe it in more detail? The aim of these open questions was to encourage the participants to talk more about and reflect on their experiences.<sup>20</sup> Some interviews with parents, paediatric nurse assistants and nurses were tape-recorded and transcribed word by word and some were carefully described in field notes. All the interviews with the management were tape-recorded and transcribed verbatim to text.

**Analysis:** The analysis was based on texts from the observations and interviews, which were treated as one text based on principles described by Dahlberg et al.<sup>19</sup> It was important that this lifeworld hermeneutic approach did not use any predetermined hypotheses or any theories or other interpretive sources decided upon beforehand. Like all forms of text analyses, the interpretative analysis was a dialogue with the message of the texts<sup>19</sup> and was aimed at finding and comparing meanings. All the text was read openly and critically several times to find the meaning of the phenomenon, the hidden as well as explanations that were not immediately obvious. The analytic phase was thus open and flexible with a distancing, reflective and critical approach. The interpretations of the parts were constantly compared with the interpretation of the whole in order to decide whether there was a discrepancy between the understanding of the parts and the understanding of the whole.<sup>c.f.19,20</sup> Four interpretative themes of the conditions for parents' participation in the care of their child were identified and finally compared and put together in a new way in a "main interpretation" in order to understand further meanings of the phenomenon.

## Results

The four interpretative themes are presented below followed by the main interpretation of the phenomenon "conditions for parents' participation in the care of their child in neonatal intensive care."

### The care environment is dominated by medical technique

Two aspects of the care environment emerged as central, both

of which facilitated and hindered parents' participation in the care of their children. These were the layout of the care rooms with their medical-technical equipment, and the specialization of the care.

Both of the NICUs had two intensive care rooms, one had one light-care room and the other had two. An individual child could be transferred between these two types of rooms depending on the child's state of health. Other important rooms were the parents' rooms where they could stay, sometimes together with their child if the child's condition allowed it. One of the NICUs had enough such parents rooms but the other had only two. "That there are no parents' rooms, you cannot then have such high expectations that they should participate in the care either." (N) This led to a lot of practical problems if the mother was discharged from the maternity ward while the child was still being treated in the NICU. It forced parents to sleep at home and to come to the NICU daily, and it usually led to shorter stays as there were no rooms for the parents to rest and be in on their own. One father who had previously been allowed to stay in a parents' room expressed how it had improved his chances of being present: "It was much better, you were with him more and it was easier to just go in." (P) Neither of the units had joint care rooms where the recently delivered mother and ill child could be cared for together, and both staff and parents expressed a need for this form of care. For a mother who has just given birth, and is sometimes seriously ill, not to have the opportunity to rest in a bed but to be directed to sit on a chair made it more difficult to be parents: "I sat next to my child out of duty because I felt that I was really too tired, I just wanted to be in my bed, I couldn't cope." (P)

The wards were a central part. At one of the units, they were quite spacious, though the technical equipment at each care place took a lot of space. At times it was cramped around the child with parents and staff sharing the space. "There can be 20-25 persons on a ward and there is a lot of equipment and things." (N) The staff made an effort to make a private sphere for the child's family around each care place with screens or curtains that were drawn, but the large number of people going through the ward, like a road junction, prevented the parents from being undisturbed with their children, because even with the curtains drawn or the screens around the care place, the noise could not be shut out. It seemed more stressful than calming for parents to be placed with their child in an environment with constant activity and loud equipment.

The activity on the wards varied with a peak in the morning, but at one of the units the working pace was constantly high with much overcrowding. At times, there was a shortage of staff at both units, which made it difficult for parents to approach the staff. "The problem every time you came was having to find staff; who was looking after my child." (P)

The medical-technical care gave the care environment a special character that signaled the priorities and explained why the parents could feel "in the way" among the equipment and staff that surrounded their child. Nonetheless, the parents seemed to become used to it after a while and they started to act like the staff, such as turning off alarms themselves. Views on whether this type of parent participation was good or bad were divided among the staff. "The parents do a lot, even with the equipment, and that terrifies me. That they pull the cables apart...the first times they are there to care for their child, someone (staff)

might say, 'Yes, you can take out these electrodes.' But that is when the staff is there; the next time the dad might turn off the alarm to the respirator." (N)

The staff showed a high level of competence in emergency and intensive care of the child and appeared to prioritise this type of care over nursing care. "If you are interested in equipment, tubes and leads, that is high status. If you are interested in meeting people, conversation, maybe it hasn't got as high a status." (M) Presence and participation by parents at the NICU was often pointed out as central by staff, but the nature of the care environment made it less important. The medical-technical care had a clear place. This may seem obvious as it supports the survival and recovery of the children, but its profile meant that less obvious nursing care was pushed out, instead of the two being complementary parts of care characterized by a holistic view. As nursing care includes a welcoming approach to the parents of sick children, the interpretation follows that presence and participation by parents was not considered to have as high a priority as the medical-technical aspects of the care.

### **The rounds focus on the medical diagnosis, while the caring needs are disregarded**

The rounds played a central part in the care environment, but here it is presented as a separate theme as it played a very prominent role in the interpretation of conditions for parents' participation in the care of their child. At both units, the round routines reinforced the medical-technical emphasis on care. Every morning, a round was carried out, the time of which was determined by the physicians' other undertakings at the hospital. During the round, the discussion focused on the medical status of the child while its nursing care needs were considered to varying degrees. This might express itself in, for example, the nurse not always having knowledge of or paying attention to the family's social situation, with factors that affected the chances of being near the child. Physician 1 asks: "How are the parents?" The nurse answers: "The father is on sick leave, but the mother is here." Physician 2 interposes: "The father is on long-term sick leave for depression and finds it difficult to care for the children. He can drop off and collect at the daycare centre and be at home alone with the three children for a maximum of 1 ½ hours, so then the mother can be here." The nurse says: "Well, I knew the father was on sick leave, but I didn't know why." (O)

At one of the units, parents were not allowed to be present during the round, even though the management thought it could be positive. The exclusion of parents from the round prevented their participation and created unnecessary worry for them, as expressed by one of the mothers as follows: "At the time of the round, there was a total ban on entering the ward, and then you wonder as a parent why you can't listen when it is a round for your child?" (P) This was in direct contrast to the other unit where the parents were invited and encouraged to take part in the round of their child: "There is much greater consideration for the parents and focus on them participating, so it has improved a lot." (M) Here the parents were seen as a resource as they could contribute valuable information about their child. It also saved the physicians' time as they could contribute valuable information about their child. It also saved the physicians' time as they could inform the parents directly of the medical state and care of their child. This seemed to ease the parents' worries, but they often had a low profile. Sometimes the physicians would ask if they wondered about anything, but

they usually said no. Often the nurse would speak for the parents, for those who were absent as well as those who “were too tired” to ask their questions. The physician’s time for each child and to inform the parents during the round was often very limited. Sometimes parents of other children were on the ward and could hear what was being said, even confidential information. The physician opens the door to the corridor, turns round and asks the mother: “Is there anything else you wonder about?” The mother answers: “No, there isn’t.” The nurse who is standing by the mother says: “But you wondered before whether your child could have a funnel instead of an oxygen mask.” The physician closes the door, goes back to mother and informs her of these two alternatives. (O) After the round, it was usual for the nurse to go round to those parents who had been present and clarify what the physician had said.

At the unit where the parents were not allowed to be present during the round, the parents were not routinely informed afterwards either. This is how one new mother expressed herself: “The nurses you asked referred to the physicians all the time, ‘we’ll see on the round in the morning,’ but as we were never given any information after the round, it was still up in the air all the time.” (P) Naturally, this led to many questions remaining unanswered. Individual parent-physician talks on the state of the child were difficult to arrange at other times, and were often at the parents’ own initiative. One mother who waited for more than a week to talk to a physician said: “I was convinced that someone in neonatal would sit down and talk to me about how it had gone but no one did...then I wouldn’t have had to be down on the maternity ward wondering what was happening and how he was, and I would have been calmer then.” (P) For a parent to have to demand to talk to a physician about the state and treatment of his/her child may seem strange as it is seen as a natural routine and right. At the unit where the parents were welcome to be present during the round of their child, there was greater access to talk to physicians, even though there was no big difference in the density of physicians at the two units to explain the differences between these contrasting routines. “The physicians are here all day, so if you have any questions just make an appointment to talk to them.” (N)

### **Participation is on the terms of the staff and the activity**

The third theme looks at the way the attitude of the staff and the other activities affect the parents’ conditions to participate in the care of their child at the NICU. It was considered professional to look after the individual needs of the parents, and by setting an example to colleagues; participation could be made easier for parents. “I have a responsibility to make sure I tolerate the presence of the parents, showing the others that this is how we should work.” (N) In the many meetings observed between staff and parents, the manner of the staff stood out. There were many examples of how staff listened in and gave support, but unfortunately also shortcomings in flexibility to the parent. The child lies in an incubator and lets out a whimper. The father turns the child, gives him the dummy and holds him with his hands. The child starts to scream and the paediatric nurse assistant comes up to them, looks at the child and says: “Little one should we turn you?” The father replies: “I have just turned him.” The paediatric nurse assistant turns the child without saying anything. (O)

When the parents arrived at the unit for the first time, they were usually received by the staff on the ward at which their child

was cared for. They were informed of the medical condition of their child and the equipment to which their child was connected, given oral and written information about the routines at the unit, encouraged to be with their child whenever they wanted, and invited to take part in the care of their child: “You can come whenever you like and help with all sorts of things, preferably everything; it is your child and although he is in an incubator that is no obstacle, we will help you.” (PNA) None of the units had a routine formal introduction talk despite the parents’ needs and management’s emphasis on the importance of such: “I would like to sit down when I come up, that is, a real introduction talk with the physician and paediatric nurse.” (P) // “I have tried for years for us to have a real introduction talk; it might be the first time you experience parenthood.” (M)

Mothers who had just given birth were usually taken to the unit by the staff from the delivery or maternity ward in a bed or wheelchair due to their medical condition or the distance between the units. Being restricted to going to and leaving the NICU based on staff availability to accompany them stood out as an obstacle to their presence and participation. When parents returned to the NICU, the staff usually took the time to tell them what had happened to their child since they were last there, but there were times when the parents were not given this attention.

“It felt as if I disturbed them when I entered.” (P) // The door opens, a father looks in on the ward and says hello. The paediatric nurse assistant does not return his greeting. He takes the mother into the ward in her wheelchair, she gets out and the wheelchair is parked in a corner. The parents go to the washbasin and wash their hands, sit down with their child and try to make eye contact with the paediatric nurse assistant who does not look in their direction. (O)

The impressions of the invitations and expectations of parents to participate were ambiguous. The parents were often directly involved in feeding their child without even being asked, as shown by the following observation: The parents are with their child for the first time and the child is going to be tube fed. The nurse connects the syringe to the tube and hands it to the father and says: “Maybe Dad would like to hold it?” The father backs off, takes the syringe in his hand and says, “Me? Ok, do I just hold it?” “Yes,” says the nurse and goes off to check the infusion pumps. (O) At other times, there was a lack of clarity and uncertainty among the staff of the extent to which requirements should be expressed to parents, and they did not routinely find out why, for example, a mother who was cared for on the maternity ward was absent for a whole “shift.” There was also a lack of routines for, for example, documenting the presence of parents, which meant that many shifts could pass with no attempt being made to find out the reason for the absence. According to one nurse, the staff ought to be clearer on what was expected such as stressing the importance to a parent who was often absent of being present more of the time and taking part in the child’s care. One explanation for this lack of clarity was a fear of making the parent feel guilty, and the welfare officer was often asked to “solve” this sensitive situation instead: “We have someone who doesn’t have a child already who only comes for one meal a day, but then maybe you have to find out why, if it’s fear or... Then you can bring in the welfare officer to solve it, she can find out a little more on another level.” (N) This conflict of wanting to demand greater parent participation, a lack of routines for documenting the presence



of parents and, at the same time, uncertainty of which demands could be made and how much involvement there should be in the family's social situation became an obstacle to parents' participation in the care of their child.

Parents of children who had been cared for at a NICU for a long time were asked more often how they wanted things to be: "We would like to remove the navel catheter, but if you'd like we can wait with that so you can take her out of the incubator." (O) The parents' wishes could also be ignored by first being invited to participate and then later not being given the opportunity to do so if it did not fit in with the activity. The parents are with their five-day-old child, the mother for the second time, and the paediatric nurse assistant asks them: "Should I show you how to cup feed him and then you can do it yourselves?" She lifts the sleeping child and is about to start feeding him when the round enters the ward. The parents are shown into the corridor and the paediatric nurse assistant cup feeds the child. The child is put to bed, the round finishes and the parents come in. They go to their child and ask: "Is he going to eat?" The paediatric nurse assistant replies: "He has had some, exemplary baby. He ate by himself, really good, it went straight down." The parents go up to the child's bed and lift the cover. The paediatric nurse assistant says: "He is sleeping now, so we'll let him sleep." The parents sit down beside the bed but cannot see their child as the canopy is drawn and leave the unit after a couple of minutes. (O)

Another activity that was adapted to the situation was the physician's discharge examination of the child and discharge talk to the parents, which were normally carried out on the ward. It usually entailed a quick medical examination of the child and a few minutes' talk with the parents. This was often followed by a longer talk with the nurse. The parents seemed to attach greater importance to this discharge talk than the opportunity they were given. One parent who questioned the format expressed the following: "Then a physician came who I had never seen before and carried out a very quick paediatrician's examination, and then he said, 'yes, great, bye,' and then I lost the plot. 'What do you call this, where is the talk,' I said, which made him quite agitated with me, because I thought, 'is this what you call a discharge talk, then I don't know how you work here.'" (P) The fast tempo of the discharge talk can be interpreted as the tasks waiting for the physicians having higher priority than the parents' needs for information and stands out as an obstacle to parent participation.

The professional role of the staff was undergoing change and a consultative role towards the parents was being worked out. "Now the staff are being outmanoeuvred by the parents, going from being an expert to being a consultative adviser and supporter of the parents." (M) There were also question marks about this new role, "The parents have a natural, prominent role, but what is our role?" (N) Parent participation was of benefit to the units. Parents were considered to relieve the staff in their work, support breast-feeding and reduce the duration of the child's care at the NICU as the parents got to know and care for their child better, "...also of economic importance as our parents look after as much as they can." (M) Even if it was considered to be beneficial that the parent took part in the care of their child, the constant presence of parents could be seen as tiring, "...it's the ones who have really been parents to their children who are the tiring ones, because they have sat on a desk chair by their incubator and observed and questioned

when people have done things in different ways with their child, and we have found that really hard work." (M) It may seem like a challenge to find a professional role that is governed by cooperation with the participating parents, and not to see the parents in this "partnership" as competitors in the care of the child.

### **Participation is important, but the economy is the controlling factor**

A fourth theme describes the management's views on the parents' participation in the care of their child at the NICU. There was a high level of awareness of the importance of this and it was central to the goals of the activity, but there were no tangible guidelines as to how this should be done: "We must create the conditions to allow them to participate and that means we must be able to offer the parents the chance to be here." (M) The management saw it as its responsibility to promote an approach to care based on respect for the needs of the parents as well as the work of the staff. One necessary condition of developing neonatal intensive care was considered to be that the different categories of staff worked for the same goal, but in practice this was not the case. One reason was considered to be the difficulty of bringing together all the professional groups: the physician group was often not part of the unit's project. "We miss the physicians in many situations when we discuss department routines or care routines." (M) Another pattern noted by the management was that the staff started from their own needs when discussing care routines and this was believed to prevent the development of care at the NICU. In discussions on basic values at the unit, the staff were given the opportunity to reflect on their approach to parents in a more self-critical way. "Sometimes I have a feeling that we forget we are here for the patient, for the parents, maybe we are more used to thinking about ourselves, putting ourselves first." (M) // "We also have a shared responsibility for driving development at the neonatal unit, and sometimes maybe personal preferences have to take a back seat to the common good." (M) // "It's more about our attitude, we should get into our heads how we should behave and what our policy should be." (M)

One way of getting parents to participate was to offer parental training, of which the management had seen positive effects. The unit nurses then talked to the parents as a group about different subjects such as what it means to be a parent of a child at a NICU. At one of the units, all the parents were invited to participate, while at the other unit only some parents were chosen. The fact that parental training was only offered to selected parents at one of the units may appear to be an expression of the management still not seeing its full value. The management at both units found that the parents who had participated in the activity took greater responsibility or became more active in their child's care.

The management was therefore greatly aware of the importance of drawing up strategies to promote parents' participation in the care of their child at the NICU, but this was subordinate to the primary goal of the activity, which was to adapt the care resources based on the order for care and the economic conditions set by the politicians. This higher goal became an obstacle to developing a care environment in which participation by parents could be improved. "Having a balanced economy is the important thing, as long as patient safety can be guaranteed. We are the implementers, but the politicians who

decide what should be done with the tax payers' money; they represent the people." (M)

### Main interpretation

A main interpretation emerges from the four themes interpreted above on the way conditions are created for parents to participate in the care of their child in neonatal intensive care. This expresses many contradictions regarding visions and goals and the prevailing reality of care. The management and staff both had high ambitions to develop ideal care that promoted parent participation in the care of their child at the NICU. In theory, they knew how they ought to behave, but observations showed that parents had limited opportunities to take the initiative and be active in the care, as individual staff decided, in a professional capacity, whether or not it was appropriate. Nursing care and the development of reliable and supporting relationships with the children's parents took on a secondary role. The lack of space for parents, shortage of staff, and recurrent overcrowding at one of the units made it more difficult for the staff to invite parents to care for their children. The format of the round at one of the units, where the parents were prohibited from being present, and the difficulty of communicating with physicians, conflicted with the invitation by the staff to the parents on their arrival at the NICU to participate in their child's care. Another contradictory aspect was the staff's expectations, on the one hand that parents should be present and participate in their child's care, and on the other their hesitance and insecurity of finding out the reasons for parents' absence. Staff in a management capacity, from section responsibility to operational responsibility at an overall level, expressed that the goal of the activity was to promote presence and participation by parents, and they dealt with this at development and training days etc. This too became a contradiction, as the economic resources were still the deciding force in the development of care at the unit.

### Discussion

All in all, the field study expresses that, in practice, there was no consistent basis of care values to guide participation by parents in the care of their child. The children "belonged" more to the ward than to the parents. This concurs with other studies.<sup>9,12,21,22</sup> At the two NICUs, the dominating medical-technical care was put against the nursing care. Medical technical care was valued more highly; it was usually being carried out first, even in so-called non-emergency situations.

It is nothing new that emergency and intensive care environments have a medical-technical focus and that the advanced medical-technical equipment is visible, separating it from the "ordinary" ward. Another Swedish study has shown that staff at an emergency unit focused on carrying out medically advanced tasks at the expense of nursing care work.<sup>23</sup> One reason may be that it is completely unthinkable, and can also be punishable, to put aside medical-technical care, but the consequences of putting aside nursing care, which includes developing good relations between parents and carers, are more unclear. However, research has shown that the parents' lack of reliable relations in the care of children at the NICU can contribute to uncertain parent identity over a long period.<sup>7</sup>

Parents are responsible for their children's needs for good care being met. According to the Swedish so-called Children and Parents Code, the parent represents the child and has a right and duty to decide on issues concerning the child when it is

cared for in hospital.<sup>24</sup> In order to take this responsibility, however, the parent must be offered sensible conditions, e.g., being able to be with and receive information about the child at the NICU. It may seem strange that the parents at one of the units in the field study accepted being sent out into the corridor during the round, though it can be explained by it being difficult to demand access to a child in a critical situation, as the child requires highly specialised care. The parents were then in a very strong position of dependence on the staff who cared for their sick children, and they needed some kind of invitation to participate from the staff. The responsibility that should be taken by the parent ought to be made clear in a dialogue between the staff and parent.

Our result is similar to other research into parental participation in the paediatric care context, which has concluded that in order to identify and satisfy parents' needs, staff should initiate communication with parents.<sup>25-27</sup> The care of children at the NICU includes support for the child's parent. Staff often has clear ideas about what parents could be involved in and often take parent participation for granted.<sup>26,28</sup> The person who knows most about which kind of support is needed is the parent himself/herself, or to use the words of philosopher Lögstrup<sup>29</sup>: "in order to help another person, we must let the person himself/herself decide what is most helpful," ie, give the parent the opportunity to decide what he/she wishes to participate in.

The managers of the NICUs were unanimous in wanting the staff to operate the care with the participation of parents, and they arranged training days and discussions to raise awareness of the importance of this. For the staff to be aware of how the best care ought to be conveyed, however, and to be partly prevented from giving it due to the layout of the rooms, overcrowding and staff shortage, would probably lead to frustration. The management carries much of the responsibility for this frustration and should work to make the goals of participative parents possible. Being a skillful professional "carer" means having not only medical-technical skills but also nursing skills including creating good relations with parents. However, it emerged from the field studies that the meetings and invitations to the parents to take part in their child's care often failed. In an environment with care focused on the sick newborn child and with parents being faced with the fact that their child needs care at the NICU, the meeting and relationship with the staff is a necessary link between parent and child. The management has a responsibility to create tools that ensure quality of care and include allowing parents to participate in their child's care at the NICU. One way of doing this is to define staff guidelines on working with children's families.<sup>28</sup>

### Methodological reflections

The research process used in this field study showed limitations and strengths. If the researcher is an expert in the area being studied, there is a risk he/she will forget his/her role as an observer and act like a nurse. The opposite can also happen. The study can be influenced by suspiciousness when a researcher coming from the "outside" is not able to understand what it is really all about.<sup>19</sup> The strength of this study, however, was that the first author was familiar specifically with caring and the complex environment in the NICU. Reflections on how this influenced the interpretation were necessary throughout the research process. An awareness of pre-understanding and openness, closeness and distance to the studied phenomenon was of importance and included the uniqueness of people's

lifeworld and the complex environment in which the phenomenon took place. An objective understanding was not possible, but the cooperation between the three authors was an asset to this process,<sup>20</sup> ie to understand more about the meaning of conditions for parents' participation in the care of their child.

## Conclusions

The result of the field study points to a number of contradictions in the way parents are given conditions to take part in neonatal intensive care. The goal of the activity was to promote presence and participation by the parent, but this was subordinate to the economic resources and the individual assessment by the staff of what is practically appropriate. Dominating medical-technical care, a shortage of staff and space for parents also made it more difficult for the staff to involve the parents and there were not tangible strategies to develop optimal conditions for parents to be present and involved. Furthermore, greater knowledge and understanding of the parents' conditions for participating in the NICU can create conditions for tangible measures such as the availability of parents' rooms and joint care of mother and child with the mother's bed next to the child.

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# Breastfeeding, Breast Milk and Viruses

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## Abstract

**Background:** There is seemingly consistent and compelling evidence that there is no association between breastfeeding and breast cancer. An assumption follows that milk borne viruses cannot be associated with human breast cancer. We challenge this evidence because past breastfeeding studies did not determine “exposure” of newborn infants to colostrum and breast milk.

**Methods:** We conducted a prospective review of 100 consecutive births of infants in the same centre to determine the proportion of newborn infants who were “exposed” to colostrum or breast milk, as distinct from being fully breast fed. We also report a review of the breastfeeding practices of mothers of over 87,000 newborn infants in the Australian State of New South Wales.

**Results:** Virtually all (97 of 100) newborn infants in this center were “exposed” to colostrum or breast milk whether or not they were fully breast fed. Between 82.2% to 98.7% of 87,000 newborn infants were “exposed” to colostrum or breast milk.

**Conclusion:** In some Western communities there is near universal exposure of new born infants to colostrum and breast milk. Accordingly it is possible for the transmission of human milk borne viruses. This is contrary to the widespread assumption that human milk borne viruses cannot be associated with breast cancer.

## Background

Human immunodeficiency virus (HIV), cytomegalovirus (CMV), human T cell leukaemia virus (HTLV) and other viruses may be transmitted by human milk and cause infections and disease.<sup>1</sup> In animals, viruses, such as the mouse mammary tumor virus (MMTV), are transmitted by mouse milk to new born mouse pups and are a proven cause of mouse mammary tumours.<sup>2</sup>

Accordingly, the transmission of milk born viruses which may have a role in human breast cancer has long been postulated. However, there is extensive and consistent epidemiological evidence, which indicates that breastfeeding – and hence the opportunity to transfer viruses via human mothers milk to infants, is not related to breast cancer.<sup>3,4</sup> There also appears to be no association between risk of breast cancer and breastfeeding by daughters whose mothers had breast cancer.<sup>5</sup>

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There is substantial, but not conclusive, evidence which suggests that a virus, virtually identical with mouse mammary tumor virus and additional viruses including high risk human papilloma viruses (HPVs) and Epstein-Barr virus (EBV) may have roles in the etiology of breast cancer.<sup>2</sup> However, with respect to breast cancer etiology, the transmission routes for these viruses is not known. For this reason, we re-examined the evidence relating to breastfeeding and breast cancer. We discovered there is a problem with the epidemiological studies (see meta analyses by Beral et al and Martin et al relating to breastfeeding).<sup>3,4</sup> There has been almost universal use of the seemingly simple question “did you breast feed your baby and if so, for how long?” This question does not necessarily determine if a newborn infant was “exposed” to colostrum or breast milk, whether or not the mother subsequently established breast feeding. In addition, surveys in which this question was asked were often conducted many years after the event.<sup>4</sup> Labbock et al realised that lack of precision and consistency in the definition of breastfeeding had led to misinterpretation of data and problems with comparability between studies.<sup>6</sup> In neither of the recent meta-analyses was this crucial definitional issue considered in detail.<sup>3,4</sup>

Therefore we hypothesised (i) that a high proportion of newborn infants may be “exposed” to colostrum or breast milk whether or not they were breast fed, (ii) if this hypothesis was shown to be true, that viruses could be transmitted to new born human infants. We tested the first hypothesis in a prospective study and reviewed existing data concerning exposure of newborns to colostrum and breast milk in Australia.

## Methods

We conducted a prospective review of 100 consecutive births of infants, which had all been at the same location during 2006 (Royal Hospital for Women, Sydney, Australia). We used a standard definition of “ever breastfed” as “those infants who have been put to the breast, if only once, and includes infants who have received expressed breast milk but have never been put to the breast”. The proportion of “ever breastfed infants” who were “exposed” to colostrum or breast milk was determined.

We reviewed the published data on breastfeeding practices in the Australian State of New South Wales (NSW).<sup>7</sup> Each year there are approx. 87,000 births in NSW. A record is kept by midwives of the breastfeeding practices of mothers of each new born infant (there is a near 100% response rate). The standard definition of “ever breastfed” as defined above, was used for the collection of this data.<sup>7</sup>

Statistics: One sample Chi square was used to measure the proportion of newborn infants that were exposed to colostrum or breast milk.

**Table 1: Proportion of newborn infants exposed to colostrum or breast milk**

| Number of mothers | Number of infants exposed | Number of infants not exposed | Significance at 95% level |
|-------------------|---------------------------|-------------------------------|---------------------------|
| 100               | 97                        | 3                             | p = 0.000                 |

## Results

Ninety seven (97%) of the 100 infants consecutively born at the Royal Hospital for Women during April and May of 2006, were “ever breastfed” (Table 1). Each of the mothers of the 3 infants who were not “ever breast fed” had indicated they did not wish to breast feed (Table 1). All 100 newborn infants “nuzzled” their mother’s nipple and breast, including the 3 who were not exposed to colostrum or breast milk.

The percentage of the approx 87,000 infants born during 2001 in NSW who were “ever breastfed” averaged 90.2%. This percentage varied from a high of 98.7% to a low of 82.2% for infants born of mothers from communities of high compared to lower socio-economic status respectively. “Ever breastfed” rates also varied according to the age and education of the mother. 84.5% of mothers under the age of 25 years and 90.4% of mothers aged 25 years or over “ever breast fed”. 86.8% of mothers with primary and secondary school education and 96.1% of mothers with tertiary education (University and college levels) “ever breast fed”. These percentages fell dramatically during the first year of life of these infants, 54.2% were receiving “any breast milk” at 4 months after birth, 42.5% at 6 months and 18.1% at 12 months.

## Discussion

The proportion of newborn infants “exposed” to colostrum or breast milk during recent years in NSW, Australia is far higher than that reported in any of the studies of breastfeeding practices in other Western countries. This observation suggests that there is a possibility of colostrum or milk borne transmission of viruses to virtually all infants in these Australian communities. While these findings cannot be generalised to other countries and communities, the accepted opinion that there is no association between breastfeeding and breast cancer may not be true.

With respect to studies which have sought to determine whether or not the duration of breastfeeding is associated with risk of breast cancer, it is likely that the data is sufficiently reliable to allow conclusions to be drawn.<sup>3,4</sup> This is because the data required is much less specific than that required to determine any early life exposure to breast colostrum or breast milk. These many studies have shown there is no increased risk of breast cancer associated with prolonged breastfeeding.<sup>3,4</sup> It follows that there is unlikely to be a “dose response” based on breastfeeding for months, associated with any milk transmitted virus or other agent that may be associated with breast cancer.

With the important exception of HIV, data concerning human milk borne viruses is very limited. HIV is the same family of retroviruses as MMTV and is therefore relevant. The viral load of HIV in human milk and colostrum is highest in the newborn period.<sup>8</sup> However human milk transmission of HIV is a complex phenomenon.<sup>9</sup>

There is sparse evidence which suggests MMTV-like genetic material may be present in human milk. Moore et al have

observed by electron microscopy MMTV like images in human milk.<sup>10</sup> Ford has made preliminary identification of MMTV-like DNA sequences in human milk.<sup>11</sup> As HIVs are known to be transmitted in high concentrations by human milk to newborn human infants and to a lesser extent in older infants, it is theoretically possible for MMTV to be also transmitted by only a brief exposure to colostrum and breast milk. There are no published studies of human milk transmission of MMTV.

## Conclusion

In conclusion, we have shown that the first hypothesis, that a high proportion of newborn infants may be “exposed” to colostrum or breast milk whether or not they were breast fed, is likely to be correct. The second hypothesis that viruses such as MMTV could be transmitted to newborn human infants, remains to be tested. In our view, this second hypothesis is biologically feasible.

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# Increasing Illness Severity in Very Low Birth Weight Infants Over a 9-Year Period

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## Abstract

**Background:** Recent reports have documented a leveling-off of survival rates in preterm infants through the 1990's. The objective of this study was to determine temporal changes in illness severity in very low birth weight (VLBW) infants in relationship to the outcomes of death and/or severe IVH.

**Methods:** Cohort study of 1,414 VLBW infants cared for in a single level III neonatal intensive care unit in Delaware from 1993–2002. Infants were divided into consecutive 3-year cohorts. Illness severity was measured by two objective methods: the Score for Neonatal Acute Physiology (SNAP), based on data from the 1<sup>st</sup> day of life, and total thyroxine ( $T_4$ ), measured on the 5<sup>th</sup> day of life. Death before hospital discharge and severe intraventricular hemorrhage (IVH) were investigated in the study sample in relation to illness severity. The fetal death rate was also investigated. Statistical analyses included both univariate and multivariate analysis.

**Results:** Illness severity, as measured by SNAP and  $T_4$ , increased steadily over the 9-year study period with an associated increase in severe IVH and the combined outcome of death and/or severe IVH. During the final 3 years of the study, the observed increase in illness severity accounted for 86% (95% CI 57–116%) of the variability in the increase in death and/or severe IVH. The fetal death rate dropped from 7.8/1000 (1993–1996) to 5.3/1000 (1999–2002,  $p = .01$ ) over the course of the study.

**Conclusion:** These data demonstrate a progressive increase in illness in VLBW infants over time, associated with an increase in death and/or severe IVH. We speculate that the observed decrease in fetal death, and the increase in neonatal illness, mortality and/or severe IVH over time represent a shift of severely compromised patients that now survive the fetal time period and are presented for care in the neonatal unit.

## Background

Despite continuing advances in neonatal care and decades of improving outcomes, it has recently been reported that survival

rates have leveled-off in premature infants during the 1990s.<sup>1–3</sup> In the state of Delaware, infant mortality rates improved during the early 1990s similar to national trends, only to see a more recent increase which has been attributed to increasing mortality in very low birth weight infants.<sup>4</sup> In the United States, infant mortality increased in 2002 for the first time in nearly 5 decades.<sup>5,6</sup> In 2002 the United States fetal mortality rate declined while infant mortality increased.<sup>6</sup> A shift from fetal to neonatal deaths is one possible explanation for this trend. The potential impact of increasing fetal survival on neonatal intensive care has not been explored.

Severe intraventricular hemorrhage (IVH) is a significant morbidity in premature infants and is one of the major determinants of long term outcome in very low birth weight infants.<sup>7</sup> Severe IVH has recently shown to have declined in occurrence prior to the 1990's and to have remained unchanged thereafter.<sup>8</sup> Other common morbidities in premature infants including chronic lung disease have also been recently described as increasing in survivors.<sup>9</sup> The reasons for increasing morbidities and recent lack of improvement in survival rates of preterm infants have not been conclusively explained. It has been postulated that the technology for caring for premature infants has reached its limits. One factor that has yet to be investigated is the longitudinal effect of illness severity on morbidity and mortality in premature infants. We hypothesized that illness severity in very low birth weight (VLBW) infants was increasing over time. The objectives of this study were to investigate whether illness was increasing over time and to determine the effect of illness severity on the outcomes of death and/or severe IVH in a population of VLBW infants. As the fetal mortality rate has been declining in the United States,<sup>6</sup> and may be leading to a shift from fetal death to physiologically compromised preterm infants, we also explored the fetal death rate at our institution during the study time period.

## Methods

This investigation consisted of a cohort study of VLBW infants, <1500 grams, cared for at a single level III Neonatal Intensive Care Unit (NICU) during a 9-year period, July 1993–July 2002,  $n = 1414$ . The NICU at Christiana Hospital is a level III NICU serving the state of Delaware and cares for both inborn (90%) and outborn infants. Neonatal care within the State of Delaware is regionalized. One other level III NICU in the same network serves as a referral center for VLBW infants only if they require surgical care. No other nursery in the State offers intensive care for preterm infants with birth weights <1250 grams. A small number of infants with birthweight between 1250–1500 grams are cared for at two other level II sites within the same state neonatal network. There were no changes in the number of

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hospitals providing neonatal intensive care during the study time period. The NICU at Christiana Hospital is university affiliated and staffed by residents in pediatrics, neonatal nurse practitioners, and fellows in neonatal/perinatal medicine in addition to attending neonatologists. Decisions concerning resuscitating babies at the limits of viability are made by the attending neonatologist after family consultation. In general, infants 23 to 24 weeks gestation are offered a trial of intensive-care if desired by the family following consultation. This policy did not change during the study period. Throughout the study period Christiana Hospital was the only hospital in the state offering perinatology services and high risk obstetrical care. The Institutional Review Board at Christiana Care Health Services approved this research project. Data were obtained from a computerized database and review of the medical record. Informed written consent was not obtained.

Illness severity was quantified using two objective methods: the Score for Neonatal Physiology (SNAP)<sup>10</sup> and total thyroxine (T<sub>4</sub>). SNAP was routinely calculated after 1996 and therefore was available on infants born after 1996. SNAP was calculated on physiologic data from the 1<sup>st</sup> 24 hours of life. T<sub>4</sub> was obtained from the State of Delaware Newborn Screening Program and used as a proxy for illness severity. We, and others, have previously shown that total T<sub>4</sub> is correlated with illness severity in VLBW infants.<sup>11-13</sup> T<sub>4</sub> was obtained on the 5<sup>th</sup> day of life as part of routine newborn screening. Therefore, infants who died before the 5<sup>th</sup> day of life did not have a measurement of T<sub>4</sub>. The mean  $\pm$  SD of total T<sub>4</sub> in infants in the State of Delaware during the study period was 13.1  $\pm$  4.2 g/dl. In order to analyze outcome over time, the study sample was subdivided into consecutive three-year cohorts. Cohort 1 included infants born 7/93–7/96, Cohort 2, 7/96–7/99, and Cohort 3, 7/99–7/02.

Cranial ultrasounds were routinely obtained on the 4<sup>th</sup> day of life and then monthly until discharge. Cranial ultrasounds were obtained more frequently if clinically indicated. Ultrasounds were done using a 7.5 mHZ transducer and studies were interpreted by a pediatric radiologist. IVH was graded using the classification system of Papile.<sup>14</sup> Severe IVH was considered grade III-IV. Gestational age was based on the best obstetrical estimate. Modified Ballard exam was used only if an obstetrical estimate was not available.<sup>15</sup>

A fetal death was defined as any fetus  $\geq$  20 weeks of gestation that was not live-born. No policy changes in the definition for classifying fetal death were made throughout the study period. Fetal death rate is reported per 1000 births plus fetal deaths. Mothers were classified as receiving steroids if they received any doses of antenatal steroids. Betamethasone is the steroid used routinely at our institution. Clinical chorioamnionitis was diagnosed by the attending obstetrician, based on the presence of fever, uterine tenderness and/or foul smelling amniotic fluid. Any pregnancy with two or more fetuses was considered multiple-gestation. As infertility and in vitro fertilization have

been increasing during the study period,<sup>16</sup> infertility was investigated as an independent variable. For the purposes of this study, mothers were classified as having a history of infertility if their infants were conceived by in-vitro fertilization or if they received ovulation-enhancing medications such as clomiphene citrate. Mothers were classified as having preeclampsia if given the diagnosis by the attending obstetrician per ACOG guidelines.<sup>17</sup> Oligohydramnios was diagnosed by the attending obstetrician, no criteria for a minimal amniotic fluid index was used as it was not regularly available in the medical record. Prolonged rupture of membranes was considered greater than 24 hours. Maternal age was based on age at time of birth. Infants with birth weight < 1000 grams were analyzed as a sub-group.

Statistical analyses included both univariate and multivariate analysis. Univariate analysis included chi-squared for categorical variables, and analysis of variance for continuous variables with normal distribution. Levene's test of homogeneity of variances was used to assess data distribution. Mann-Whitney U test was used for continuous variables that were not normally distributed. Kruskal-Wallis ANOVA was also used to compare ordinal data over time. Pearson correlation was used to compare two continuous variables. Multivariate analysis included logistic regression and linear regression. The contributions of increased to death and/or severe IVH were calculated by comparing observed to predicted death and or IVH during Cohort 3. Data from the logistic regression models were used to calculate a standardized rate<sup>18</sup> for the outcome of death and/or severe IVH. A p value < .05 was considered statistically significant. Statistica (V7.0, Tulsa, OK) was used for all statistical calculations.

Results

A total of 1414 VLBW infants were cared for in the neonatal intensive care unit during the 9-year time period and comprised the study sample. Cohort 1 (1993–1996) consisted of 393 infants; there were 485 infants in Cohort 2 (1996–1999), and 536 in Cohort 3(1999–2002). In the study sample, 610 infants (43%) were < 1000 grams birth weight. The proportion of infants with birthweights <1000 grams, 42%, 41%, and 46% (p = .26) in Cohorts 1, 2, and 3 respectively, did not change over time. The distribution of infants, in 250 gram increments did not differ between Cohorts (Table 1). Of the 1414 infants, 1207 (85%) survived until the 5<sup>th</sup> day of life and had a measurement of T<sub>4</sub>.

Birthweight and maternal age were not different between the first, second and third cohorts (Table 2). There was a small but significant decrease in gestational age over time. There was no difference in the percentage of inborn infants over time. There was an increased use of antenatal steroids and antibiotics during the 2<sup>nd</sup> and 3<sup>rd</sup> Cohorts compared to the 1<sup>st</sup> Cohort. There was also an increased occurrence of preeclampsia and cesarean delivery over time. There were no differences in the occurrence of maternal HELLP syndrome, diabetes, illicit drug use, clinical chorioamnionitis, prolonged rupture of membranes, oligohydramnios, multiple gestation, or infertility over time. In

Table 1: Distribution of birthweights in the study cohorts. Distribution of birthweights did not differ between Cohorts.

|                    | Birthweight<br><500 grams | Birthweight<br>500–749 grams | Birthweight<br>750–999 grams | Birthweight<br>1000–1249 grams | Birthweight<br>1250–1500 grams |
|--------------------|---------------------------|------------------------------|------------------------------|--------------------------------|--------------------------------|
| Cohort 1 1993–1996 | 2%                        | 19%                          | 22%                          | 26%                            | 31%                            |
| Cohort 2 1996–1999 | 2%                        | 15%                          | 24%                          | 30%                            | 29%                            |
| Cohort 3 1999–2002 | 2%                        | 18%                          | 25%                          | 27%                            | 28%                            |

**Table 2: Changes in demographics and outcomes over time in the overall population.**

|                                                        | Cohort 1 1993–1996 n = 393 | Cohort 2 1996–1999 n = 485 | Cohort 3 1999–2002 n = 536 |
|--------------------------------------------------------|----------------------------|----------------------------|----------------------------|
| Birthweight (g)                                        | 1052 ± 297                 | 1057 ± 277                 | 1028 ± 284                 |
| Gestational Age (weeks)                                | 28.3 ± 3.0                 | 28.4 ± 2.9                 | 27.8 ± 2.9 * †             |
| Maternal age (years)                                   | 26.5 ± 5.9                 | 26.6 ± 6.3                 | 26.7 ± 6.7                 |
| Inborn                                                 | 91%                        | 88%                        | 87%                        |
| Apgar score at 5 minutes (median, interquartile range) | 8 (6–9)                    | 8 (7–9)                    | 8 (7–9)                    |
| Apgar score at 5 minutes <5                            | 13%                        | 8%                         | 10%                        |
| Cesarean delivery                                      | 55%                        | 57%                        | 62% *                      |
| Antenatal steroids                                     | 48% ‡                      | 66%                        | 65% *                      |
| Antenatal antibiotics                                  | 34% ‡                      | 50%                        | 51% *                      |
| Preeclampsia                                           | 14% ‡                      | 20%                        | 24% *                      |
| HELLP syndrome                                         | 5%                         | 4%                         | 3%                         |
| Oligohydramnios                                        | 14%                        | 11%                        | 13%                        |
| Clinical chorioamnionitis                              | 9%                         | 7%                         | 8%                         |
| Maternal fever                                         | 4%                         | 2%                         | 4%                         |
| Prolonged rupture of membranes                         | 22%                        | 22%                        | 21%                        |
| Illicit maternal drug use                              | 3%                         | 2%                         | 3%                         |
| Maternal diabetes                                      | 5%                         | 3.5%                       | 5%                         |
| Multiple gestation births                              | 24%                        | 24%                        | 28%                        |
| Infertility                                            | 10%                        | 7%                         | 10%                        |
| Mechanical ventilation                                 | 78%                        | 79%                        | 83%                        |
| Rescue high frequency ventilation                      | 13%                        | 15%                        | 22% * †                    |
| Exogenous surfactant replacement                       | 63%                        | 65%                        | 75% * †                    |
| Postnatal dopamine                                     | 24% ‡                      | 31%                        | 35% *                      |
| Postnatal dexamethasone                                | 19% ‡                      | 25%                        | 16% †                      |

\*p &lt; .05, Cohort 1 vs 3

‡p &lt; .05, Cohort 1 vs 2

†p &lt; .05, Cohort 2 vs 3

the infants in the study sample, there was no change in the use of mechanical ventilation over time but the use of rescue high frequency ventilation and surfactant did increase over time. Because dopamine can inhibit pituitary hormone production,<sup>19</sup> the use of dopamine and dexamethasone in infants was investigated. The use of dopamine in infants increased progressively over time while the use of postnatal dexamethasone increased between Cohort 1 and Cohort 2 then dropped during Cohort 3.

Postnatal illness severity increased over time, as measured by total T<sub>4</sub> and SNAP (Table 3). Linear regression models were used to assess the effect of birth cohort on illness severity. Forward stepwise linear regression was used. Variables entered into the model included those that were significant on univariate analysis and variable which are known confounders for illness severity such as birthweight. Birth cohort remained significant in the models when illness severity was measured using SNAP as the dependent variable (model r<sup>2</sup> = .41, p < .01) and T<sub>4</sub> as the dependent variable (model r<sup>2</sup> = .35, p < .01). Other than birth

cohort, gestational age and birthweight were the only independent variables contributing more to the variability in both models of illness severity. In addition to gestational age and birthweight, the models controlled for maternal antibiotics, multiple gestation birth, race, maternal steroids, preeclampsia, cesarean delivery and inborn status.

There was no difference in the rate of mortality over time (Table 3). However, those infants who died during Cohort 3, died earlier compared to those infants who died during both the 1<sup>st</sup> and 2<sup>nd</sup> Cohorts. There was an observed increase in both severe IVH and the combined outcome of death and/or severe IVH over time. In the sub-group of infants less than 1000 grams, illness severity increased over time as measured by both SNAP and T<sub>4</sub> (Table 4). Similar to the general study sample, mortality did not increase over time, but there was an increase in severe IVH as well as the outcome of death and/or severe IVH in the infants <1000 g. Table 5 shows changes in T<sub>4</sub> and SNAP in the study cohorts based on 250 gram birthweight increments. Illness severity decreased with increasing birthweight in each cohort (as measured by

**Table 3: Changes in illness severity and outcomes over time**

|                                            | Cohort 1 1993–1996, n = 393 | Cohort 2 1996–1999, n = 485 | Cohort 3 1999–2002, N = 536 |
|--------------------------------------------|-----------------------------|-----------------------------|-----------------------------|
| T <sub>4</sub> (μg/dl)                     | 7.6 ± 3.8 ‡                 | 7.0 ± 3.4                   | 6.5 ± 3.9 * †               |
| SNAP                                       | NA                          | 11.2 ± 5.8                  | 13.4 ± 7.6 †                |
| Death                                      | 14%                         | 13%                         | 16%                         |
| Day of death (median, interquartile range) | 7 (2–21)                    | 10.5 (2–22)                 | 3 (2–10) * †                |
| Severe IVH                                 | 9%                          | 9%                          | 14% * †                     |
| Death and/or Severe IVH                    | 18%                         | 19%                         | 26% * †                     |

\*p &lt; .05, Cohort 1 vs 3

‡p &lt; .05, Cohort 1 vs 2

†p &lt; .05, Cohort 2 vs 3

**Table 4: Changes in illness severity and outcomes over time in infants <1000 g**

| Infants <1000 g        | Cohort 1 1993–1996, n = 165 | Cohort 2 1996–1999, n = 199 | Cohort 3 1999–2002, n = 246 |
|------------------------|-----------------------------|-----------------------------|-----------------------------|
| T <sub>4</sub> (μg/dl) | 5.4 ± 2.9                   | 5.3 ± 3.1                   | 4.7 ± 3.3 *                 |
| SNAP                   | NA                          | 15.3 ± 7.4                  | 18.3 ± 8.9 †                |
| Death                  | 30%                         | 27%                         | 33%                         |
| Severe IVH             | 16%                         | 14%                         | 23% †                       |
| Death/Severe IVH       | 35%                         | 36%                         | 46% * †                     |

\*p < .05, Cohort 1 vs 3

†p < .05, Cohort 1 vs 2

‡p < .05, Cohort 2 vs 3

increasing SNAP and decreasing T<sub>4</sub>.) Illness severity increased over time in each birthweight subgroup as measured by increasing SNAP. Illness severity, as measured by decreasing T<sub>4</sub>, increased over time in each birthweight subgroup, with the exception of infants 500–750 grams which approached statistical significance.

**Effect of Illness on death and/or severe IVH:** The combined rate of death and/or severe IVH was 19% in Cohorts 1 and 2 combined. Logistic regression models were created to control for the potential confounding effects of gestational age and birthweight on illness severity. After controlling for gestational age alone by logistic regression, the odds of death and/or severe IVH increased 1.3 (95% CI 1.2–1.5) for every 1 g/dl drop in total T<sub>4</sub>. When birthweight was added to the model along with gestational age, the odds of death and/or severe IVH increased to a similar degree 1.2 (95% CI 1.1–1.3) for every 1 g/dl drop in total T<sub>4</sub>. Using T<sub>4</sub> as a marker for illness severity, the rate of death and/or severe IVH would have been predicted to increase to 25% (95% CI 23–27%) in Cohort 3. The observed rate of death and/or severe IVH was 26% (Table 3). If the rate of death and/or IVH would have remained unchanged at 19%, between Cohorts 1 and 3, 102 cases of death and/or IVH would have been expected (.19 × 536 infants). In fact, 139 cases of death and/or severe IVH were observed (+37 cases). The observed increase in illness severity would be expected to increase the number of cases of death and/or IVH during Cohort 3 by 32 cases (95% CI 19–43 cases). Thus, 32 of the 37, or 86% (95% CI 57–116%) of the observed increase in death and/or severe IVH in Cohort 3 could be accounted for by the observed increase in illness severity observed during Cohort 3.

Data from the logistic model were also used to calculate a standardized rate.<sup>18</sup> Standardized rate, a tool used for quality assurance, was used to evaluate the possibility that changes in quality of neonatal care were responsible for the observed changes in outcomes. The standardized rate compared the

observed rate of death and/or severe IVH to the expected rate of death and or severe IVH based on illness severity, gestational age, and birthweight. Compared to the earlier Cohorts, the standardized rate of death and or severe IVH dropped in Cohort 3 when illness severity was accounted for using either T<sub>4</sub> or SNAP [Figure].

**Fetal death rate:** During the study period the fetal death rate at Christiana Hospital decreased over time. The fetal death rate was 7.8/1000 in Cohort 1, 6.7/1000 in Cohort 2, and 5.3/1000 in Cohort 3 (p = .01, Cohort 1 vs 3).

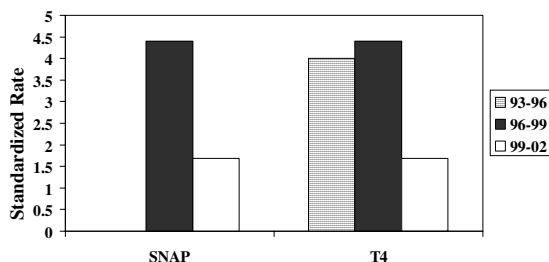
## Discussion

Our data show an increase in illness severity in VLBW infants over a 9-year period at a regional level III NICU in the State of Delaware. During this same time period, there was an associated decrease in the fetal death rate, and an increased occurrence in severe IVH. The contribution from increased illness accounted for a majority of the variability of the observed increase in the composite outcome of death and/or severe IVH during the final cohort.

To our knowledge this is the first report of increasing illness severity in a population of VLBW infants. Our report is consistent with data from Vermont-Oxford Network and others who have recently reported no improvement in survival of VLBW infants during the 1990's.<sup>1–3</sup> Although the reasons behind these plateaus in survival rates were not clear, it has been hypothesized that neonatal care has reached its limits. In our population of VLBW infants, the increase in severe IVH was temporally associated with an increase in illness severity as quantified by both SNAP and T<sub>4</sub>. Our data suggest that a majority of the increase in the combined outcome of death and severe IVH could potentially be accounted for by increasing illness. In addition, VLBW infants who died during the 3<sup>rd</sup> Cohort (1999–2002), died at an earlier time compared to the first 2 cohorts. The increased illness severity, documented on the 1<sup>st</sup> day of life by SNAP scores, and

**Table 5: Illness severity by 250 gram birthweight increments. Data for infants <500 grams are not provided due to small numbers.**

|                              | Birthweight<br>500–749 grams | Birthweight<br>750–999 grams | Birthweight<br>1000–1249 grams | Birthweight<br>1250–1500 grams | Birthweight p |
|------------------------------|------------------------------|------------------------------|--------------------------------|--------------------------------|---------------|
| <b>T<sub>4</sub> (μg/dl)</b> |                              |                              |                                |                                |               |
| Cohort 1 1993–1996           | 4.5 ± 2.3                    | 6.1 ± 3.1                    | 8.0 ± 3.5                      | 9.8 ± 3.6                      | <.01          |
| Cohort 2 1996–1999           | 4.3 ± 3.3                    | 5.8 ± 2.9                    | 7.4 ± 2.9                      | 8.9 ± 3.2                      | <.01          |
| Cohort 3 1999–2002           | 3.6 ± 2.3                    | 5.0 ± 2.9                    | 6.9 ± 3.7                      | 8.3 ± 3.7                      | <.01          |
| Cohort, p                    | .20                          | .03                          | .04                            | .03                            |               |
| <b>SNAP</b>                  |                              |                              |                                |                                |               |
| Cohort 2 1996–1999           | 17.1 ± 6.7                   | 13.6 ± 7.0                   | 10.1 ± 5.0                     | 8.0 ± 4.6                      | <.01          |
| Cohort 3 1999–2002           | 22.0 ± 9.3                   | 15.8 ± 7.6                   | 11.4 ± 5.4                     | 9.3 ± 5.7                      | <.01          |
| Cohort, p                    | .01                          | .03                          | .04                            | .05                            |               |



**Figure 1**

Standardized rate for death and/or severe IVH. Standardized rate is a ratio of observed/expected rate of death and/or severe IVH. Expected rate of IVH was calculated using logistic regression models (see text) using either SNAP or  $T_4$  to adjust for illness severity. Checkered box indicates 1993–1996, black boxes 1996–1999, white boxes 1999–2002.

the earlier time of death, suggest an antenatal or perinatal etiology for the observed increase in illness.

We speculate that a decrease in fetal death rate has resulted in an increased number of compromised infants and an increase in neonatal illness. Fetal compromise has previously been shown to be associated with neonatal death.<sup>20</sup> In our study sample, there was an increase in cesarean delivery, antibiotics, and steroids over time as has been observed in other recent studies.<sup>1,19,21</sup> Despite these obstetrical interventions, we observed no improvement in survival and increase in severe IVH, one of the major morbidities in VLBW infants over time. Changes in perinatal management of VLBW infants, in an attempt to aggressively care for pregnancies that may have previously been considered non-viable from a medical or gestational age standpoint, may be contributing to the decrease in fetal mortality and subsequent increase in neonatal illness. Alternatively, the observed increase in illness severity may be attributed to other factors, which we were unable to quantify in this study, such as increasing maternal stressors in the antenatal period. The fact that survival rates have remained consistent despite increasing illness suggests that neonatal care may be continuing to advance but not at a rate fast enough to overcome a steady increase in illness severity. Although the VLBW infants in Cohort 3 had a similar occurrence of death compared to the older cohorts, increasing illness may be contributing to an increase in neonatal morbidities such as severe IVH in survivors. Consistent with our study, other important neonatal morbidities including bronchopulmonary dysplasia,<sup>9</sup> retinopathy of prematurity<sup>22</sup> and neurodevelopmental disabilities<sup>21</sup> have all been recently shown to be increasing in surviving preterm infants.

The present investigation used  $T_4$  as a proxy for illness as we and others have previously shown the association of  $T_4$  and illness severity.<sup>11-13</sup> We feel that  $T_4$  is a valid marker of illness severity as confirmed by the inverse correlation between SNAP and  $T_4$  in our study sample. Previous research has shown equivalent ROC curves for  $T_4$  and SNAP in relationship to the outcomes of severe IVH and death.<sup>11</sup> In support of the fact that  $T_4$  is a marker for illness severity, rather than an important part of the causal pathway, studies of thyroxine supplementation in preterm infants have failed to improve neonatal outcomes.<sup>11,23-25</sup> Because  $T_4$  was measured on the 5<sup>th</sup> day of life, we can not rule out the possibility that early management of VLBW infants may have influenced illness severity and  $T_4$ . This possibility, however, remains unlikely as management strategies did not change

dramatically at our center during the study period. The use of dopamine, which inhibits thyroid stimulating hormone production,<sup>19</sup> did increase over time. However, increasing dopamine use would be expected with an increase in illness and would not explain an increase in SNAP. It also remains a possibility that low  $T_4$  is an important part of the causal pathway in illness severity and that some primary change in thyroid function over time in our population contributed to the observed increase in illness severity. Even if a primary decrease in  $T_4$  was responsible for the observed increase in illness, the importance of a progressive decrease in  $T_4$  is highlighted by the association of hypothyroxinemia with death,<sup>26</sup> IVH,<sup>27</sup> cystic periventricular leukomalacia,<sup>28</sup> and cerebral palsy<sup>29</sup> in VLBW infants.

Our study has a number of other important limitations. First, since our study sample was from a single region our findings may not apply to other populations. Replication of these analyses from other regions would be needed to determine whether the observed increase in neonatal illness is occurring elsewhere. Our study is also limited by the unavailability of SNAP on infants born during the 1<sup>st</sup> Cohort and the unavailability of  $T_4$  on those infants who died prior to the 5<sup>th</sup> day of life. However, those infants who died prior to thyroid screening would have been expected to have an increase in illness severity compared to infants who survived. Thus our data may have potentially underestimated the trend of increasing illness. Because a small number of infants with birth weight between 1250 and 1500 grams are cared for at other centers in the state of Delaware they were not included in this analysis. There were no changes in the number of hospitals providing neonatal intensive care or maternal-fetal medicine services during the study duration. Furthermore, the increased illness in our region was present in infants <1000 grams, all of which were captured in this study sample. Because all infants <1000 grams born in the state of Delaware during the study period were captured in our cohorts it is unlikely that any changes in referral patterns influenced the results. Although the number of infants <1500 grams increased in our neonatal intensive care unit over time, the proportion of infants <1000 grams did not change over time. Multivariate modeling also adjusted for changes in gestation over time. We can not conclusively rule out the possibility that head ultrasounds were interpreted differently over time. Our data however are from a single center with uniform ordering of cranial sonograms and definitions of severe IVH. Although we were able to look at many variables influencing illness severity including clinical chorioamnionitis, there may have been other variables such as histologic chorioamnionitis<sup>30</sup> or time of birth<sup>31</sup> which we were unable to explore. Finally, although also unlikely, we can not rule out a change in the quality of obstetrical or neonatal care as a cause for increasing death on/or severe IVH. The similarities in the distribution of Apgar scores over time do not suggest that any changes in early delivery room management are responsible for the observed outcomes. The drop in the standardized rate observed over time suggests an improvement in neonatal outcomes, given the magnitude of increased illness severity.

Recent national data have shown that mortality in VLBW infants is no longer declining despite advances in neonatal care.<sup>1-3</sup> Our data are important in showing an increase in illness severity over a 9-year period in VLBW infants. We were also able to document an associated decrease in the fetal death rate during this same period. Infant mortality in the United States has been reported to have increased for the 1<sup>st</sup> time since 1958.<sup>5</sup> Similar to our regional



findings, the recent increase in infant mortality in the United States was associated with a decrease in the fetal death rate.<sup>5</sup> Based on our data we can not determine the cause of the observed increase in illness in VLBW infants, but speculate that there may be a shift of fetal deaths to live, but severely physiologically compromised newborns. Future investigations and other regional data analysis will be necessary to confirm these findings.

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# Imparting Carrier Status Results Detected by Universal Newborn Screening for Sickle Cell and Cystic Fibrosis in England: A Qualitative Study of Current Practice and Policy Challenges

Hilda Parker, Nadeem Qureshi, Fiona Ulph, Joe Kai

## Abstract

**Background:** Universal newborn screening for early detection of children affected by sickle cell disorders and cystic fibrosis is currently being implemented across England. Parents of infants identified as carriers of these disorders must also be informed of their baby's result. However there is a lack of evidence for most effective practice internationally when doing so. This study describes current or proposed models for imparting this information in practice and explores associated challenges for policy.

**Methods:** Thematic analysis of semi-structured interviews with Child Health Coordinators from all English Health Regions.

**Results:** Diverse methods for imparting carrier results, both within and between regions, and within and between conditions, were being implemented or planned. Models ranged from result by letter to in-person communication during a home visit. Non-specialists were considered the best placed professionals to give results and a similar approach for both conditions was emphasised. While national guidance has influenced choice of models, other factors contributed such as existing service structures and lack of funding. Challenges included uncertainty about guidance specifying face to face notification; how best to balance allaying parental anxiety by using familiar nonspecialist health professionals with concerns about practitioner competence; and extent of information parents should be given. Inadequate consideration of resource and service workload was seen as the main policy obstacle. Clarification of existing guidance; more specific protocols to ensure consistent countrywide practice; integration of the two programs; and normalizing carrier status were suggested as improvements.

**Conclusions:** Differing models for communicating carrier results raise concerns about equity and clinical governance. However, this variation provides opportunity for evaluation. Timely and more detailed guidance on protocols with clarification of existing recommendations is needed.

## Background

Part of the newborn bloodspot program, universal newborn screening for sickle cell disorders (SCD) is now fully implemented across England and will be for cystic fibrosis (CF) by mid-2007. In addition, a linked antenatal hemoglobin disorder (HD) screening program is being rolled out; universal in areas with a high prevalence and selective in low prevalence areas. High prevalence areas are those where sickle cell disease is estimated to affect more than 1.5 per 10,000 pregnancies and low prevalence those with less than 1.5 per 10,000. Newborn screening aims to identify babies affected by these conditions; however screening also identify infants who are carriers. While concerns have been raised about identifying carriers of genetic conditions by population screening and how to (even whether to) communicate results, English policy is that parents have to be informed. Despite decades of universal newborn screening for SCD in the USA, and more recently for CF, there is no clearly established model for effective communication of carrier status internationally.

Both SCD and CF are recessively-inherited disorders and carriers are healthy. Newborn screening for SCD identifies all carriers of structural hemoglobin variants (screening identifies carriers of 'unusual hemoglobins' of which the most common is Sickle Cell; for ease of reference, SCD is used in this paper when referring to all unusual hemoglobins detected by screening ) but not thalassemia carriers and there is no available method of testing without detecting carriers. The national protocol for CF screening in England aims to identify a maximum number of children with CF whilst minimising the number of carriers. The protocol involves an initial immunoreactive trypsinogen (IRT) measurement which identifies babies at high risk for CF. These samples are further tested by a two-stage DNA screen for a small panel of CF mutations. Those with two mutations will have CF. For those with only one mutation or no mutation detected but with a very high initial IRT, a second blood sample will be requested and a

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The authors are with the Division of Primary Care, University of Nottingham, Graduate Medical School, Derby City General Hospital, Derby, UK. The authors wish to thank the interviewees for taking part and to offer special thanks to Jim Bonham and Bernadette Modell for their very helpful comments on an earlier draft of this paper. The study was funded by the NHS National Institute for Health Research, Health Technology Assessment Program. Reprinted from BioMed Central, BMC Health Services Research, © 2007 Parker et al, licensee BioMed Central Ltd. This is an open access article distributed under the terms of the Creative Commons Attribution License.

further IRT measurement performed at 21-28 days when it is more discriminatory. While an elevated IRT itself does not select in favour of carrier status, most of these babies will be carriers defined by limited DNA testing. However, because not all mutations are identified, a small proportion of those defined as carriers may actually have two CF variants and have the condition (because they have inherited two CF variants, one identified by IRT and one not identified).

With a SCD incidence of 1:2400 affected babies per year in the UK, the NHS Sickle Cell and Thalassemia Screening Program estimate that about 8000 newborn carriers were detected in 2006 from about 550,000 babies screened. Cystic fibrosis has a slightly lower incidence (1:2500 affected babies per year born in the UK) with approximately 1 in 25 of the population estimated to be a carrier of which only a small proportion will be identified by newborn screening. In England annually about 240 babies with CF are born and current screening protocols are expected to identify an equivalent or slightly higher number of carriers. Thus, compared to CF, numbers of newborn SCD carriers detected are considerable. For example at a regional level, during a 12-month period 573 SCD carriers and 16 CF carriers were detected in a population with an annual birth rate of 70,000.

Prior to national programs, newborn screening was mostly offered on an ad hoc basis, with universal CF screening available to 20% of babies (areas served by laboratories in East Anglia, East Midlands, South Yorkshire and Leeds) for over 15 years and over 10 years for SCD in some areas in London, East of England and Birmingham. Over this period, although practice for informing parents of their infants' carrier status has varied according to condition and locality, the need for clear protocols for communicating carrier information is recognised. In England, thus far, guidance issued by the UK Newborn Screening Program Centre recommends that carrier results should be given to parents as soon as possible; by a well-informed health professional; in person, or by phone, and followed up in person as soon as possible; and supported by written information. This guidance does not distinguish between CF and SCD carrier status. However there are no data on models being used, extent of variation, and experience of implementation following the advent of universal screening across England.

This paper reports findings from a descriptive study, part of a larger study funded by the Health Technology Assessment program also exploring parents' and health professionals' experience, on models for giving newborn carrier results and emerging policy in this context.

## Methods

Semi-structured telephone interviews were conducted (by HP) with the Regional Child Health Co-ordinator from each of the nine English health regions during the second half of 2006. Consent to be interviewed was initially obtained by email and again verbally on tape at the start of the interview.

Participants were invited to reflect on the extent of regional implementation of CF and SCD newborn screening, actual or proposed models for giving results, the need for condition specific models, who should give the results, and suggestions for improving current practice and policy. Respondents were also able to raise other issues of importance relevant to the

subject. Where informants were unable to provide sufficient details, brief telephone calls or emails to specialist services were used to acquire supplementary information. Interviews were tape-recorded and transcribed verbatim. Data were thematically coded and analysed according to emergent themes. Interviewees were invited to give feedback on a draft version of this paper prior to submission for publication.

## Results

Participants reported a variety of models, proposed or already operational, for imparting carrier results (see table 1 for summary of practice across England). Of note is diversity of models both within and between regions and both within and between conditions. Only one region is implementing the same model for both conditions. All regions are informing parents of CF carriers in person compared to a range of methods, from notification by letter alone to personal contact, for SCD carriers. Health Visitors (HVs) have a prominent role, including family's usual HV and those specially trained to communicate carrier results.

National guidance (as issued by the UK Newborn Screening Program Centre) for implementation most commonly influenced choices of methods for communicating carrier results. The perception was that guidance was more specific for the CF compared to the SCD program. However, experience of implementing SCD screening first has informed thinking about CF.

"Because there were lines being drawn in the sand as to who should actually do this information, who should actually give this information and obviously we knew that Cystic Fibrosis was coming... I adopted the model for the Sickle screening program as well." (CHC 04)

Inadequate funding has affected implementation of both the delivery of screening and in particular the choice of methods for communicating carrier results. This has necessitated efforts to secure funding from local sources; often short term and dependent on an individual manager's resourcefulness or sway within the local health system. Where no additional funds could be realised, existing staff have had to take on communication of results in addition to their usual workload. Inevitably, these financial constraints have, in some regions, led to compromise and 'quick fix' models for communicating carrier results.

"I don't think there was due consideration given to the workload associated with giving carrier results and I think that was an oversight. There doesn't seem to have been any thoughts on how it would be... It needs to be properly accounted for, like we introduce services and they give four quid a baby for the lab but it affects every different component part of the service. It affects the midwives and their counselling, it affects the health visitors giving the results and it affects the child health record departments who have to adapt their systems of working to record the results." (CHC 02)

"It's [informing carriers] all done on goodwill, the PCTs are asking where's the funding for this? And obviously it does take up some time, some practitioners' time." (CHC 04)

Specialist services have been operational in high prevalence HD areas long before the introduction of universal newborn screening. Bringing distinct advantages, such as expertise and

referral protocols, a consequence is that regional plans for models of carrier results have to incorporate existing practice and organisational structures, resulting in less scope for innovation in some areas. Requesting changes to existing practice was a challenge, leading some interviewees to prefer starting service planning from scratch.

“It was easier to do the area that was a blank sheet because then you could do how best fitted what the geography and, you know, where the funds and all those sorts of things available were and you’ve also got some handle on what they do and can say what they should or shouldn’t do. Whereas when there’s already something in place it’s harder isn’t it?” (CHC 08)

In contrast, there were concerns about reporting results in low prevalence HD areas due to lack of resources and practitioner knowledge. Thus, although low prevalence settings provided opportunities for trying out new models of result giving, in some areas urgency of need necessitated rapid implementation before localities were sufficiently prepared to deliver results.

“Our real problem has been our low prevalence areas... it was little bit hit and miss to be quite honest. We had a case. . .where we found 60 children hadn’t been given results. And that was a bit. . .because people didn’t know quite what to do with it, how to do it.” (CHC 05)

Regional implementation groups were a common mechanism for discussion and planning of proposed models. For some, the challenge was to find a fit between national guidance and local resources and preferences. Regions who consulted widely about this specific issue and ensured extensive health professional (e.g. Directors of Public Health, Primary Care Trust screening leads, paediatricians, heads of midwifery and health visiting, etc) engagement found that the process benefited implementation of the screening program as a whole.

“I think without doubt the implementation has brought more people around the table... and trying to ensure that there is linkage and involvement across the whole of the screening profession. So making sure that every professional group, primary, tertiary and secondary level specialists have been involved in that decision making has been beneficial.” (CHC 07)

With some exceptions, most interviewees expressed a strong preference that conveying carrier results should be a task undertaken by non-specialist health professionals. During interviews respondents used the term ‘specialists’ when referring to genetic counsellors, Hemoglobinopathy counselors and Cystic Fibrosis nurses and regarded all other health professionals involved in communicating carrier status information as non-specialists. Key to this position was the view that carriers were healthy. Utilizing a specialist practitioner in this role could cause parents to believe that their baby was ill and increase their anxiety. Specialist time was more appropriate for providing further information to families who wanted to know more or wanted to discuss future reproductive decisions. While support for non-specialists giving results was consistent, informants were uncertain about how best to balance allaying parental anxiety by using a non-specialist and concerns about practitioner competence.

“We would like for them [specialist HD counsellors] to spend more time doing the specialist stuff that a health visitor couldn’t

possibly do... For the carriers it’s quite a large workload and yet it doesn’t need super-specialist people, it needs somebody with some extra training and some expertise and it’s sort of half-way house.” (CHC 06)

Respondents working in regions where specialists were currently involved in giving results did not see this as a problem, though they were not insistent that specialists should be involved. In one region concern had arisen about non-specialists giving CF carrier results because of the small risk that some carriers may be affected.

The importance of involving the family’s usual HV in giving results was highlighted as the best way to minimise parental anxiety; either as the sole professional giving the results, or visiting the family together with a specialist or purpose trained nonspecialist. Ensuring appropriate training for HVs was an important consideration. Whether to train all to give results, knowing that some may never come across a carrier case, or to concentrate training to a selected group who would take on this role and accompany the family HV remained an ongoing debate for some regions.

“It seems to me that the best person to give the results so that it isn’t worrying is in the middle of a routine health visitor visit without the phone call to say, ‘hey can I see you,’ especially because in a sense that’s making anxieties. But how do we maintain competence if even at local level you know no health visitor is going to be doing it every week say or even once a month so I think there’s actually a real dilemma.” (CHC 06)

None of the interviewees were in favor of separate models for the two conditions. Two respondents, who had not yet implemented CF newborn screening, wanted to await further experience while others expressed strong preference for similar models and for close working between the two screening

Table 1: Proposed English Regional methods for imparting newborn carrier results

| Region               | SCD carriers                                                                                                                                                                                                      | Screening started in | CF carriers                                                                                          | Screening started in     |
|----------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|------------------------------------------------------------------------------------------------------|--------------------------|
| North West           | <b>In person</b> by purpose trained health visitor                                                                                                                                                                | 2005                 | <b>In person</b> by purpose trained health visitor                                                   | Not yet started          |
| West Midlands        | <b>In person</b> by Haemoglobinopathy counsellor<br><b>OR</b><br><b>Letter</b> with result plus appointment for counselling                                                                                       | 2004                 | <b>In person</b> specialist counsellor plus family health visitor                                    | Not yet started          |
| South West           | <b>In person</b> by family health visitor or Haemoglobinopathy counsellor<br><b>OR</b><br><b>Letter</b> with result plus option to attend Haemoglobinopathy service                                               | 2004 - 2006          | <b>In person</b> by genetic counsellor or antenatal screening co-ordinator                           | Not yet started          |
| London               | <b>In person</b> by family health visitor or Haemoglobinopathy counsellor<br><b>OR</b><br><b>Letter</b> with result plus appointment for counselling, or option to attend specialist service, or 'drop-in' clinic | 1995 - 2005          | Undecided at the time of data collection                                                             | Not yet started          |
| North East           | <b>In person</b> by Haemoglobinopathy counsellor plus family health visitor                                                                                                                                       | 2005                 | <b>In person</b> by purpose trained health visitor plus family health visitor                        | Not yet started          |
| East of England      | <b>In person</b> by Haemoglobinopathy counsellor or purpose trained health visitor<br><b>OR</b><br><b>Letter</b> with result plus appointment for counselling                                                     | 1997 - 2005          | <b>In person</b> by specialist CF nurse                                                              | 1980's in Cambridgeshire |
| South Eastern        | Haemoglobinopathy counsellors contact and inform parents (details on exact methods not collected)                                                                                                                 | 2003 - 2006          | <b>In person</b> by purpose trained midwife                                                          | 2006 in Thames Valley    |
| East Midlands        | <b>In person</b> by General Practitioner plus referral to clinical genetics or follow-up by Haemoglobinopathy counsellor                                                                                          | 2004                 | <b>In person</b> by screening specialist nurse                                                       | 1989                     |
| Yorkshire and Humber | <b>In person</b> by purpose trained health visitor or Haemoglobinopathy counsellor<br><b>OR</b><br><b>Letter</b> with result plus appointment for counselling                                                     | 2004                 | <b>In person</b> by family health visitor plus specialist CF nurse or by family health visitor alone | 1997 -2007               |

programs. Another suggested that the difference between carrier results for the two conditions was overstated.

"I think there should be [the same model]... I've thought about this quite a lot because with cystic fibrosis the results can be difficult to interpret and some of the mutations the significance of those isn't known. But then I thought with sickle cell screening some of the hemoglobin variants, the significance of those is unclear so the results of that can be equally as difficult to interpret and not always straightforward." (CHC 01)

A common view was that there were more similarities, such as carrier status, recessive inheritance, and skills required to inform parents, than differences between the conditions. Therefore, it appeared logical to have the same protocol and organisational structure, albeit with some variation, for giving results.

"When we were putting the whole system [SCD newborn screening] into place in the back of our mind all the time was the fact that CF has got to roll out and it makes sense to use the same mechanism because the counselling skill is the same isn't it? You know, telling somebody that there's a problem with their baby and this is the genetics and you know, that sort of skill... A counseling skill is a counseling skill really isn't it?" (CHC 08)

"I would think it should be the same method, you know, I think it should be. Ideally I mean it's the same recessive condition that you're describing, the same genetics involved so you know I'd be of the opinion you could do both." (CHC 03)

Parity in methods for the two conditions was also seen as a way of addressing longstanding inequity in NHS service provision for HD compared to CF.

"I think it [methods for giving carrier results] should be standard... because I do find it personally irritating that there's this difference between sickle cell and CF. And professionally I think, well sickle cell is a genetic condition so why don't clinical genetics see it as their remit a little bit more because it is an inherited condition... but that's always been the way. Sickle cell services seem to have existed running parallel to clinical genetics and... it's [hemoglobinopathy disorder] probably a bit of Cinderella area." (CHC 01)

The need to clarify what was meant in the guidance by 'communicating in person' was a priority. Personal informing was seen as a costly process and some respondents suggested that an appropriate leaflet with contact details for further information could be as effective as a personal visit. Others considered using only written information unsatisfactory as varying reading levels would increase misunderstanding and service providers would not know that parents had received the information.

"I think we need a better definition of what is 'communicated in person' because you could interpret that, couldn't you, as here's the leaflet, read it; it could be here's the leaflet shall we go through it together... through the whole thing about, you know, a specialist ringing up and saying nothing to worry about but I need to see you... The other thing is in the 'in person.' I mean if you've got a family that don't speak English... if the health visitor doesn't speak their language but goes in with a leaflet in the right language, is that a face to face contact or whatever?" (CHC 06)

A nationally agreed on protocol for informing carriers with clear expectations of what information needs to be communicated to parents and practitioner roles, more detailed than current guidance and similar for both conditions, was suggested.

"Well, it's about clear expectations. About making sure that there is clear linkage of what you do next. I think if you are going into a family to give a result, it is not just good enough to give a result and to give a leaflet. You must provide the next level of intervention. And that next level in intervention is about listening, and then signposting very clearly where you go next. And it isn't just about saying 'go to your GP and they might refer you to clinical genetics' because some GPs may not. So I think that needs to be really agreed before we sort this out. What is the kind of things [to do] if people want further support. The other thing that needs to be clear, so that the Health Visitors are very clear, is [that] we are not asking them to become genetics experts and we are not asking them to become Sickle Cell experts... We need to have some very clear role boundaries of what is expected and that is agreed boundaries, and part of it is you may have a Health Visitor that is really interested and wants to do a lot more, but is it appropriate?" (CHC 05)

Explicit national policy regarding cascade screening (testing of other family members), and whether and how to report results detecting non-significant hemoglobin variants would also be helpful. More practical proposals included scripts on what parents should be told, especially when handling contentious scenarios such as non-paternity; a leaflet for parents of SCD carriers (similar to the current CF leaflet); simplification of current leaflets; and review of when (timing) parents are told what the bloodspot test is for.

As part of the call for continuity across both conditions, integration of the two programs was presented as imperative to ensure consistency in practice (and arguably, equity).

"The other stuff that we really, really need to do is to not do something totally different for CF and for Sickle because we do an awful lot of going down different pathways and I don't think that makes any sense... The integration of the two programs is just so important because it's really hopeless if they don't... because you get these mixed messages and you know you get it all being very special and very different. I mean it's one of the issues. I think all children with chronic disease or carriers, they've got more in common through being children than they have in having a disease, and it seems to me we shouldn't be taking people into different pathways simply because they've got one type of disease." (CHC 06)

Respondents felt that giving results should be normalized and incorporated into usual healthcare practice. Where possible, lessons could be learnt from other screening programs where results may be equally worrying. Increased public awareness of the conditions and screening programs was also mentioned as a way of allaying parental concerns about carrier status.

"I think the biggest problem for the counselors is getting across to the parents that carrier status isn't a disease and I think if we could raise the public's understanding of what Sickle Cell was, I think that would help them enormously because [otherwise] they've got to start from zero, haven't they. And bring parents up because it can come out of the blue can't it; they don't even know anything about it and then you're telling them that there's



something wrong with their perfect baby.” (CHC 08)

Although confident that this task was within a non-specialist remit, participants noted concerns about practitioner competence. In particular, General Practitioners’ (family physicians) limited knowledge about the implications of carrier status was perceived as concerning and needed to be addressed.

Creation of a new post for a designated health professional within a specific locality, described as a “newborn bloodspot practitioner,” to take responsibility for newborn screening carrier results for all conditions was proposed. This was seen as a practical way forward to facilitate continuity in liaison with laboratories and other stakeholders, and maintenance of professional competence in result giving.

The pressing need for research evidence to inform current practice was emphasised. Participants wanted to know the cost-effectiveness of various models and parental preference for delivery format and information content.

## Discussion

Recent US reports on CF newborn screening conclude that policymakers must consider the need for genetic counselling services and ensure adequate resources to support information giving prior to introducing newborn screening programs. European experience echoes this call for clearly defined referral pathways to support maximum gain and minimise negative outcomes.

Research with parents following newborn screening supports disclosure of carrier status and preference for being informed by a familiar, non-specialist, health professional. Prior warning to expect the result and the need for concise information about newborn screening to be given during the antenatal period are further parental needs. In a retrospective study of parental attitudes following carrier identification, no long-term adverse outcomes were noted in the majority of families. However, the cost-effectiveness of face to face consultation has been questioned and rigorous evidence on methods for communicating carrier results remains lacking.

Our data on proposed models for imparting newborn carrier results across England suggest marked diversity, both within and between regions, and within and between conditions. Although influenced by national policy, other factors have shaped practice leading to pragmatic rather than ideal choices. Despite overwhelming support for a similar process for both conditions, only one region was implementing a similar model for both conditions and variance of methods was particularly noticeable for SCD carriers. This creates concerns about equitable service provision.

Policy and accompanying funding may not address the full implications of introducing new newborn screening programs in relation to giving carrier results and dealing with parental information needs. As funding has supported only the front end costs of the process, such as laboratory tests, health communities have had to find additional resources within existing budgets, which may result in less than ideal models for giving results.

Though modest in scale, these interviews with stakeholders tasked with coordinating the implementation of newborn

screening programs are likely to have covered the full range of current models for giving carrier results in England. Our respondents’ views may not have embraced perspectives beyond their own roles, for example those from antenatal screening or primary care, though, this would be unlikely to change the key messages and issues for debate raised here.

## Conclusions

Universal newborn screening for SCD and CF heralds a new era for genetic screening in England. While early diagnosis of children affected by these disorders is the aim, screening of populations will increasingly require provision of information for those identified as gene carriers (and their families) with consequent challenges for appropriate service models and workforce planning and training.

Findings from this study raise important policy and practice issues for professionals with strategic and operational responsibility for implementing newborn screening. For example, the costly process of reporting in person, especially in terms of numbers of SCD carriers; challenges of maintaining non specialist informant competence given small number of carriers per condition per year (while carrier numbers will be far greater for SCD relative to CF, when translated to a primary care practice level, carriers of either condition will still be a rare occurrence within a GP or HV caseload); the need for more detailed national protocols; and equity and clinical governance concerns.

Our description of current practice may encourage shared learning as newborn screening is rolled out, as well as a context to stimulate evaluation and research about methods for imparting carrier results. Immediate priorities are for practical support for implementation such as good information leaflets, national protocols for information giving, and additional resources to support carrier result communication. Evidence for best practice when imparting results will emerge over time as practice models evolve and adjust.

# A Randomized Controlled Trial of Sucrose and/or Pacifier as Analgesia for Infants Receiving Venipuncture in a Pediatric Emergency Department

Sarah J Curtis, Hsing Jou, Samina Ali, Ben Vandermeer, Terry Klassen

## Abstract

**Background:** Although sucrose has been accepted as an effective analgesic agent for procedural pain in neonates, previous studies are largely in the NICU population using the procedure of heel lance. This is the first report of the effect of sucrose, pacifier or the combination thereof for the procedural pain of venipuncture in infants in the pediatric emergency department population.

**Methods:** The study design was a double (sucrose) and single blind (pacifier), placebo-controlled randomized trial – factorial design carried out in a pediatric emergency department. The study population was infants, aged 0 – 6 months. Eighty-four patients were randomly assigned to one of four groups: a) sucrose b) sucrose & pacifier c) control d) control & pacifier. Each child received 2 ml of either 44% sucrose or sterile water, by mouth. The primary outcome measure: FLACC pain scale score change from baseline. Secondary outcome measures: crying time and heart rate change from baseline.

**Results:** Sucrose did not significantly reduce the FLACC score, crying time or heart rate. However sub-group analysis revealed that sucrose had a much greater effect in the younger groups. Pacifier use reduced FLACC score (not statistically significant), crying times (statistically significant) but not heart rate. Subgroup analysis revealed a mean crying time difference of 76.52 seconds ( $p < 0.0171$ ) (0–1 month) and 123.9 seconds ( $p < 0.0029$ ) (1–3 month). For subgroup age  $> 3$  months pacifier did not have any significant effect on crying time. Age adjusted regression analysis revealed that both sucrose and pacifier had

significant effects on crying time. Crying time increased with both increasing age and increasing gestational age.

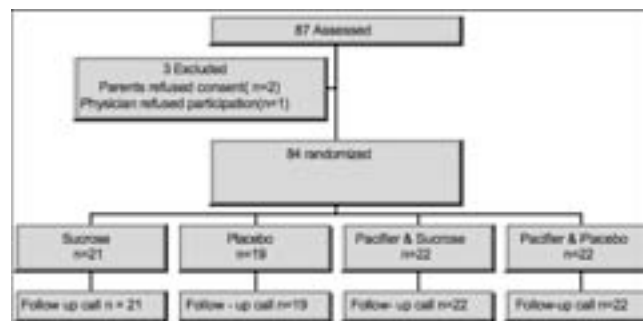
**Conclusion:** Pacifiers are inexpensive, effective analgesics and are easy to use in the PED for venipuncture in infants aged 0–3 months. The benefits of sucrose alone as an analgesic require further investigation in the older infant, but sucrose does appear to provide additional benefit when used with a pacifier in this age group.

## Background

To facilitate proper assessment, diagnosis and management many children must undergo painful procedures such as venipuncture for blood work or treatment, making the emergency department an ideal location to evaluate effective methods of pain control. Research suggests that prompt and accurate recognition and treatment of pain in young infants is important for their immediate comfort and for their best possible lifelong development.<sup>1,2</sup> Despite the recent interest in pediatric pain assessment, prevention and treatment, many children are still not adequately treated to alleviate pain.<sup>1,3,4</sup>

The ideal analgesic for procedural pain in the emergency department should have quick onset, be effective, and have no side effects. Sucrose has been extensively studied as analgesia for short procedures such as heel lance in neonates. A Cochrane systematic review concluded that sucrose is safe and effective in reducing procedural pain from single short procedural events in neonates.<sup>5</sup>

The authors are with the Department of Pediatrics, University of Alberta, Edmonton, Alberta, Canada. This research was supported by the pediatric residents training committee research award to Dr Curtis at the Department of Pediatrics, Stollery Children's Hospital. The authors thank the infants and parents who participated in this study. The authors also thank Geri Siebenga and her team of nurses for excellent coordination of this study in the PED, and thank Rita Pon and the pharmacy at the SCH for the generous donation of time and supplies for this study. Reprinted from BMC Pediatrics, BioMed Central, © 2007 Curtis et al; licensee BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License.



**Figure 1**  
Study Flow Diagram.

**Table 1: FLACC pain scale**

| Categories           | Scoring                                     |                                                                            |                                                       |
|----------------------|---------------------------------------------|----------------------------------------------------------------------------|-------------------------------------------------------|
|                      | 0                                           | 1                                                                          | 2                                                     |
| <b>Face</b>          | No particular expression or smile           | Occasional grimace or frown, withdrawn, disinterested.                     | Frequent to constant quivering chin, clenched jaw.    |
| <b>Legs</b>          | Normal position or relaxed                  | Uneasy, restless, tense.                                                   | Kicking, or legs drawn up.                            |
| <b>Activity</b>      | Lying quietly, normal position moves easily | Squirming, shifting back and forth, tense.                                 | Arched, rigid or jerking.                             |
| <b>Cry</b>           | No cry, (awake or asleep)                   | Moans or whimpers; occasional complaint                                    | Crying steadily screams or sobs, frequent complaints. |
| <b>Consolability</b> | Content, relaxed.                           | Reassured by occasional touching hugging or being talked to, distractible. | Difficulty to console or comfort.                     |

Adapted from The FLACC: A behavioral scale for scoring postoperative pain in young children, by S Merkel and others, 1997, *Pediatr Nurse* 23(3), p. 293–297. Copyright 1997 by Jannetti Co. University of Michigan Medical Center.

This taste-induced analgesia is thought to be mediated by endogenous opiod mechanisms,<sup>6,7,8</sup> although this has been questioned in other papers. Gradin et al have demonstrated that administration of an opiod antagonist to newborns did not reduce the pain relieving effect of oral glucose.<sup>9</sup> This contradicts findings in previous animal studies. Also, Eriksson et al showed that tolerance did not develop in neonates who were given repeated doses of glucose.<sup>10</sup> Infants receiving immunizations up to 12 months of age had similar findings.<sup>11</sup> Other theories for the analgesic actions of sucrose are through non-opiod endogenous pain inhibiting systems, activation of the pleasure center with dopamine release and initiation of the sucking response.

The effect of non-nutritive sucking using pacifiers has also been studied in neonates. Sucking is thought to trigger release of serotonin, which may modify the perception of pain. In general the magnitude of the decrease in pain is greater when sucking and sucrose are combined than with sucking alone.<sup>7</sup>

From the neonatal literature, which most frequently examined pain responses to heel lance, it seems that sucrose is a safe, easy-to-administer, inexpensive and effective analgesic for short painful procedures. A growing number of studies, looking at infants undergoing immunizations, suggest that this analgesic effect may indeed extend past the neonatal period into infancy.<sup>11-16</sup> Nevertheless, the upper limit of this effect is unknown in terms of age and appropriate sucrose strength. Also, the analgesic effect of non-nutritive sucking for infants older than one month has not been previously studied.

We wished to know if the analgesic effect of sucrose or pacifier holds true for neonates and young infants in the emergency

department, particularly for the procedure of venipuncture, which unlike heel lance and intramuscular injection, is commonly performed in that setting. Patients frequenting the emergency department generally differ in physiology and pathology from that of neonates in intensive care units where the majority of previous studies were carried out. We anticipated that this study would provide direction as to whether the use of sucrose, plus or minus pacifiers, as analgesia for venipuncture is useful for infants undergoing assessment in pediatric emergency departments.

## Methods

**Location:** This study took place at the Pediatric Emergency Department at the Stollery Children's Hospital in Edmonton, Alberta, Canada. The Stollery Children's Hospital houses the only specialized pediatric emergency in central and northern Alberta and has one of the largest catchment areas in North America with its referral base of more than 1.7 million. The PED sees 50 to 60 children per day with annual figures totaling just over 20,000 patients. Approximately 15 per cent of these emergency patients require admission to hospital.

**Protocol:** This study received approval from the hospital's institutional ethics review board, the department of pediatrics and from the division of emergency medicine. Figure 1 outlines the study flow.

**Study population:** All infants up to 6 months corrected age that required venipuncture as part of their emergency department management were eligible for the study. Participants were required to have had nothing by mouth for 5 minutes prior to study commencement. Previous animal and human studies have

**Table 2: Mean clinical and demographic characteristics of the four groups**

| Mean Values (Standard Deviation) | Sucrose N = 21 | Placebo N = 19 | Pacifier & Sucrose N = 22 | Pacifier & Placebo N = 22 |
|----------------------------------|----------------|----------------|---------------------------|---------------------------|
| <b>Age (days)</b>                | 63 (71)        | 64 (55)        | 68 (61)                   | 38 (39)                   |
| <b>Weight (kg)</b>               | 4.7 (1.8)      | 4.9 (1.4)      | 4.9 (1.2)                 | 4.2 (1.1)                 |
| <b>Gest Age (wks)</b>            | 37 (3.9)       | 39 (1.3)       | 39 (2.9)                  | 38 (2.1)                  |
| <b>NPO (min)</b>                 | 43 (36)        | 43 (60)        | 73 (169)                  | 42 (50)                   |
| <b>Rectal Temp (°C)</b>          | 37 (1.0)       | 37 (0.9)       | 37 (0.6)                  | 37 (0.8)                  |
| <b>O2 Sat (%)</b>                | 97 (2.0)       | 96 (2.3)       | 97 (2.0)                  | 97 (2.8)                  |
| <b>Resp Rate (bpm)</b>           | 40 (8.5)       | 40 (10.7)      | 40 (10.6)                 | 40 (10.4)                 |
| <b>Male Sex</b>                  | 11             | 13             | 11                        | 9                         |
| <b>Admitted</b>                  | 13             | 12             | 14                        | 17                        |
| <b>Previous Analgesia</b>        | 0              | 2              | 5                         | 2                         |

**Table 3: Mean variables and 95% confidence intervals of the four groups**

|                          | Sucrose              | Placebo              | Pacifier & Sucrose  | Pacifier & Placebo   |
|--------------------------|----------------------|----------------------|---------------------|----------------------|
| <b>N =</b>               | 21                   | 19                   | 22                  | 22                   |
| <b>FLACC Difference</b>  | 3.71 (1.58, 5.84)    | 4.84 (2.80, 6.88)    | 2.64 (0.88, 4.40)   | 2.45 (0.92, 3.98)    |
| <b>Crying Time (sec)</b> | 209.1 (162.1, 255.2) | 251.2 (215.8, 286.7) | 129.6 (80.7, 178.4) | 157.0 (115.9, 198.1) |
| <b>Heart rate (bpm)</b>  | 19.6 (9.1, 30.2)     | 28.2 (20.3, 36.0)    | 36.2 (17.7, 46.7)   | 24.9 (15.6, 34.2)    |

**Table 4: Differences between sucrose and placebo with 95% confidence intervals**

|                                         | n  | Change in FLACC score | Crying Time (seconds) | Change in heart rate (bpm) |
|-----------------------------------------|----|-----------------------|-----------------------|----------------------------|
| <b>Total Sample</b>                     |    |                       |                       |                            |
| <b>Unadjusted</b>                       | 84 | -0.40 (-2.20, 1.41)   | -32.3 (-77.7, 13.1)   | 1.7 (9.0, -12.4)           |
| <b>Adjusted</b>                         | 84 | -0.86 (-2.50, 0.78)   | -47.6 (-84.5, -10.7)  | 0.9 (-9.8, 11.6)           |
| <b>Unadjusted Results by Age Groups</b> |    |                       |                       |                            |
| <b>0–1 month</b>                        | 36 | -1.22 (-3.50, 1.06)   | -52.7 (-117.5, 12.2)  | -3.6 (-16.7, 9.6)          |
| <b>1–3 months</b>                       | 28 | -1.66 (-5.27, 1.96)   | -52.2 (-142.1, 37.6)  | 4.6 (-20.2, 29.3)          |
| <b>3–6 months</b>                       | 20 | 1.50 (-1.82, 4.82)    | 6.3 (-61.9, 74.5)     | 6.9 (-14.3, 28.0)          |

shown that sucrose analgesia lasts for up to five minutes. Exclusion criteria included any infant deemed critically ill at the discretion of the attending physician, fructose intolerance, and EMLA application at site of venipuncture.

**Blinded randomization:** The subjects were randomized to the treatment groups using computer-generated block randomization organized by the hospital research pharmacist. Each pre-prepared syringe holding either sucrose or sterile water was labeled by numbers 1–84 and was indistinguishable by color, smell and flow during administration. The study syringes were placed in a sealed package and stored in a fridge in an area of the ED to which only the ED nurses had access. After written informed consent was obtained, the study nurse obtained the next labeled syringe. The number on the syringe was recorded with the patient's data and on a separate list containing the patient's name, which was kept separate from the data.

The research pharmacist held the numbered code list containing the identity of the solution used in each syringe until the study had officially ended and data analysis was completed. It was then released to the primary author and statistician so that correct identification of groups could occur. Thus throughout the study all of the researchers, outcome assessors, subjects and statistician were blinded to the identities of the solutions.

Pacifier use could not be blinded to the research nurse or parent since visualization of the face was required to score the primary outcome measure. The addition of a second research nurse to stand behind a curtain to take crying time measurements would have added considerable expense to the study and was not feasible. Random assignment of pacifier use was again computer generated by the pharmacist, so that each numbered syringe included instructions to use or omit pacifier. The researchers and statistician were blinded as to which patients had used pacifiers until after completion of analysis.

**Outcome measurements:** The pain related to venipuncture was primarily measured using the Face, Legs, Activity, Cry, and Consolability Pain Scale (FLACC).<sup>17-19</sup> This scale was validated by Merkel et al for measurement of pain in preverbal or cognitively impaired children, and is used by the pediatric pain service at SCH. The FLACC tool assesses changes in the above five categories of behavior, rating each on a scale of 0–2 (Table 1). Ten is the maximum score indicating severe pain and a score < 2 generally indicates absence of pain. FLACC scores were assessed before procedure and after venipuncture and change from baseline was our outcome measure. Interrater reliability for this scale has been demonstrated to be acceptable as kappa values for each of the five categories range between 0.52 and 0.82. It is generally acknowledged that interrater reliability coefficients over 0.41 demonstrate acceptable agreement between users.<sup>19</sup> Several different research nurses were trained by our research nurse coordinator in performing FLACC scores and other details related to outcome assessment prior to each of the study periods. One refresher session was offered throughout each study period also to ensure skills remained consistent.

Because pediatric pain in young infants is so difficult to clearly identify, we felt that it would be prudent to use other secondary outcome measures such as crying time and heart rate. Both of these measures have been widely used in the neonatal studies on sucrose efficacy for procedural pain, and crying time has been used as the primary outcome measure in many.<sup>2,4,5</sup> Crying time was monitored by a stopwatch from the infant's first cry after venipuncture and recorded as the number of seconds that vocalizations were sustained, up to 5 minutes. From previous studies of similar procedures, the majority, but not all infants ceased to cry within three-minutes.<sup>15</sup> Heart rate was measured pre procedure and at 1 minute intervals after the procedure for 5 minutes. The heart rate outcome measure is the difference between the highest value recorded over that 5-minute period and the baseline measure recorded prior to the procedure. We alighted upon this method of assessing heart rate from a review

**Table 5: Differences between pacifier and no pacifier with 95% confidence intervals**

|                                         | n  | Change in FLACC score | Crying Time (seconds)  | Change in heart rate (bpm) |
|-----------------------------------------|----|-----------------------|------------------------|----------------------------|
| <b>Total Sample</b>                     |    |                       |                        |                            |
| <b>Unadjusted</b>                       | 84 | -1.70 (-3.47, 0.07)   | -85.8 (-127.8, -43.8)  | 6.9 (-3.8, 17.5)           |
| <b>Adjusted</b>                         | 84 | -1.44 (-3.08, 0.20)   | -80.5 (-117.1, -43.9)  | 8.1 (-2.7, 18.9)           |
| <b>Unadjusted Results by Age Groups</b> |    |                       |                        |                            |
| <b>0–1 month</b>                        | 36 | -1.77 (-4.01, 0.47)   | -76.5 (-138.6, -14.5)  | 9.3 (-3.6, 22.1)           |
| <b>1–3 months</b>                       | 28 | -2.08 (-5.66, 1.50)   | -123.9 (-201.6, -46.3) | 0.9 (-23.9, 25.7)          |
| <b>3–6 months</b>                       | 20 | -0.70 (-4.02, 2.62)   | -42.4 (-105.9, 21.1)   | 11.2 (-9.0, 31.4)          |

of previous studies in this area as it is commonly used as an outcome measure and seemed reasonable and similar in concept to those previous studies.<sup>5</sup> For the FLACC score, the outcome measure is the difference between pre and post procedure.

All patients aged 0 – 6 months who arrived during study hours were identified in the PED, and the research nurse was contacted. The research nurse recruited and followed patients if eligible. Eligible patients were those meeting inclusion and exclusion criteria. The research nurse explained the study to the family, obtained written consent and gathered some baseline information about the subjects' past medical history. Patients were randomly assigned to one of four groups as follows: a) sucrose b) sucrose & pacifier c) placebo d) placebo & pacifier. Each child received, by mouth, 2 ml of either 44% sucrose or sterile water, two minutes prior to venipuncture. These solutions were prepared and coded in advance by pharmacy such that all other study participants and investigators were blinded to their identity.

Timers were used by the research nurse to coordinate all of the following events. The solution was administered by the research nurse to the anterior aspect of the tongue over 30 seconds via syringe and a pacifier was inserted orally according to randomization. At 2 minutes after commencement of solution administration, venipuncture took place as performed by the PED nurses and as per standard nursing practice. Parents interacted with voice or touch as per normal.

The research nurse collected all data. Baseline vitals such as temperature, weight and BP were recorded. A baseline pain score pre- venipuncture was assigned by the research nurse using the FLACC scale. Each child had continuous cardiac and oxygen saturation monitoring throughout the intervention and data collection. Heart rate and oxygen saturation were noted each minute over a 5-minute period post venipuncture. Crying time post venipuncture was measured by stopwatch. The research nurse assigned a FLACC score between 30 seconds and one minute after the procedure. If initial venipuncture was unsuccessful, a second attempt only took place after the full 5-minute interval. All data was recorded on a data collection sheet and was entered into a spreadsheet by the research nurse for analysis. The research nurse called each participant within 72 hours to assess for adverse effects. All documentation was locked in a secure cabinet, kept confidential for the length of the study and will be destroyed in five years. Data was entered into Microsoft Excel by the research nurse. The data was later

downloaded into S- Plus where the majority of the data-analysis was done.

### Data analysis

Sample size: Based on previous measurements of pain on the Premature Infant Pain Profile (PIPP- a 20 point scale), we estimated that the standard deviation of pain scores on the FLACC scale (a 10 point scale) to be approximately 1.75. Assuming an alpha level of 0.05 and a power of 90%, we required a total sample size of 84 infants to be able to detect a 1.25 -point average FLACC scale difference between two groups using a paired t-test. Sample size was based on our primary variable of interest and primary outcome (sucrose/pacifier effect on pain reduction) and calculated using nQuery Advisor version 4.0. Although pacifier/sucrose interaction effect was unknown we assumed no interaction in making this calculation.

Statistical analysis: A two-way analysis of variance was used to ascertain any interaction effects between our primary variables. Differences in intervention groups were computed both in unadjusted (via unpaired t-tests) and adjusted (via regression analysis) analyses for all continuous outcomes of interest (i.e. FLACC change score, crying time, and maximum heart rate difference). For the adjusted analysis, co-variables included in the regression were age, sex, weight, NPO time, and gestational age. The gestational ages for nine children were unavailable, and thus the mean of the remainder of the children was used to impute a value for these nine for purposes of the regression analysis.

The intention to treat principle was used in all our analyses – all subjects were analyzed in the groups to which they were initially assigned. Means, standard deviations, and/or 95% confidence intervals are presented for all continuous outcomes. P-values of statistical tests are presented for all outcomes.

### Results

Over two 3-month periods from February 2004 – June 2005, 87 patients were assessed for eligibility and 84 were randomized to the four groups. Timing of recruitment was dependent on research nurse availability, patient volume and cost. Two parents refused to participate and one patient was deemed too ill to engage in the study. Baseline characteristics of subjects in all groups are presented in Table 2. Most of the baseline characteristics were similar and did not differ between study periods. The most notable difference was that by chance the pacifier & placebo group had a mean and median age that was half of the other three groups. This group also had the highest

admission rate. The baseline FLACC score and heart rates were similar between the groups. None of the babies were crying before venipuncture occurred. All of the subjects had successful initial IV attempts.

Table 3 presents the means and 95% confidence intervals of the outcome variables by the four study groups. The ANOVA did not show any signs of an interaction effect between pacifier and sucrose with respect to any of the outcomes examined, thus direct t-test comparisons could be used to ascertain the effects of both sucrose and pacifier using the full sample.

**Unadjusted effects:** Estimates for FLACC score and heart rate are presented as mean change from baseline  $\pm$  standard deviation.

**Sucrose:** The FLACC score in the 43 sucrose infants increased from baseline by an average of  $3.2 \pm 3.6$  which was not significantly different from the  $3.6 \pm 3.3$  average of the 41 placebo infants ( $p = 0.66$ ). There were also no significant differences in crying time (sucrose:  $168.4 \pm 112.2$ , placebo:  $200.7 \pm 96.0$ ;  $p = 0.16$ ) or heart rate change (sucrose:  $28.1 \pm 29.3$ , placebo:  $26.4 \pm 18.7$ ;  $p = 0.75$ ).

**Pacifier:** The 40 infants that did not receive a pacifier had an average increase from baseline in FLACC score of  $4.3 \pm 4.5$  compared to the average increase from baseline of  $2.5 \pm 3.7$  in the 44 infants that did receive a pacifier. The difference between the two groups was very close to being statistically significant ( $p = 0.06$ ). The difference in crying time between the two groups was statistically significant (pacifier:  $143.3 \pm 101.7$ , no pacifier:  $229.1 \pm 90.6$ ;  $p = 0.0001$ ) while the difference in heart rate change was not (pacifier:  $30.6 \pm 27.7$ ; no pacifier:  $23.7 \pm 20.4$ ;  $p = 0.20$ ).

**Adjusted effects:** We ran a regression analysis on our three outcomes (FLACC difference, crying time, and heart rate difference) including our two interventions, as well as age, sex, weight, NPO time, and gestational age.

For change in FLACC score, age was the only variable that was found to significantly affect the pain score (older children experienced more pain,  $p = 0.006$ ). Neither sucrose nor pacifier was found to significantly affect FLACC score change.

It was a different story with crying time, as both sucrose (sucrose group  $47.6 \pm 18.8$  seconds less crying time than placebo;  $p = 0.01$ ) and pacifier (pacifier group  $80.5 \pm 18.7$  seconds less crying time than no pacifier;  $p < 0.0001$ ) had significant effects. Crying time increased with both increasing age (older children cried longer,  $p < 0.0001$ ) and increasing gestational age (children with higher gestational age cried longer,  $p = 0.02$ ). This was estimated such that every week of age gain resulted in crying 8.5 seconds longer.

For change in heart rate, none of our co-variates had a significant effect.

**Subgroup analysis:** The results of the regression analysis prompted us to do a post-hoc subgroup analysis, stratifying by age. We divided the children into three subgroups: 0–1 month, 1–3 months, and 3–6 months (Tables 4 and 5).

Due to the small sample sizes in this analysis, none of the subgroups showed a statistically significant difference for either

pacifier or sucrose with respect to change from baseline in FLACC score, although interestingly both interventions showed much greater effect in the 0–1 month and 1–3 month groups than the older than 3 month group.

For crying time, the sucrose intervention was not significant in any of the three groups, but again showed greater improvement in the younger two groups. Crying time was significantly reduced for pacifier versus non-pacifier in both the 0–1 month and 1–3 month groups, despite the small sample sizes. Subgroup analysis revealed a mean crying time difference of 76.52 seconds ( $p < 0.0171$ ) (0–1 month) and 123.9 seconds ( $p < 0.0029$ ) (1–3 month). For subgroup age  $> 3$  months pacifier did not have any significant effect on crying time.

**Other:** The only adverse event that was noted was one episode of vomiting which occurred in a total of three children, one in each of the groups except for the sucrose only group.

## Discussion

Our results suggest that venipuncture is a procedure that causes moderate pain in infants. A FLACC score increase of 4.84 (placebo group), post venipuncture falls into the rating of moderate pain as per the authors of the FLACC scale.<sup>17-19</sup>

Currently the standard practice during venipuncture in young infants in the PED is not to administer any analgesia. Even though neonatal studies have previously demonstrated the effectiveness of sucrose and/or pacifiers, this practice has not been adopted in general in emergency departments as well as other pediatric departments.<sup>20</sup> We hope that this study will demonstrate the ease of use of sucrose and/or pacifier and we hope that this will inspire practice change in this area.

Our choices of outcome measures were a result of a review of the literature. It should be noted that without direct verbal corroboration from the infants we cannot be entirely sure that any of the above outcome measures actually reflect degree of pain. Previous studies have relied on assessments of behavioral and physiological changes as indirect indicators of pain. We felt that the most comprehensive approach was to use a combination of a validated pain scale, total crying time and change in heart rate. The FLACC scale uses parameters similar to many of the neonatal pain scales, is highly reliable, has been validated, is very easy to use and teach and was best suited to the age group we wished to study. Although crying is associated with pain, it is not exclusive to pain, and thus must be interpreted with caution. In this study, none of the infants were crying prior to the procedure and all cried after it, so it is likely that the pain of this procedure induced this behavioral response. Thus we feel that in this study, crying time is a reasonable measure of pain or discomfort and have interpreted the results in such a light.

Our results show that pacifier appears to be an effective analgesic for the procedural pain of venipuncture in infants. Even though statistical significance was only narrowly missed for the primary outcome measure ( $p = 0.06$ ), a change in average FLACC score from 4.3 (no pacifier) to 2.5 (pacifier) would be considered by most to be of clinical significance. Pacifier use significantly reduced crying time (statistically and clinically), particularly in the 0–3 month age group, despite small sample sizes of sub-group analysis. It is promising to see that this analgesic effect seems to extend beyond the neonatal period,



perhaps up to three months of age. It appears that the effect wanes with age beyond three months. Further trials with larger sample sizes in this age group would be helpful to clarify this matter however.

One caution in the interpretation of results surrounding pacifier use was the fact that the observer was not blinded. This presents potential bias that was unavoidable for the primary outcome measure assessment, as it was necessary to look closely at the infants' faces to give a rating to this parameter on the FLACC scale. The addition of a second observer for the outcome measure of crying time would nearly have doubled the budget of our study and was thus impractical in our setting.

Also, heart rate measurements were assessed at the minute marks only and it is possible that these data points do not accurately represent interim variabilities. This may explain why differences in heart rate were not found. Another possibility is that heart rate monitoring may not be a reliable indicator of the amount of pain experienced. One adult study observed a decrease in heart rate in some patients, likely due to vagal stimulation, on insertion of an IV.<sup>21</sup> Two adult observational studies have noted lack of correlation of heart rate with pain or changes in pain intensity.<sup>21,22</sup> Review of neonatal studies reveals that heart rate data collection methodology is highly variable and there often does seem to be dissociation between pain scale findings and physiological responses such as heart rate.<sup>5,23</sup> Pereira et al evaluated the validity of heart rate measurements for neonatal pain assessment in an RCT and concluded that heart rate variations are an inconsistent and insensitive way to evaluate pain in that population.<sup>24</sup> Further clarification as to the reliability of this outcome measure as an indicator of pain across the pediatric spectrum may be warranted.

For sucrose as analgesia, the results are less clear. T-test results demonstrated no significant benefit; however age adjusted regression analysis showed significant reduction in crying time. Trends seem to show greater reduction in the younger age subgroups. Sucrose appears to be less effective with increasing age at the dosage studied. Further study with larger sample sizes and perhaps using stronger concentrations of sucrose would be required to determine the upper age limit for the effectiveness of sucrose. It seems that sucrose and pacifier have an additive beneficial effect when used together and perhaps this is where the best use for sucrose as analgesia lies- to be used in conjunction with pacifier.

One must consider the dose of sucrose used. We chose 0.88 g (2 ml of a 44% solution) as this was easily prepared by our pharmacy, which uses an 88% sucrose solution to mix oral pediatric medications, and diluted this solution for the purposes of our study. Doses up to 0.5 g have been studied and determined to be safe for use in the neonatal period<sup>5</sup> and immunization studies have used doses as high as 2.5 g for older infants<sup>14,16</sup> without adverse events. Future studies could look closely at the issue of optimal doses, especially with older infants.

There are several limitations to our study. One limitation to our study was that the study population was a convenience sample of patients and a few potentially eligible patients were not enrolled. The research nurses were available for 8–16 hours during the day so some children arriving overnight may have been missed. It is unlikely, however that these children would have been different from our study population.

Another limitation of this study was that despite accurate randomization, our randomization produced somewhat of an "unlucky sample" in that there were imbalances in some of the baseline statistics particularly age, NPO, and rate admitted. NPO was found in our adjusted analyses to not have an effect on our outcomes, while admission rates were not too unbalanced, and would be unlikely to have an effect on our final outcomes. Due to our determination in the adjusted analysis that, older children tend to experience more pain, the lower age in the pacifier/ placebo group could lead to slight overestimation of pain relief in pacifiers and an underestimation of pain relief in the sucrose. These results may need to be interpreted with caution.

The intention of this study was to recruit infants between the ages of 0 and 6 months. Although infants across this entire age spectrum were recruited, numbers at the upper end of this range were less than had been desired, reflecting the visit and illness spectrum of this group and also chance (Tables 4 and 5). For the 84 infants recruited, the median age was 48 days, the mean age was 30 days and only 20 infants fell into the 3–6 month age range. Thus younger infants were represented strongly and older infants were underrepresented in this study. Therefore we could not draw valid conclusions about the effectiveness of our interventions on infants older than 3 months of age.

We also observed a higher standard deviation than we had originally anticipated. As a result, statistical significance was not achieved when examining age related effects although intriguing trends towards significance were seen which warrant further examination.

## Conclusion

This study demonstrates that venipuncture in infants is a moderately painful procedure. The use of pacifier with sucrose as procedural analgesia for venipuncture in the PED is effective in reduction of pain in infants 0–3 months old, as shown by decrease in crying times. Pacifiers and sucrose are inexpensive, easy to use, have quick onset, short duration of action, and no serious side effects. They should be used in the pediatric emergency department and other pediatric units to help prevent pain from venipuncture for infants aged 0–3 months. Further study to clarify effects of age and sucrose concentrations, as well as effectiveness for other painful procedures is required.

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# Lactate: Creatinine Ratio in Babies With Thin Meconium Staining of Amniotic Fluid

Rishi Kant Ojha, Saroj K. Singh, Sanjay Batra, V. Sreenivas, Jacob M. Puliye

## Abstract

**Background:** ACOG states meconium stained amniotic fluid (MSAF) as one of the historical indicators of perinatal asphyxia. Thick meconium along with other indicators is used to identify babies with severe intrapartum asphyxia. Lactate creatinine ratio (L:C ratio) of 0.64 or higher in first passed urine of babies suffering severe intrapartum asphyxia has been shown to predict Hypoxic Ischaemic Encephalopathy (HIE). Literature review shows that meconium is passed in distress and thin meconium results from mixing and dilution over time, which may be hours to days. Thin meconium may thus be used as an indicator of antepartum asphyxia. We tested L:C ratios in a group of babies born through thin and thick meconium, and for comparison, in a group of babies without meconium at birth.

**Methods:** 86 consecutive newborns, 36 to 42 weeks of gestation, with meconium staining of liquor, were recruited for the study. 52 voided urine within 6 hours of birth; of these 27 had thick meconium and 25 had thin meconium at birth. 42 others, who did not have meconium or any other signs of asphyxia at birth provided controls. Lactate and creatinine levels in urine were tested by standard enzymatic methods in the three groups.

**Results:** Lactate values are highest in the thin MSAF group followed by the thick MSAF and controls. Creatinine was lowest in the thin MSAF, followed by thick MSAF and controls. Normal babies had an average L:C ratio of 0.13 ( $\pm 0.09$ ). L:C ratio was more among thin MSAF babies ( $4.3 \pm 11.94$ ) than thick MSAF babies ( $0.35 \pm 0.35$ ). Median L:C ratio was also higher in the thin MSAF group. Variation in the values of these parameters is observed to be high in the thin MSAF group as compared to other groups. L:C ratio was above the cutoff of 0.64 of Huang et

al in 40% of those with thin meconium. 2 of these developed signs of HIE with convulsions (HIE Sarnat and Sarnat Stage II) during hospital stay. One had L:C Ratio of 93 and the other of 58.6. A smaller proportion (20%) of those with thick meconium had levels above the cutoff and 2 developed HIE and convulsions with L:C ratio of 1.25 and 1.1 respectively.

**Conclusion:** In evolving a cutoff of L:C ratios that would be highly sensitive and specific (0.64), Huang et al studied it in a series of babies with severe intrapartum asphyxia. Our study shows that the specificity may not be as good if babies born through thin meconium are also included. L:C ratios are much higher in babies with thin meconium. It may be that meconium alone is not a good indicator of asphyxia and the risk of HIE. However, if the presence of meconium implies asphyxia then perhaps a higher cut-off than 0.64 is needed. L:C ratios should be tested in a larger sample that includes babies with thin meconium, before L:C ratios can be applied universally.

## Background

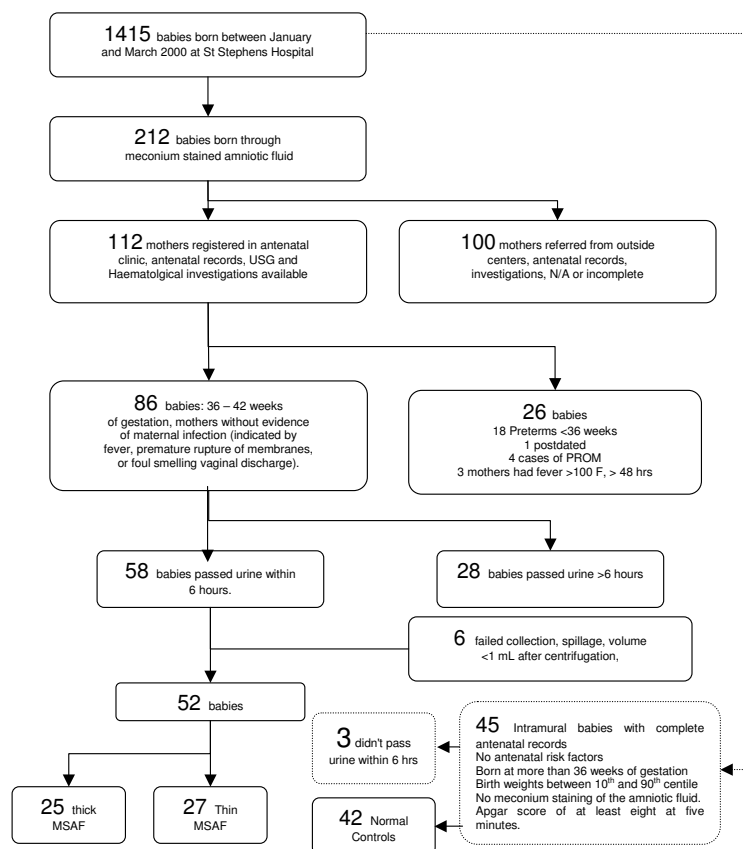
Anoxic injury to the fetal brain as a result of birth asphyxia may lead to cerebral palsy. Intrapartum asphyxia alone however accounts for only a small proportion of cases of cerebral palsy (CP).<sup>1,2</sup> In a consensus statement, the Australian and New Zealand Perinatal Societies have estimated that around 10% of cases of cerebral palsy stem from adverse intrapartum events.<sup>3</sup> In the majority, the cause of CP is antepartum.<sup>4</sup> Intrinsic fetal causes like intracranial malformations and inborn errors of metabolism contribute to a miniscule number of cases.

The American College of Obstetricians and Gynecologists (ACOG) has laid down compulsory criteria, all of which must be met for establishing a plausible link between intrapartum asphyxia and neurological deficit. These are – profound acidemia, Apgar score of 3 or less for more than 5 minutes, neonatal neurological sequelae (like seizures), and multiorgan system dysfunction.<sup>5</sup>

The manifestations of antepartum asphyxia are poorly understood and most are not specifically related to brain damage. Reduced fetal movements, non-reassuring fetal heart rate patterns (FHRT),<sup>6</sup> fetal ECG,<sup>7</sup> fetal scalp blood sampling<sup>8</sup> and in-utero passage of meconium<sup>9</sup> are some of them. Lack of

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**Figure 1**  
Schematic representation of the study population to show how the cases were recruited for the study.

specificity of these indicators limits their use in medicolegal issues. Epidemiologically, as most damage in cases of cerebral palsy is antepartum, each of these 'nonspecific' indicators need careful scrutiny to identify antepartum asphyxia.

As with intrapartum asphyxia, most babies with antepartum asphyxia escape damage. In only a few babies with asphyxia is there neonatal encephalopathy. Some of these may progress to Hypoxic ischaemic encephalopathy (HIE), and only a subset of those with HIE eventually sustain brain damage.<sup>10</sup>

12%-22% of all pregnancies are complicated by meconium, but 50% of those who develop HIE had been born through meconium stained amniotic fluid<sup>11</sup>(MSAF). Meconium in labor may indicate fetal distress or asphyxia. There are at least three theories explaining meconium passage: in-utero relaxation of the anal sphincter<sup>12</sup> vagal stimulation<sup>12,13</sup> and postmaturity.<sup>14</sup> Numerous investigators have concluded that presence of meconium in the amniotic fluid is a sign of fetal hypoxia or acidosis.<sup>15-19</sup>

Recent studies<sup>20,21</sup> have reported much higher levels of fetal erythropoietin, and lower fetal oxygen saturation<sup>22</sup> in pregnancies complicated by meconium and concluded that in-utero passage of meconium reflects chronic asphyxia. In summary, it is understood that, (though not an independent predictor of poor neurodevelopmental outcome), intrauterine passage of meconium may reflect an asphyxial event.

Some babies pass meconium due to intrauterine infections, chorioamnionitis, and premature rupture of membranes and up to 35% of postmature babies (born after 42 weeks of gestation)

may pass meconium.<sup>23</sup> Clearly, asphyxia cannot alone be implicated for in-utero meconium passage especially in post-mature babies and in the presence of intrauterine infections.

When freshly passed, meconium is a thick, viscous, green liquid<sup>24</sup> except perhaps in cases of fetal diarrhea due to Listeriosis. Meconium stains the amniotic fluid and presents as thick meconium. The consistency is altered over time by dilution and fetal movement<sup>25</sup> resulting in thin meconium. Arguably, thinner and more uniformly mixed meconium has been retained in the amniotic fluid for a longer duration (hours to days),<sup>25</sup> than meconium that appears thick. The exact time interval between passage of meconium to its complete dilution is not available in literature.

After excluding postmature babies and those who are likely to be infected, we assume for purposes of this study that all babies who pass meconium have asphyxia. Those who pass thick meconium are assumed to have intrapartum asphyxia and those with thin meconium to have antepartum asphyxia. We tested the premise with Lactate: Creatinine ratio (L:C ratio)- a proven marker of asphyxia.

Combining lactate- a product of anaerobic metabolism resulting from hypoxia, and creatinine-a measure of renal function whose excretion is reduced in renal compromise caused by ischaemia, L:C ratio in urine has been shown to predict HIE and future neurodevelopmental outcome. Huang et al<sup>26</sup>

studied a group of severely asphyxiated newborns, identified by well-established criteria of perinatal asphyxia (thick meconium among others) and reported that L:C ratio of 0.64 or higher in first passed urine was highly specific for HIE.<sup>5</sup>

We used L:C ratio as a marker to study antepartum and intrapartum asphyxia. We tested L:C ratio in a group of term babies, born to mothers without a history of intrauterine infection, through thin and thick meconium, and for comparison in a group of normal babies without meconium.

## Methods

The study was conducted at St Stephen's Hospital, Delhi India. It is a 600 bedded tertiary level postgraduate teaching hospital, conducting 5000 deliveries annually, equipped with a 75 bedded nursery and level III neonatal intensive care unit.

Of 1,415 deliveries between January to March 2000 at our hospital, 212 babies were born through MSAF. Some of these mothers were referred from other centers in labor and antenatal records were not available. These mothers were excluded. The number of eligible mothers was thus 112. From among these, post term mothers and mothers with a history suggestive of infection were excluded. 86 consecutive newborns of 36–42 weeks of gestation with meconium staining of amniotic fluid, without evidence of maternal infection (indicated by fever, premature rupture of membranes, or foul smelling vaginal discharge), were thus subjects of the study. None of the babies had any renal abnormality, or other congenital anomalies detected at antenatal ultrasonographic examination. 28 babies did not pass urine within six hours. Urine from 6 babies could

**Table 1: Characteristics of newborns in the study: 27 newborns with thin MSAF, 25 newborns with thick MSAF and 42 controls**

| Characteristic                                | Normal infants<br>(n = 42) | Thin (n = 27)    | Infants with MSAF (n = 52)<br>Thick (n = 25) | p- Value <sup>§</sup> |
|-----------------------------------------------|----------------------------|------------------|----------------------------------------------|-----------------------|
| <b>Birth weight (±SD)</b>                     | 2885.7 ± 374 g             | 2767.0 ± 289.9 g | 2654.8 ± 311 g@                              | <b>0.03</b>           |
| <b>Gestational Age (±SD)</b>                  | 40 Wks ± 1.57 Wk           | 39 Wks ± 2.0 Wks | 39 Wks ± 2.0 Wks                             | <b>0.96</b>           |
| <b>Sex</b>                                    |                            |                  |                                              |                       |
| Male                                          | 18 (42.9%)                 | 19 (70.4%)       | 13 (52.0%)                                   | <b>0.08</b>           |
| Female                                        | 24 (57.1%)                 | 8 (29.6%)        | 12 (48.0%)                                   |                       |
| <b>Apgar Score</b>                            |                            |                  |                                              |                       |
| >6 at 5 min                                   | 42 (100.0%)                | 25 (92.5%)       | 22 (88.0%)                                   | <b>0.07</b>           |
| <6 AT 5 min                                   | 0 (0.0%)                   | 2 (7.4%)         | 3 (12.0%)                                    |                       |
| <b>Maternal problems</b>                      |                            |                  |                                              |                       |
| None                                          | 38 (90.5%)                 | 25 (92.6%)       | 13 (52.0%)                                   | <b>&lt;0.01</b>       |
| Significant maternal problems*                | 4 (10.0%)                  | 2 (7.4%)         | 12 (48.0%)@                                  |                       |
| <b>Mode of Delivery</b>                       |                            |                  |                                              |                       |
| Normal vaginal delivery                       | 39 (92.9%)                 | 18 (66.7%)       | 16 (64.0%)                                   | <b>&lt;0.01</b>       |
| Forceps Delivery                              | 3 (7.1%)                   | 4 (14.8%)        | 3 (12.0%)                                    |                       |
| Caesarian section                             | 0 (0.0%)                   | 5 (18.5%)        | 6 (24.0%)@                                   |                       |
| <b>Postnatal problems</b>                     |                            |                  |                                              |                       |
| None                                          | 42 (100%)                  | 23 (85.2%)       | 18 (72.0%)                                   | 0.001                 |
| Other problems**                              | 0 (0.0%)                   | 4 (14.8%)        | 7 (28.0%)@                                   |                       |
| <b>Hypoxic Ischaemic Encephalopathy (HIE)</b> |                            |                  |                                              |                       |
| No                                            | 42 (100%)                  | 25 (92.6%)       | 23 (92.0%)                                   | 0.12                  |
| Yes                                           | 0 (0.0%)                   | 2 (7.4%)         | 2 (8.0%)                                     |                       |

\*Thick MSAF babies had significantly more antenatal problems – 3 cases of maternal hypertension, 2 cases of gestational diabetes, 3 cases of fetal heart rate abnormality (FHRT), 2 cases of breech delivery, and one case each of cephalopelvic disproportion, and intrauterine growth retardation. Thin MSAF Babies had fewer problems in the mothers with two cases of hypertension of which one mother also had cephalopelvic disproportion.

\*\*2 children born through Thin MSAF developed Group B Streptococcal septicaemia, 2 developed respiratory distress attributable to aspiration pneumonia, and one child developed hyperbilirubinaemia requiring phototherapy. In the Thick MSAF Group, 4 developed respiratory distress attributable to aspiration pneumonia, 2 developed hyperbilirubinaemia requiring phototherapy and one child had congenital heart disease.

§ Based on One-Way ANOVA/Fisher's Exact test

@Significant difference of thick MSAF group in comparison to controls.

not be analyzed as volume available, after centrifugation (to remove the heavy precipitates in neonatal urine), storage, and transportation to the laboratory was found inadequate. Finally more than 1 ml of clear supernatant urine passed within six hours of birth was available for testing from 52 babies and this group of samples was analyzed. Figure 1 shows a flow diagram of how the cases were recruited.

Meconium was categorized into thick or thin, based on its naked-eye appearance, by the pediatrician or nurse attending the delivery. Among the babies whose urine was available, 27 had had thick meconium and 25 had thin meconium. For comparison, we collected samples of urine, passed within six hours of birth from 42 normal babies born at more than 36 weeks of gestation with no staining of the amniotic fluid. These babies had Apgar score of at least eight at five minutes. This was essentially a 'convenience sample' collected from babies of consenting parents who met the above criteria to act as controls.

The pediatric unit looked after all babies during their hospital stay. Blood gas analysis was done when indicated as per hospital protocol. For staging of HIE, the classification of Sarnat and Sarnat<sup>28</sup> was used. The score uses clinical parameters like heart rate, respiration, pupils, consciousness, muscle tone, posture

and neonatal reflexes and electroencephalographic (EEG) criteria, as well as incidence of seizures not attributable to transient metabolic derangements. Whereas a detailed clinical scoring, and incidence of seizures was recorded in all suspected babies, EEG was not done. The hospital research committee approved the study. Informed consent was obtained from parents of babies participating in the study, prior to urine collection.

Samples of the first voided urine were centrifuged and clear supernatant was transferred to 1-ml plain Greiner cones (Greiner Labortechnik GmbH, Maybachstra, Frickenhausen, Germany) and preserved at minus 32°C in a deep freezer. All samples were tested together for urine lactate and creatinine by conventional enzymatic method by a Randox™ kit (Randox Laboratories, Co. Antrim, UK) on Olympus (Reply) autoanalyzer (Olympus Optical Co. Ltd, Shinjuku-ku, Tokyo, Japan).

The oxidase enzyme in the kit converts lactate to pyruvic acid and hydrogen peroxide, which results in oxidative conversion of chromogen to produce a coloured dye with absorption maximum at 540 nm, the amount of which is directly proportional to the amount of lactate in the sample. Creatinine in urine was measured by the concentration of a yellow orange colored dye

**Table 2: Urine Lactate, Creatinine and L: C Ratio in first passed urine within six hours of birth from normal babies, those with thick and thin meconium staining of liquor at birth. (p-values comparing the means by ANOVA on log transformed values**

|                           | Controls (n = 42)    | Thin MSAF (n = 27)  | Thick MSAF (n = 25) | P value <sup>\$</sup> |
|---------------------------|----------------------|---------------------|---------------------|-----------------------|
| <b>Lactate (mg/dL)</b>    |                      |                     |                     |                       |
| Mean ± SD                 | 3.3 ± 2.79@          | 21.6 ± 34.83        | 5.1 ± 5.34          | <b>0.02</b>           |
| Median (IQR)              | 1.8 (1.30 – 5.05)    | 6.7 (1.10 – 14.60)  | 3.5 (1.49 – 6.40)   |                       |
| <b>Creatinine (mg/dL)</b> |                      |                     |                     |                       |
| Mean ± SD                 | 25.3 ± 10.08@        | 17.7 ± 13.32        | 20.4 ± 13.71        | <b>&lt; 0.01</b>      |
| Median (IQR)              | 26.2 (19.58 – 32.00) | 15.7 (7.00 – 25.70) | 20.3 (8.50 – 30.80) |                       |
| <b>L:C Ratio</b>          |                      |                     |                     |                       |
| Mean ± SD                 | 0.13 ± 0.09@         | 4.33 ± 11.94        | 0.35 ± 0.35         | <b>&lt; 0.01</b>      |
| Median (IQR)              | 0.09 (0.06 – 0.18)   | 0.29 (0.09 – 1.11)  | 0.23 (0.11 – 0.48)  |                       |

<sup>\$</sup> Based on One-way ANOVA

@: Significant difference between Controls and Thin MSAF (on Bonferroni adjusted multiple comparisons).

formed from the reaction with Picric acid under alkaline conditions, which had its absorption maximum at 500 nm.

The continuous and quantitative variables like birth weight, gestational age were compared among the three groups of subjects, namely normal babies, those with thin and thick MSAF, using the analysis of variance technique. Lactate, creatinine and L:C ratio values were analyzed with ANOVA after logarithmic transformation followed by Bonferroni adjustment for multiple comparisons. The Bonferroni correction is part of the one-way command of Stata ver 8.0, which gives the actual p values for each specific comparison. It, like any other multiple comparison procedure, is relevant only when one finds a significant difference among the groups being compared by ANOVA. Bonferroni correction is a more conservative procedure than other multiple comparison procedures. Thus, if Bonferroni correction leads to a significant result, we can be more confident of the significance of the result.

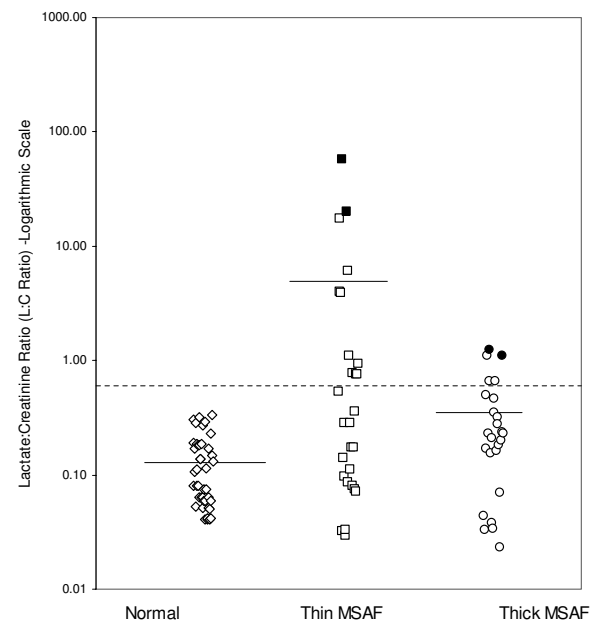
Qualitative variables like sex, Apgar score (categorization into two groups, <6 at 5 minutes and ≥ 6 at 5 minutes), maternal and postnatal problems (again categorized-present or absent) were compared among the three groups by Fisher's exact test. All the statistical analyses were carried out using STATA 8.0. p – value of less than 0.05 was considered to be statistically significant.

## Results

Table 1 shows the population characteristics of the three groups of babies: those born with thin MSAF, those with thick MSAF and normal babies. They were comparable in terms of gestational age, gender distribution, and Apgar scores at 5 minutes. Problems during gestation like pregnancy induced hypertension, cephalopelvic disproportion, and fetal heart rate abnormalities, were associated more with thick meconium stained babies compared to controls ( $p < 0.01$ ) than with thin meconium compared to controls. Four mothers in the control group had antenatal problems. Two mothers had gestational diabetes (on diet control), along with hypertensive (on treatment), one had hypertension alone (on treatment) and one mother had leaking of nearly 20 hours duration. Normal babies on the average weighed 120 grams more than babies with thin MSAF and 230 grams more than babies with thick MSAF. However, only thick MSAF babies weighed significantly lower compared to controls (Bonferroni corrected  $p = 0.02$ ). Difference in the birth weights

between thin and thick MSAF babies was not statistically significant (Bonferroni corrected  $p = 0.69$ ).

Thick MSAF babies had three cases of maternal hypertension, 3 cases of fetal heart rate abnormality (FHRT), two cases of breech delivery, and one case each of cephalopelvic disproportion, and intrauterine growth retardation. Thin MSAF Babies had fewer problems in the mothers with two cases of hypertension and one case of cephalopelvic disproportion. Two babies born through thick MSAF who developed HIE had history



**Figure 2**

Lactate: Creatinine ratio (L:C ratio) in the normal population compared against thin and thick meconium stained babies, logarithmic scale. The cutoff for ratio of Huang and Wang indicative of HIE (= 0.644) is shown in broken lines and means in each population by solid lines. The dark boxes and circles represent the babies who developed HIE. HIE developed in babies with the highest value of L:C ratio. The mean L:C ratio in the Thin MSAF group is skewed upwards due to outliers but these are the two babies who develop HIE (at values, a 100 fold of the cut-off of 0.64)

of maternal hypertension, neither had FHRT and both were delivered vaginally, and had low apgar scores. The two babies born through thin MSAF who developed HIE were without any maternal hypertension, no FHRT, and hence both were delivered vaginally. Apgar score of one was 3 at 5 minutes but the other had an Apgar score of 8, developed neuromotor excitability and excessive crying and later developed seizures. All controls were born vaginally, 24% (n = 6) with thick MSAF and 18% (n = 5) with thin were born through Caesarian section.

Postnatally, 2 babies born through thin MSAF developed Group B Streptococcal septicaemia, 2 developed respiratory distress attributable to aspiration pneumonia, and one child developed hyperbilirubinaemia requiring phototherapy. In the Thick MSAF Group, 4 developed respiratory distress attributable to aspiration pneumonia, 2 developed hyperbilirubinaemia requiring phototherapy and one child had congenital heart disease. None of the babies with HIE had any congenital malformation detected at antenatal ultrasonography, clinical examination at birth or postnatal cranial ultrasonography.

Table 2 compares the values of lactate, creatinine and L:C ratios in babies with thin MSAF, thick MSAF and normal babies. Lactate values are highest in the thin MSAF group followed by the thick MSAF and controls. Creatinine, on the other hand, was lowest in the thin MSAF, followed by thick MSAF and controls. Normal babies had an average L:C ratio of 0.13 ( $\pm$  0.09). It can be noted that the L:C ratio was more among thin MSAF babies ( $4.3 \pm 11.94$ ) than thick MSAF babies ( $0.35 \pm 0.35$ ). Median L:C ratios were also higher in the thin MSAF group. Variation in the values of these parameters is observed to be high in the thin MSAF group as compared to other groups.

Though there are significant differences in the means of the three parameters among the three groups, multiple comparison procedures showed the difference as significant only when normal babies were compared to babies with thin MSAF (Bonferroni corrected p values: lactate 0.02, creatinine 0.01, LC ratio < 0.001). In other words, differences between thin and thick MSAF groups are not significant (Bonferroni corrected p values: lactate 0.34, Creatinine 0.75, LC ratio 0.09) and also that between thick MSAF and control groups (Bonferroni corrected p values: lactate 0.90, creatinine: 0.26, LC ratio 0.14). There was no significant difference between thick MSAF and controls.

Median values of the three parameters also show similar pattern in the three groups.

Figure 2 shows distribution of L:C ratios in normal controls and in babies with thin and thick meconium on logarithmic scale. No babies in the control group had L:C ratios of more than 0.64. Five (20%) babies born with thick meconium had levels above 0.64 and 2 of these developed HIE stage II during hospital stay. 11 babies with thin meconium (40%) had levels above the cut-off of 0.64 and among these, HIE developed in the extreme range of figure at L:C ratio of 58.6 and 93.

## Discussion

We have looked at babies who had probable asphyxia long before the time of birth as indicated by thin meconium, against babies asphyxiated around the time of birth, indicated by thick meconium.<sup>12,20-22</sup> We found that the mean L:C ratio in babies with thin meconium was 12 times higher than in those with thick meconium. The two highest values in babies with thin meconium

were 93 and 58.6, and in those with thick meconium 1.25 and 1.10. It is significant that it is these four babies (two in each group) who developed convulsions and HIE stage II during hospital stay.

We found that 7% of babies with thin meconium progress to HIE stage II during hospital stay. Similar incidence (6.3%) of severe birth asphyxia (HIE stage II and beyond) in babies born through thin MSAF has been reported earlier.<sup>28</sup> Although, in our series, we had 2 cases of asphyxia each in babies born through thick and thin MSAF, babies with thick meconium are known to suffer more HIE.<sup>9,28,29</sup>

As a priori we have assumed that meconium staining of amnion suggests intrauterine asphyxia. Not all authors are agreed that this is a marker of distress. Some authors consider the presence of meconium as a physiological event.<sup>9,30</sup> Jazayeri et al,<sup>20</sup> and Richey et al<sup>21</sup> reported much higher levels of fetal erythropoietin and Carbonne et al<sup>22</sup> reported fetal anoxia in babies with early passage of meconium. We have shown high levels of L:C ratio among babies with thin meconium. We believe that based on these reports and our findings in this paper, it can be stated that early passage of meconium suggests chronic intrauterine asphyxia.

Thin meconium babies show considerable skewness in their L:C ratio suggesting it to be a heterogeneous group and the ratio a nonspecific marker of asphyxia in this group of newborns. A closer scrutiny (Figure 2) shows at least two groups – one is a compact cluster of babies with L:C ratios comparable to babies with thick meconium and no HIE. The other group of babies with L:C ratios, 10–100 times higher than the mean L:C ratio in the previous cluster and cases of HIE occurred in this extreme group. The first group probably reflects milder ‘compensated’ asphyxia whereas the latter group probably suffered more severe asphyxia. The latter group can perhaps be better defined when a combination of other antenatal risk factors like FHRT, low apgar score at birth, and thin meconium are used along with L:C ratio.

High L:C ratios in babies with thin meconium need a rational explanation. Lactate is produced by anaerobic metabolism during an asphyxial insult<sup>31-33</sup> and continues to be excreted for long after the insult.<sup>34</sup> Creatinine excretion is dependent upon glomerular filtration and is reduced in asphyxia<sup>35</sup> whereas lactate is cleared partly by hepatic and renal metabolism and partly by tubular secretion<sup>36</sup> using high capacity H<sup>+</sup>/monocarboxylate cotransporter<sup>37</sup> – operative even in shock<sup>34</sup> and its excretion is reflective of blood levels rather renal status. Babies continue to excrete lactate and creatinine excretion is reduced, the ratios increasing accordingly. Very high lactate in experimental and clinical asphyxia is well known<sup>34,38</sup> and L:C ratios 10–100 times the baseline have been reported previously.<sup>26</sup>

The bladder capacity is limited, and repeated voiding occurs in-utero. Once asphyxia occurs, there is continuous excretion of lactate for a long time afterwards. High urine lactate has been seen as much as 48–72 hours after the insult,<sup>26</sup> and raised cerebral lactate has been demonstrated up to a month after asphyxia.<sup>34</sup> If the asphyxia occurs early – long before delivery, it may be assumed that all the urine in the bladder consists of post asphyxial urine. If on the other hand, asphyxia occurs just before delivery, the secreted lactate in urine dilutes in the urine already formed in the bladder and, the overall level may be lower. A similar sequence occurs with creatinine and post-asphyxial low-creatinine-urine is diluted in the urine containing normal



creatinine levels. In summary high lactate in thin MSAF babies results from continued excretion over long periods and a serial accumulation of lactate.

Thin meconium is a common event in obstetric practice and is generally considered innocuous. We have not looked at the issue of brain damage in this paper and we do not offer any suggestion to the contrary. In our sample of babies with thin meconium, it is those who have L:C ratio 100 times larger than the cut-off of 0.64 who develop HIE. A suitable cutoff of L:C ratio for babies with thin meconium can be evolved by larger studies.

Our study has two important limitations. Firstly, babies were followed only up to discharge from the nursery, and no long-term follow-up for HIE is available. It limits the study from commenting on the issue of brain damage. Secondly we used a 6-hour cutoff for urine collection. It is not unusual for normal babies not to pass urine in up to 24 or even 48 hours. The most severely asphyxiated newborns are oliguric and may not pass urine for even longer. The L:C ratio was not studied in them. Studies on ischemia – reperfusion induced cell damage suggest that the damage is complete by six hours. The “window of opportunity” for rescue medications thus, is only a few hours and in no case more than six hours.<sup>39</sup> Therefore it would perhaps be futile to know about asphyxia outside of this window of six hours, where interventions may not be useful.

In this study we used conventional enzymatic methods to assay lactate and creatinine. Zuppi et al have shown earlier that lactate levels in urine by conventional enzymatic methods are comparable to levels by proton NMR spectroscopy of urine<sup>40</sup> and that two methods can be used interchangeably.

In conclusion, we report that babies with thin meconium normally have much higher L:C ratios and HIE occurs at much higher levels in this group. Larger studies are needed to evolve a cut-off that performs with acceptable sensitivity and specificity in babies with thin meconium.

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# Discordant Twins with the Smaller Baby Appropriate for Gestational Age – Unusual Manifestation of Superfetation: A Case Report

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## Abstract

**Background:** Documentation of superfetation is extremely rare in humans. The younger foetus has invariably been small for gestational age (estimated from the date of the last menstrual bleed) in all the cases reported in the literature. We report a case where the younger twin was of appropriate size for gestation.

**Case Presentation:** The first of twins was of 32 weeks gestation and the baby was of appropriate size and development for the gestational age. The second twin was of 36 weeks gestation. Gestational age was estimated with the New Ballard score, x-ray of the lower limbs, dental age on x-ray, and ophthalmic examination.

**Conclusion:** Bleeding on implantation of the first foetus probably helped demarcate the two pregnancies. Dental age and the New Ballard score can be used to diagnose superfetation in discordant twins, when detailed first trimester ultra-sound data is not available.

## Background

Superfetation implies fertilization and subsequent development of an ovum when a foetus is already present in the uterus. Growth discordance in multiple pregnancies due to placental insufficiency, twin to twin transfusion or aneuploidy need to be differentiated from superfetation. In most instances the larger twin is nearer appropriate size for gestational age calculated from the last menstrual period (LMP). We report a case where superfetation was likely superfetation because the smaller of the twin was of appropriate maturity, weight and length for gestational age. These circumstances argued against intrauterine growth retardation in the smaller twin.

## Case Presentation

A 21-year-old mother of two had an antenatal ultrasound

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examination done 26 weeks after her last menstrual period (LMP). This showed twins, one was of appropriate size for duration of amenorrhea while the other was approximately four weeks too large. The ultrasound findings are described in Table 1. Six weeks later, after 32 weeks of amenorrhoea, live twins were delivered. They had not received antenatal steroids.

The first of the twins (Twin A) weighed 980 grams and the next baby (Twin B) weighed 2,160 grams. Detailed neurological assessment using the New Ballard Scoring,<sup>1</sup> was done on the second day. The score for Twin A was 15, pointing to a gestational age of 30 weeks (+/- 2 weeks) and the score for Twin B was 32, appropriate for 36 weeks (+/- 2 weeks). Table 2 lists the differences between the twins. Radiological examination for bone age done on the second day of life revealed the absence of epiphysis at the lower end of femur and upper end of tibia in Twin A while they were present in Twin B (Figure 1, 2). The epiphysis at the lower end of femur appears normally between 31 and 40 weeks and for the upper end of tibia between 34 weeks and 5 postnatal weeks.<sup>2</sup> Thus, Twin A had a bone age of less than 31 weeks and Twin B had a bone age of at least 34 weeks.

X-ray chest with mandible showed absence of calcified crowns of the first and second deciduous molar in Twin A and both crowns calcified in Twin B (Figure 3, 4). The crowns of the first and second molars are never seen prior to 33 and 36 weeks respectively and are invariably seen after that.<sup>3</sup> This suggests that twin A was at less 33 weeks and twin B was at least 36 weeks old.

Retinal vessels normally reach nasal ora serrata by 36 weeks and periphery on the temporal side by 40 weeks.

Ophthalmological examination of Twin A showed a hazy cornea and the underlying papillary membrane was not visualised. The retinal vessels had not reached the nasal ora serrata. In Twin B the cornea was clear, there was no papillary membrane and the retinal vessels migration was complete on the nasal side and near complete on the temporal side.

## Conclusion

Intrauterine growth retardation (IUGR) is the usual cause of discordance in multiple pregnancies. We did not find any report



**Figure 1.** Radiological examination for bone showing absence of epiphysis at the lower end of femur and upper end of tibia in Twin A.



**Figure 2.** Radiological examination for bone showing epiphysis at the lower end of femur and upper end of tibia in Twin B.



**Figure 3.** X-ray chest with mandible showed absence of calcified crowns of the first and second deciduous molar in Twin A.



**Figure 4.** X-ray chest with mandible showed calcified crowns of the first and second deciduous molar in Twin B.

in the literature of discordance due to one baby being large-for-date. In this case the smaller twin was of appropriate size and maturity for gestation assessed from LMP. The second twin was approximately a month too large and mature. Superfetation was considered as a possible explanation for the observation. Bleeding one month after conception occurs in about 8% pregnancies and represents a physiological response to implantation or slight bleed from the endometrium in early pregnancy.<sup>4</sup> We therefore also considered the possibility that both twins were conceived simultaneously a month prior to the presumed date of the LMP, and the smaller Twin A was small-for-date.

Detailed neurological and physical assessment is considered the most reliable method of estimation of gestational age, in circumstances where IUGR is suspected and there is uncertainty in using LMP.<sup>2</sup> Using the New Ballard Score<sup>1</sup> the first of the twin was 30 weeks and the second was 36 weeks ( $\pm 2$  weeks). This evidence of disparity in the gestational ages of the 'twins', was corroborated by the estimation of age based on anthropometric measurements, weight, length and head circumference, ophthalmic examination, bone age and dental age estimates. The twins had not received antenatal steroids which, which had they been given, may have influenced some of the markers of foetal maturity. The evidence taken together, suggests that there was a real difference of approximately 4 weeks in the gestational ages of the twins and this was in keeping with the findings of the ante-natal ultrasound examination.

Among the evidence listed above, anthropometric measurements and bone maturation are delayed in first trimester-malnutrition and results in symmetric growth retardation.<sup>2,5</sup> However the work of Kuhns et al<sup>3</sup> suggest that the age of calcification of the crowns of the molars is not affected by IUGR and we use this criterion along with the New Ballard Score and the ophthalmic examination to confirm the disparity in gestational ages of the neonates. Harrison et al<sup>6</sup> have recently reported a case of superfetation and suggested that in growth-discrepant multiple deliveries, skilled neurosonography and ophthalmic examination may be used to support the diagnosis of superfetation when detailed first trimester data is lacking. We would like to add the role of the New Ballard Scoring and, as they may help clinch the diagnosis, even where suggestive fortuitous circumstances as in this case (distinct marker separating the two fertilizations in the form of bleeding on implantation of first ovum) are not available.

**Table 1: Ante-natal ultrasonography findings at 26 weeks after LMP**

|                    | <b>Twin A</b>               | <b>Twin B</b>               |
|--------------------|-----------------------------|-----------------------------|
| Presentation       | Cephalic                    | Breech                      |
| Placenta           | Anterior                    | Posterior                   |
| Biparital diameter | 65 mm                       | 77 mm                       |
| Femur Length       | 49 mm                       | 48 mm                       |
| Head circumference | 235 mm                      | 276 mm                      |
| <b>Gestation</b>   | <b>26 weeks +/- 2 weeks</b> | <b>30 weeks +/- 2 weeks</b> |

**Table 2: Differences between the twins at birth**

|                                                    | <b>Twin A</b><br>(Gestational age range in weeks +/-2SD) | <b>Twin B</b><br>(Gestational age range in weeks +/-2SD)                                  |
|----------------------------------------------------|----------------------------------------------------------|-------------------------------------------------------------------------------------------|
| Weight (gm)*                                       | 980 (26–30)                                              | 2160 (30–36)                                                                              |
| Length (cm)*                                       | 36.5 (27–29)                                             | 42.5 (30–34)                                                                              |
| Circumference head (cm)*                           | 27 (27–31)                                               | 31 (31–37)                                                                                |
| New Ballard Score                                  | 15 (30 +/- 2 weeks)                                      | 32 (36 +/- 2 weeks)                                                                       |
| Epiphysis lower end of femur                       | Absent (Less than 31 weeks)                              | Present (31 – 40 weeks)                                                                   |
| Epiphysis upper end tibia                          | Absent (Less than 34 weeks)                              | Present (34 – 5 post natal weeks)                                                         |
| Calcified crown of 1 <sup>st</sup> deciduous molar | Absent (less than 33 weeks)                              | Present (more than 33 weeks)                                                              |
| Calcified crown of 1 <sup>st</sup> deciduous molar | Absent (less than 36 weeks)                              | Present (more than 36 weeks)                                                              |
| Cornea                                             | Haze present                                             | Transparent                                                                               |
| Retinal vessels migration                          | Not reached nasal ora serrata (less than 36 weeks)**     | Complete on the nasal side and near complete on the temporal side. (more than 36 weeks)** |

\*Norms for anthropometry: Usher R et al J Ped 1969 74 901

\*\*Ophthalmological norms: Moller HU. Milestones and normative data. In: Taylor D. editor Pediatric Ophthalmology 2<sup>nd</sup> en. Blackwell Science 1997; pp 42–54.

References for other norms are described in the text

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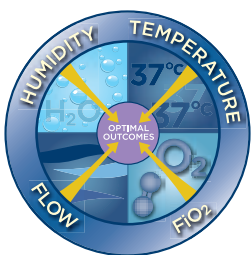
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