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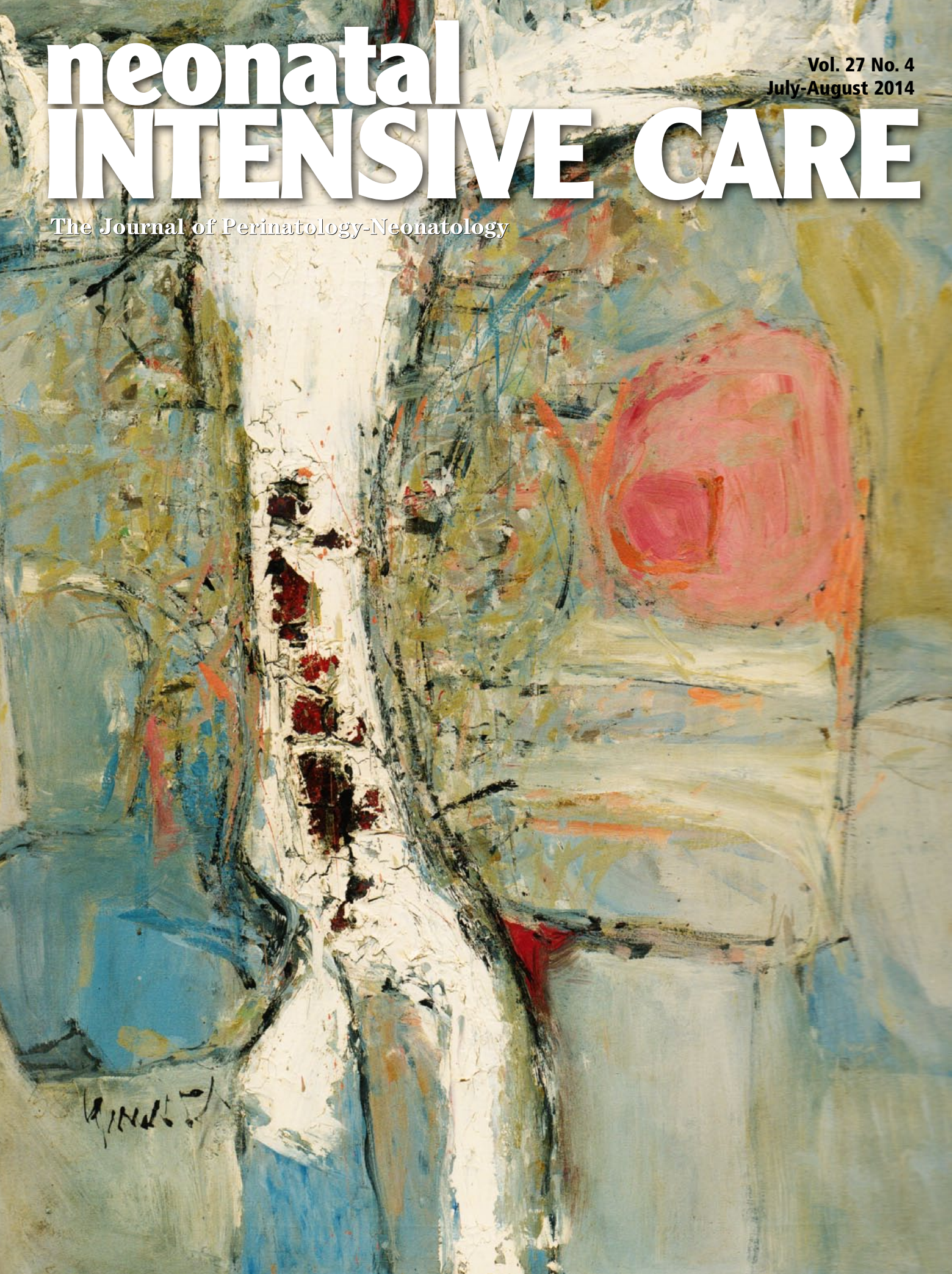

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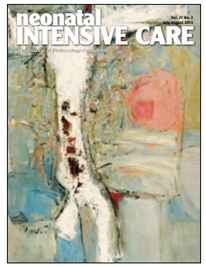

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Targeted Neonatal Echocardiography (TNE) in the Neonatal Intensive Care Unit

Azif Safarulla, MD, Aysha Syed, MD, and Muhammad Aslam, MD

With advancements in neonatal care, the role of echocardiography has changed remarkably over the last few years. It has transitioned from echocardiograms being performed by pediatric cardiologists to diagnose and monitor congenital heart disease (CHD) and patent ductus arteriosus (PDA) to being used by neonatologists of late as a tool for assessment of hemodynamic instability. This wave of change has been spawned by an increasing awareness and desire to better manage neonates, as well as due to the unavailability of pediatric cardiology services in certain remote areas in the United States and Europe.

Dr Mertens and associates published the following article in 2011, "Targeted Neonatal Echocardiography (TNE) in the Neonatal Intensive Care Unit—Practice guidelines and recommendations" in the European journal of echocardiography. This article examines the current trend of TNE being performed by non-cardiologists. It clearly defines what constitutes TNE and indications for the same, the practical applications, and more importantly establishes realistic guidelines on how to create and maintain quality in recording and interpreting data, which is in accordance with standards set by the American Society of Echocardiography, European Association of Echocardiography and Association for European Pediatric cardiologists. These guidelines include a training period of 4 to 6 months dedicated to pediatric echocardiography with performance of at least 150 studies and interpretation of 150 additional studies to achieve core/basic training to perform TNE; and an additional period of 4 to 6 months dedicated to performance of 150 neonatal echocardiographic studies and review of an additional 150 studies to achieve advance training to perform and independently review TNE.

Understandably with the emergence of this new entity called TNE there is a lot of concern in the pediatric cardiology community in terms of potential to miss an infant with a critical CHD, maintaining quality of studies, losing exclusivity, challenge to income, medico-legal implications to name a few. The most important aspect of TNE is that it is NOT intended to be a substitute for evaluation of a neonate with a suspected CHD which rightfully should be assessed by a pediatric cardiologist and imaged by personnel trained in pediatric echocardiography. TNE should be viewed as an extension of clinical assessment which would enable the non-cardiologist to better understand and manage the changing hemodynamics in a neonate in the first few days of life, which often is the most critical time. In addition, it has other applications in terms of assessing organ blood flow, suspected effusion (pleural, pericardial), position of central line, ECMO cannulae, etc. As our clinical knowledge expands, the applications will continue to evolve. In case of patient with a strong clinical suspicion of CHD, significant PDA, systemic hypotension, the initial assessment should be done by comprehensive echocardiography to rule out CHD. Once ruled out, follow up studies can be performed by personnel sufficiently trained in performing and interpreting TNE.

In conclusion, TNE has arrived at the scene and it is here to stay. TNE is an extremely useful tool which if utilized in the appropriate manner will enable clinicians to better manage neonates in an array of clinical situations. It represents an opportunity for the Neonatology and Pediatric Cardiology to work together to improve clinical care and for cardiology to take a leadership role in properly training and maintaining quality of information obtained via TNE.

Dr Safarulla is a Neonatal-Perinatal Medicine Fellow at University of California Irvine (UCI) School of Medicine and UCI Medical Center. Dr Syed is a Pediatric Resident at Sinai Children's Hospital, Chicago. Dr Aslam is an Associate Professor of Pediatrics at UCI School of Medicine and a staff Neonatologist and Director of Education and Scholarly Activities, Division of Neonatology, Department of Pediatrics at UCI Medical Center.

News

☐ July-August 2014

New Name Helps Chiesi Turn Corner

Cornerstone Therapeutics Inc., a specialty pharmaceutical company focused on commercializing products for the U.S. hospital and adjacent specialty markets, today announced an official name change to Chiesi USA Inc. following the completion of its acquisition by Chiesi Farmaceutici S.p.A. The acquisition, making Cornerstone a wholly-owned subsidiary of Chiesi, and this name change are the last steps in a process that began when Chiesi became Cornerstone's majority shareholder in 2009. "As Chiesi USA, we look forward to offering our patients and providers more benefits than ever before," said Ken McBean, President of Chiesi USA. "The additional resources made available by this merger will allow Chiesi USA to provide greater support for research and development initiatives while maintaining our commitment to the key therapeutic areas we serve. Being part of a global company also offers our employees additional opportunities for growth and additional support needed to build upon our success." Chiesi USA will continue to market its existing portfolio of products to the hospital and adjacent specialty markets and will actively pursue licensing and acquisition activities in these areas. Chiesi USA's headquarters will remain in Cary, N.C.

Complications Weigh on Mothers

New research suggests that jumps in maternal body mass index (BMI) are associated with increased risks of adverse perinatal and neonatal outcomes, according to the Journal of the American Medical Association. Dagfinn Aune, of Imperial College London, and colleagues conducted a systematic review and meta-analysis of cohort studies examining maternal BMI and its association with risk of fetal death, stillbirth, and infant death. The researchers found that the summary relative risk (RR) per 5-unit increase in maternal BMI was 1.21 for fetal death (95% confidence interval [CI], 1.09-1.35), 1.24 for stillbirth (95% CI, 1.18-1.30), 1.16 for perinatal death (95% CI, 1.00-1.35), 1.15 for neonatal death (95% CI, 1.07-1.23), and 1.18 for infant death (95% CI, 1.09-1.28). Women who had a BMI of 20 (used as the reference standard), 25, and 30 kg/m^2, respectively, had absolute risks per 10,000 pregnancies of 76, 82, and 102 for fetal death; 40, 48, and 59 for stillbirth; 66, 73, and 86 for perinatal death; 20, 21, and 24 for neonatal death; and 33, 37, and 43, for infant death. "Even modest increases in maternal BMI were associated with increased risk of fetal death; stillbirth; and neonatal, perinatal, and infant death," the authors write. "Weight management guidelines for women who plan pregnancies should take these findings into consideration to reduce the burden of fetal death, stillbirth, and infant death."

That Awkward Moment After Birth

A new study has found that an awkward maneuver—in which doctors hold a wet, screaming infant at the level of the mother's vagina for a crucial minute or longer so that gravity will help blood flow—is probably unnecessary. Babies who were placed on their mothers' stomachs before clamping fared just as well as those who were held lower, the researchers found. Doctors in the delivery room are increasingly urged to hold off cutting the umbilical cord of a newborn. Delayed clamping, as it's called, allows blood to continue flowing from the placenta, improving iron stores in the baby. The study out of the National Institute of Child Health and Human Development found no difference whether the baby was at abdomen level or on the chest, or the baby was held at the vagina—it made no difference in terms of extra blood the baby got. The authors hope their finding will convince doctors reluctant to delay cord clamping to start the practice. The study assigned 194 healthy full-term babies to be placed on their mother's abdomen or chest for two minutes and 197 babies to be held at the level of the vagina for two minutes.

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All of the newborns were still attached to umbilical cords, and weighed before and after the allotted time. The group placed on their mothers' abdomens gained 53 grams of blood, while the babies held lower gained 56 grams.

Cash is the C in C-sections

Despite the fact that unnecessary C-sections produce worse outcomes for more money, America's C-section rate is growing fast—it has risen 50 per cent in the last 10 years and now is used in a third of all births. This is not because of aging mothers or assisted reproduction—these make up a small fraction of births. Nor is it due to rising obesity. The biggest increase in C-section rates is among women under 25. Most of the increase has come in low-risk births. Sometimes C-sections are necessary. Most are probably not. They are done (very rarely) for the convenience of the mother, or, far more commonly, for the convenience of the doctor. But this practice isn't benign. Having a C-section puts a woman at increased risk for hysterectomy, hemorrhage, infection and deep vein thrombosis, and the risk rises with each subsequent C-section. They are also more expensive. The California Maternal Quality Care Collaborative, a group that works to improve birth outcomes, said commercial insurers pay 60 per cent more for a C-section than a vaginal delivery—and this is the most commonly performed surgery in America. Another puzzle is the enormous disparity in C-section rates. In 2012, Los Angeles Community Hospital did C-sections in 62.7 per cent of the lowest-risk births: mothers who have never had a C-section, single baby, normal presentation, full term. The comparable rate for San Francisco General Hospital was 10.1 per cent. Hospitals with low rates of C-section have no difference in outcomes for babies, and better outcomes for mothers. San Francisco General has the state's best rate on another crucial measure: vaginal births after C-section, or V.B.A.C. At General, 36.6 percent of women who have had a previous cesarean section deliver vaginally. The state average for V.B.A.C. is just under 10 per cent, but many hospitals do zero—they have a policy of never letting a woman who had a C-section try labor. Obstetric experts believe that V.B.A.C.s are vastly underused, and that most women who have had a C-section, or even two, should be allowed to try labor. Yet V.B.A.C. rates nationwide today are only a third of what they were in 1996. The scarcity of V.B.A.C. means that a first C-section puts a woman on track to have every child by C-section. A doctor may choose a C-section casually for a first birth knowing that it carries very little risk—for that particular birth. But the risk rises with each subsequent C-section; that first decision may have medical consequences a baby or two later. If cesarean rates for low-risk births vary by 500 per cent from hospital to hospital, then clearly hospital policies matter. Examining what San Francisco General does to achieve its low rates might show what other hospitals could do as well. Probably the single most important factor is that doctors at General are salaried and on shifts. Their pay doesn't vary by the number of patients they see or tests they order. They're paid for their time: 12-hour shifts during the weekday, 24 hours on weekends. Paying doctors for their time removes the two most powerful incentives encouraging private-practice doctors to do C-sections. One is money. California's Medicaid program, Medi-Cal, wisely pays the same for all births, so doctors have no financial incentive to do a C-section with Medi-Cal patients. That's not the case with commercial insurers, according to the Maternal Quality Care Collaborative. But this is not the most important way that the financial incentives push doctors in the wrong direction. Perhaps more important is the fact that most of what a private-practice ob-gyn doctor earns from taking care of a pregnant woman comes from the delivery. That means doctors have a strong financial incentive to deliver their patients' babies themselves. How is this a problem? It leads to more C-sections scheduled for the doctor's convenience, and scheduled inductions of labor that often end in C-sections. Even for unscheduled deliveries, it contributes to the most important syndrome behind unnecessary C-sections: failure to wait. Salaried doctors, nurses and midwives can help increase the rates of vaginal births. Information in this article is by Tina Rosenberg and first appeared in the New York Times.

Drugs Linked to Early Births

New research showing a link between depression medication and early births highlights the need for women to talk with their doctors before taking one of the drugs during pregnancy, physicians say. The risk of preterm birth, defined as earlier than 37 weeks, was 53% higher in women who took an antidepressant while pregnant, according to a paper published in PLOS One. The risk was even higher, an increase of 96%, among pregnant women who took an antidepressant during their final trimester. Taking an antidepressant during pregnancy "is not a decision to be taken lightly," says Krista Huybrechts, a researcher at Harvard Medical School and Brigham and Women's Hospital who led the study. The paper was a systematic review of 41 studies that looked at use of antidepressants by pregnant women. Overall, 11.6% of infants born in the U.S. in 2012 arrived in a preterm birth, according to the Centers for Disease Control and Prevention. A normal pregnancy lasts between 37 and 41 weeks, the CDC says. Researchers said it is the most thorough analysis of antidepressants and preterm births to date and that it accounted for other potential causes of early delivery, including depression itself. The study wasn't a randomized trial, which is considered to be more definitive. More than 10% of pregnant U.S. women experience a bout of depression, and 8% take an antidepressant, studies have found. About 180,000 fetuses are exposed to one of the drugs each year, according to a 2007 study in the American Journal of Obstetrics & Gynecology. Many of the drugs belong to a class of so-called selective serotonin reuptake inhibitors, or SSRIs, such as Prozac and Zoloft. Such antidepressants can help pregnant women cope with their depression and avoid giving birth to babies with complications like low birth weight, doctors say. For these reasons, many physicians say pregnant patients should keep taking one of the depression drugs.

Double Your Pleasure, Double Your Complications

While many women who struggle with infertility say having twins is a blessing, medical experts are increasingly calling for measures to be taken to reduce the country's rate of multiple births. In an analysis posted online in the journal Fertility and Sterility, researchers from the Hastings Center, an independent bioethics research institute, and the Yale Fertility Center called for a number of policy changes to encourage doctors and patients to try to avoid multiple pregnancies. Multiples have a greater risk of preterm birth, which is associated with an increased risk of death and many long-term health problems, including neurological disabilities, the article said. The analysis was funded by the March of Dimes, a nonprofit whose goals include reducing premature births. A new report recommends changes in fertility treatments to reduce risky outcomes including multiple births and preterm births. The

article recommended encouraging single embryo transfers during IVF, expanding insurance coverage of IVF and improving patient education about the risks of multiple pregnancies. It also recommended limiting the use of controlled ovarian stimulation, a separate fertility treatment that is believed to account for more multiple births than IVF. Over the past two decades, the rate of twin births in the U.S. has increased by about 76%, fueled by older maternal age and increased use of fertility treatments. In 2012, 3.3% of births resulted in twins, according to the Centers for Disease Control and Prevention. A New England Journal of Medicine article last year estimated that by 2011 about 36% of twin births and 77% of triplet and higher births resulted from conception assisted by fertility treatments.

Infant Helmets Studied

New research says that a common remedy for the problem of flattened infant skulls—an expensive custom-made helmet—in most cases produces no more improvement in skull shape than doing nothing at all. Pediatricians have long urged parents to put newborns to sleep on their backs to help prevent sudden infant death syndrome. While the practice undoubtedly has saved lives, it also has increased the numbers of babies with flattened skulls. Roughly one baby in five under the age of 6 months develops a skull deformation caused by lying in a supine position. A report in the journal BMJ, is the first randomized trial of the helmets. The authors found "virtually no treatment effect," said Brent R. Collett, an investigator at Seattle Children's Research Institute. Skull flatness at back of the head may be accompanied by facial asymmetry; one ear may be slightly farther back than the other, and sometimes the side of the head can flatten. Until now, less rigorous studies had mostly shown helmets did help normalize head shape. The helmets are sometimes adorned with stickers, and are sometimes painted to resemble a pilot's helmet or with the logo of a beloved football team. Still, the study leaves open the possibility that the helmets may still be useful for infants with severe skull flattening and those with tight neck muscles, which make it hard for infants to turn their heads, so they remain in one position.

Don't Blame the Doctors

A new report by a committee of experts in obstetrics, pediatrics, neurology and fetal-maternal medicine has found that blaming doctors—especially through malpractice suits that have prompted many obstetrician-gynecologists to abandon the delivery room—for brain injuries in newborns via insufficient oxygen during labor or delivery might be misplaced. It turns out many conditions that occur during or even before pregnancy can lead to neurological damage to full-term babies. The document, called Neonatal Encephalopathy and Neurologic Outcome, updates a version published in 2003 that focused on oxygen deprivation, or asphyxia, around the time of birth. The new report, which highlights significant advances in diagnosis and treatment in the decade since, was published by the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics. Brain injuries affect about three in 1,000 babies born full-term in the United States, but only half of these cases are linked to oxygen deprivation during labor and delivery, according to the new report. And even in those instances, a problem that occurred long before birth might have exaggerated the effects of a reduced oxygen supply that would have not otherwise caused a lasting brain injury. There may be other reasons for neonatal encephalopathy as brain disorders in full-term newborns are called. These include genetic factors and maternal health problems like hypothyroidism, placental abnormalities, major bleeding during pregnancy, infection of the fetal membranes and a stroke in the baby around the time of birth.

Simulator Helps Re-create Emergencies

A team from Christiana Care Health System is working with staff from local hospitals using a newborn simulator mannequin to help them anticipate and respond to emergency situations. The mannequin, known as Newborn HAL, mimics a full-term baby at birth. The interactive simulator looks and sounds like the real thing, from the way it cries, its heart beats and even the way its skin coloring changes. It can be programmed to have the kind of problem a newborn might have at birth, such as an audible heart defect, breathing difficulties or requiring an IV insertion. Staff can identify and treat these issues in advance of an actual emergency, so they are prepared if one arises. Nurses, respiratory therapists, pediatricians and even emergency department staff are among those who are trained using Newborn HAL's programmable emergencies. The simulator lets staff run through different scenarios, such as a baby who is born not breathing. They have to run through how they would handle that. Then they are debriefed and taught how the situation could have gone better.

Twin-Twin Transfusion Syndrome Reduced

The number of children suffering severe disabilities after treatment for a deadly condition affecting just over 10% of all identical twin pregnancies could be significantly cut after University of Birmingham, UK, researchers developed a laser-based treatment, in collaboration with other experts in Europe. A team led by Birmingham's Prof. Mark Kilby carried out a study into a modified laser treatment to reduce the number of babies born with a disability arising from Twin-Twin Transfusion Syndrome (TTTS). The study, published in medical journal The Lancet, says that the new technique, known as the "Solomon method", can reduce both the recurrence of TTTS and associated disabilities. Kilby, who is Professor of Fetal Medicine in the University's College of Medical and Dental Science and Centre for Women's & Children's Health and director of the Fetal Medicine Centre at Birmingham Women's NHS Foundation Trust, worked on a collaborative trial with experts from five centres in Europe, to compare the Solomon technique with a more conventional laser technique. Although the number of babies that died was similar for both treatments, the Solomon technique led to fewer babies being born with severe complications that could lead to disability; 8% rather than 13% for the conventional treatment. The usual treatment for TTTS is to insert a thin needle, called a fetoscope, through the mother's abdomen, visualising the placental blood vessels and, with a laser, selectively coagulating the blood vessels to stop the flow of blood between the two babies. The Solomon technique involves lasering the entire placental vascular equator; that is, lasering the blood vessels, but then also a circuit around the placenta in a bid to try to sever any tiny blood vessels which are not visible but may cause problems after treatment. The new technique, which is now set to become the clinical standard technique, will reduce the incidence of TTTS returning and the incidence of twins having to be delivered so early in the pregnancy. In the study, just 1% of the 137 women who were treated with the new technique then suffered a recurrence of the TTTS, compared to 7% of the 135 women who were treated with the more conventional lasering.

MRSA Infection Risks

There is an increased risk for MRSA infection during hospitalization if patients are colonized with MRSA on admission, according to recent study findings published in Pediatrics. "The development and implementation of molecular diagnostic methods, strict compliance with infection control policies, and establishment of decolonization policies with favorable results among pediatric patients seem to be the necessary next steps in this effort," the researchers wrote. **Fainareti N. Zervou, MD**, and colleagues from the infectious diseases division at Rhode Island Hospital and Warren Alpert Medical School of Brown University, both in Providence, R.I., conducted a meta-analysis to determine the burden of colonization on admission, the time trends and the significance of colonization. The researchers evaluated 18 studies published from 2006 to 2013 that reported the prevalence of MRSA colonization on ICU admission.

Camera Offers NIC Access

Nationwide Children's Hospital, one of the largest and most comprehensive pediatric hospitals in the United States, just finished installing NICVIEW, which supports their philosophy of family-centered care in a unit where the length of stay is longer. NICVIEW, the NICU camera system, helps extend family-centered care by giving parents a virtual window to their newborns. Many of the babies in the NICU, ICC and SCN are born prematurely and are released within a few days. However, the length of stay for some on this unit at Nationwide Children's can be months. While not a replacement for visiting in person, this password-protected system allows parents and extended family members 24/7 access to the new bundle of joy.

Screening Shown to be Effective

A study out of Sweden has found that neonatal screening may be effective for salt wasting congenital adrenal hyperplasia. Congenital adrenal hyperplasia is mostly caused by mutations in the CYP21A2gene, resulting in 21α-hydroxylase deficiency. The severity can range from life-threatening salt wasting to signs of excessive androgen levels. Some recent studies have called into question the rationale for screening, while others have reported that salt wasting CAH may be missed. A longitudinal study from Sweden showed that the screening sensitivity for salt wasting CAH was 100%, although the sensitivities were lower for other forms of CAH. The strength of this study was that it was a nationwide study over a long period. This also poses a problem in analysis since the screening test went through many changes over the time period, and the reported values are from an amalgamation of tests rather than from one test that is currently used. Furthermore, since healthcare is centralized in Sweden, the investigators were able to account for almost all births and standardize their testing. Therefore, their results are not generalizable to a country such as the US, where accounts of births and lab testing are more variable.

Neonatal Abstinence Syndrome to be Tracked

A bill sent to Indiana Governor Pence would force the state's hospitals to report every time a baby was born with drugs in its system. The bill would help the state track what's known as Neonatal Abstinence Syndrome (NAS), which is difficult right now since hospitals don't have to keep track of when it takes place. "This is a program that for the first time allows us as a state to grasp the problem of infants born with drugs in their system," said Senator Jean Breaux (D, Indianapolis), a co-sponsor of the bill. If the governor signs it, several groups - including the state Department of Health and the Indiana Medical Association - will also be directed to better study the problem, based on the data gathered by hospitals. "It allows us to partner with hospitals so we can reduce the instance of babies born with drugs and allow them the opportunity of a better quality of life," Breaux said during an appearance with Attorney General Greg Zoeller, who also supported the bill. State agencies would also begin a grant program to help reduce Indiana's infant mortality rate under the bill.

Canada Not Hearing the Message

In Canada, only four provinces screen every child for hearing loss and fewer still have standards in place to ensure timely follow-up and treatment for children who do have auditory problems. Speech-Language and Audiology Canada (SAC), along with the Canadian Academy of Audiology, have issued a report card on the state of newborn screening. Eight of the 13 provinces and territories get a failing grade, four (Ontario, Nova Scotia, Prince Edward Island and New Brunswick) get a passing grade and only one (British Columbia) gets top marks. The grades are based on having a program with standardized procedures to detect hearing loss, and then a series of measures to ensure timely intervention, including diagnosis, treatment and monitoring. A Quebec study estimated that by increasing screening to 100 per cent of babies from the current 25 per cent, the province would save $1.7-million a year. That's because the cost of educating children whose hearing loss is detected later is considerably more – almost $18,000 a year for a hard-of-hearing student compared to $5,000 for a hearing student.

Aspirin Recommended for Some Pregnant Women

A federal task force is recommending that some pregnant women take low-dose aspirin daily to avoid getting preeclampsia, a condition that can lead to preterm birth and other complications. Aspirin in general isn't recommended during pregnancy because it can contribute to maternal and fetal bleeding. However, low-dose aspirin is sometimes prescribed for pregnant women with certain health conditions. The recommendation by the U.S. Preventive Services Task Force comes after the nation's biggest obstetrics association issued similar advice last fall. The task force said that women who have had preeclampsia during previous pregnancies should take a pill of 81 milligrams—often called "baby aspirin"—each day after the 12th week of pregnancy. The recommendation applies to pregnant women whose doctors consider them at high risk for the condition, as long as they haven't had previous bad medical experiences with aspirin. Preeclampsia affects about 4% of pregnant women in the U.S., and is most often managed with drugs and other medical therapy. Preeclampsia symptoms include high blood pressure, protein in the urine and fluid retention. It can lead to preterm birth and, in a small fraction of cases, it can progress to eclampsia, which results in seizures and coma.

Wrong Direction With High Road

Pregnant women with chronic hypertension (high blood pressure) are highly likely to suffer from adverse pregnancy outcomes such as preterm delivery, low birth weight and neonatal death, which highlights a need for heightened surveillance, suggests a paper published on bmj.com. Chronic hypertension complicates between 1-5% of pregnancies, and the problem may be increasing because of changes in the antenatal population. A recent study in the US suggests the prevalence of chronic hypertension increased from 1995-1996 to 2007-2008, after adjustment for maternal age. Obesity and metabolism are likely to contribute and therefore the number of women entering pregnancy with chronic hypertension is set to rise. Researchers from King's College London carried out a study to assess the strength of evidence linking chronic hypertension with poor pregnancy outcomes. They combined data from studies from 55 studies done in 25 countries. The researchers looked at the following outcomes: preterm delivery (delivery before 37 weeks' gestation); low birth weight (below 2500g); perinatal death (fetal death after 20 weeks' gestation including stillbirth and neonatal death up to one month) and admission to neonatal intensive care or special care baby units. The relative risk of pre-eclampsia (a condition in pregnancy characterized by high blood pressure) in women with chronic hypertension was on average nearly eight times higher than pre-eclampsia in non-hypertensive women. All adverse neonatal outcomes were at least twice as likely to occur, compared with the general population. The researchers conclude that "chronic hypertension is associated with a high incidence of adverse pregnancy outcomes compared with a general population." They stress the importance of increased antenatal surveillance for women with chronic hypertension and suggest they should receive pre-pregnancy counseling to optimize their health prior to pregnancy. They also say that strategies to predict those at greatest risk are needed.

Got Milk?

Prolacta Bioscience, the pioneer in human milk-based nutritional products, announced the introduction of Prolact CR, the world's first and only human milk caloric fortifier made from pasteurized human milk cream, for preterm infants in the neonatal intensive care unit (NICU). Prolact CR is composed of approximately 25% fat, provides 2.5 Cal/mL and contains no added minerals. Prolact CR is used with either mother's own breast milk or human donor milk to standardize milk at 20 Cal/fl oz, which facilitates individualized fortification for premature infants in the NICU. Standardizing human milk helps these babies increase weight and length while in the NICU. Prolact CR is available by prescription only and is intended for use in the NICU for premature infants. The results of a randomized clinical study of 78 premature infants to evaluate the effects of adding human milk-derived cream product to a standard feeding regimen in preterm infants were presented at the Pediatric Academic Societies and Asian Societies for Pediatric Research conference taking place in Vancouver, Canada on May 3-6, 2014. Prolact CR joins a complete line of human milk-based, nutritional products that are clinically proven to improve health outcomes of critically ill preemies.

Early Elective Deliveries Drop

The last four years has seen a vertiginous drop in the practice of early elective deliveries, according to a survey of hospitals released by The Leapfrog Group, an organization funded by businesses that are large purchasers of health care to work for quality and safety improvement. Last year the national average was down to 4.6 per cent—a fall of 73 per cent in three years. "In health care, we talk about a 1 to 2 per cent change as spectacular—wow, we've really improved," said Leah Binder, the president and chief executive of The Leapfrog Group. "I have never in my career seen anything like the progress we're seeing on early elective deliveries." The American College of Obstetricians and Gynecologists had been warning against early elective delivery since 1979. The March of Dimes, one of the most respected advocacy groups in America, had long campaigned to discourage the practice. Delivery at 37 or 38 weeks was widely considered benign—but infant mortality is at least 50 per cent higher for babies at 37 or 38 weeks than at 39 or 40 (at 41 weeks the rate rises again). These babies are also more likely to suffer breathing, feeding and developmental problems. The reasons for the drop, according to Leapfrog, include better reporting of the use of this practice, leading to more states educating hospitals about discouraging it, and payment reform. For example, Texas in 2011 barred Medicaid (that's a state program; Medicare is federal), which pays for 55 per cent of births, from reimbursing hospitals for early elective deliveries.

VBACs Still Being Discouraged

Guidelines issued by the American Congress of Obstetricians and Gynecologists in 2010 said that vaginal births after cesareans—the shorthand is V.B.A.C.s—are largely safe. Despite this, many hospitals and doctors still do not perform them for fear of complications. Hospitals note that V.B.A.C.s carry a slightly higher risk of uterine rupture, and some say they cannot afford to keep staff at the ready if something goes wrong. The reluctance to adopt the guidelines has been especially strong in rural areas, where medical resources are sparse and doctors tend to prefer repeat cesareans, despite a nationwide push to reduce the number of women having these procedures. The proscription upsets many women who want to give birth vaginally—to avoid the discomfort and potential complications of repeat cesareans—but find they have to travel considerable distances to do so. While it is unclear how many hospitals still have restrictive V.B.A.C. policies, public health data show little change despite the new guidelines. A 2012 study by researchers at the University of California, San Francisco, and elsewhere found that nearly half of California hospitals that handle births still do not offer V.B.A.C.s. Many hospitals that allow the procedure have just a few doctors handling them, the study found; many doctors are unwilling to perform V.B.A.C.s because of requirements that they be present during labor. "Time is money for physicians, and they don't want to have to spend their time hanging around waiting for women in labor," said Mary Barger, an associate professor of nursing at the University of San Diego, and one of the study's authors. Dr Jeanne A. Conry, president of the national obstetrics group, said she was concerned and surprised that more hospitals had not made it easier for women to have V.B.A.C.s. "When the statement came out, we had hope that it was going to bring about changes. It hasn't," said Dr Conry, assistant physician in chief at the Permanente Medical Group in Roseville, Calif. Dr Conry said she and other doctors at her hospital strongly encouraged V.B.A.C.s because they are less invasive. Information in this article originally appeared in the New York Times.

Painkiller Use Surges for Pregnant Women

Doctors are prescribing opioid painkillers to pregnant women in astonishing numbers, new research shows, even though risks to the developing fetus are largely unknown. Of 1.1 million pregnant women enrolled in Medicaid nationally, nearly 23 per cent filled an opioid prescription in 2007, up from 18.5 per cent in 2000, according to a study published in the journal Obstetrics & Gynecology. That percentage is the largest to date of opioid prescriptions among pregnant women. Medicaid covers the medical expenses for 45 per cent of births in the United States. The lead author, Rishi J. Desai, a research fellow at Brigham and Women's Hospital, said he had expected to "see some increase in trend, but not this magnitude. One in five women using opioids during pregnancy is definitely surprising." A study of 500,000 privately insured women found that 14 per cent were dispensed opioid painkillers at least once during pregnancy. From 2005 to 2011, the percentage of pregnant women prescribed opioids decreased slightly, but the figure exceeded 12 per cent in any given year, according to Dr Brian T. Bateman, an anesthesiologist at Massachusetts General Hospital, and his colleagues. Their research was published in Anesthesiology. Information in this article originally appeared in the New York Times.

Playing NICE With Infants

Neonates with suspected early onset sepsis are often treated aggressively with antibiotics before infection is confirmed. National Institute for Health and Care Excellence (NICE) has recommended a gentler approach. NICE (2012) recommends treating neonates who have risk factors for sepsis but are clinically well with only 36 hours of IV antibiotics provided that they remain well, inflammatory markers remain within normal limits and their microbiological tests are negative. This is supported by a recent audit study in which 236 term babies who had low inflammatory markers and negative blood cultures were safely discharged after 36 hours of antibiotic therapy; none of whom were readmitted with sepsis.

Clinical Experience Using Inhaled Epoprostenol (Flolan) in Neonatal and Pediatric Patients at Children's Hospital Central California

Lawrence Nicol, AS, RRT

Prostacyclin (also called prostaglandin I2 or PGI2), is an arachidonic acid metabolite formed by a prostacyclin synthase in the vascular endothelium. Prostacyclin stimulates adenyl cyclase in vascular smooth muscle cells, which increases intracellular cAMP, resulting in vasodilation. As a drug, it is also known as epoprostenol or Flolan. These terms are often used interchangeably.

Intravenous epoprostenol (Flolan) is approved to treat Primary Pulmonary Hypertension (PPHN), but its use is limited by adverse effects including systemic hypotension and worsening of intrapulmonary shunting. When inhaled, epoprostenol (Flolan) may reduce pulmonary hypertension and improve oxygenation without decreasing systemic blood pressure. Aerosolized epoprostenol (Flolan) has been shown to be as effective as inhaled nitric oxide in reducing pulmonary vascular resistance in heart transplant candidates, in decreasing pulmonary artery pressures in primary and secondary pulmonary hypertension, and in improving right ventricular function in animals with hypoxic pulmonary vasoconstriction. It has also been shown to be as effective as a selective pulmonary artery vasodilator with improvement in oxygenation in patients with Acute Respiratory Distress Syndrome (ARDS).

Inhaled prostacyclin was first used in humans in 1978.[1] In 2004, based on the knowledge above and in journal articles written by Kelly in 2002, and Bindl in 1994, we started using inhaled epoprostenol or Flolan in the Neonatal Intensive Care Unit (NICU) at Children's Hospital Central California. Based on the recommendations of our Cardiologists in collaboration with the Medical Director of the NICU we used it on a limited basis initially with success to treat pulmonary hypertension. The nebulizers (Mini Heart) we used then were efficient, but sometimes created problems associated with the extra flow of gas that was added to the ventilator circuit. In pressure modes of ventilation the peak pressures had to be adjusted down once the nebulizer was running. Tidal volumes increased and could not be measured accurately because of the extra flow of gas into the circuit from the nebulizer.

Nitric oxide has been the standard of care for treatment of pulmonary hypertension in infants greater than 34 weeks of gestation. In April 2010, because of the rising costs associated with the administration of nitric oxide along with our previous experience with inhaled Flolan, we started a program using inhaled Flolan as an adjunct or alternative to nitric oxide, first in the Pediatric Intensive Care Unit (PICU), and then the NICU. We contacted 16 centers across the country for their advice and expertise. Specifically for the NICU, we researched the articles of Zwissler, Soditt, Lowson, DeLuca, Olmsted and Konduri/Kim. We purchased the highly efficient vibrating mesh type of nebulizers made by Aerogen. The Aerogen nebulizers are efficient and they do not add any additional gas to the breathing circuit so that peak pressures and tidal volumes are not affected. We also purchased Aerogen's proprietary syringes and tubing sets to further ensure patient safety. We used Medfusion IV pumps, and utilized a team approach with nursing in programming the pumps. Initially, we only introduced inhaled Flolan to the ventilator circuits after nitric oxide was already in use, and then tried to wean the nitric oxide if possible while closely assessing the patient. We have utilized inhaled Flolan successfully with patients on ventilators, SiPAP, high flow nasal cannulas, and oxygen masks.

To date in the PICU and NICU combined, we have used inhaled Flolan on fifty-six patients and have successfully weaned forty-two of them (75%) off of inhaled nitric oxide. The smallest patient was 870 grams.

We have used inhaled Flolan on twenty-two NICU patients. The majority were in the NICU itself but some were recovered and kept in the PICU after their cardiac surgery. Fifteen of these patients (68%) were successfully weaned off nitric oxide. Of the seven who were not, two of them had such an improvement in their oxygenation status after the initiation of inhaled Flolan (they were already receiving nitric oxide) that we were able to send them out for ECMO. One of the seven patients had hypotension that was thought to be caused by the Flolan so it was discontinued. Other than the one possible case of hypotension, we have not seen any untoward effects in using inhaled Flolan.

We use a high-efficiency expiratory filter to prevent moisture and drug from getting into our ventilator exhalation valves. We have not observed any problems with the viscosity of the diluent in endotracheal tubes or ventilator systems even on patients less than 1000 grams. We have not observed tracheitis from the Flolan pH.

We started this program to see if we could provide the same safe level of care to our patients and cut costs at the same time. We were able to successfully and safely wean some patients off of nitric oxide. We did see a cost savings in decreasing our nitric oxide use especially when we ran out of contract hours with Ikaria. What we found was the benefit of having another biochemical pathway to treat pulmonary hypertension. In two instances the patients were already receiving nitric oxide and not improving significantly. The addition of inhaled Flolan did make a significant difference in improving their oxygenation status. The other advantage we observed was that some patients on low doses of nitric oxide had rebound reactions when coming off nitric oxide. These patients could be successfully weaned off nitric oxide by the addition of inhaled Flolan. Weaning the Flolan was accomplished without rebound pulmonary hypertension. Therefore, we feel that we have been able to safely provide an additional pathway for pulmonary vasodilation for our neonatal and pediatric patients.

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Birth Preparedness and Complication Readiness (BPCR) Interventions to Reduce Maternal and Neonatal Mortality in Developing Countries: Systematic Review and Meta-Analysis

Dieudonné Soubeiga

Abstract

Background: Birth Preparedness and Complication Readiness (BPCR) interventions are widely promoted by governments and international agencies to reduce maternal and neonatal health risks in developing countries; however, their overall impact is uncertain, and little is known about how best to implement BPCR at a community level. Our primary aim was to evaluate the impact of BPCR interventions involving women, families and communities during the prenatal, postnatal and neonatal periods to reduce maternal and neonatal mortality in developing countries. We also examined intervention impact on a variety of intermediate outcomes important for maternal and child survival.

Methods: We conducted a systematic review and meta-analysis of randomized trials of BPCR interventions in populations of pregnant women living in developing countries. To identify relevant studies, we searched the scientific literature in the Pubmed, Embase, Cochrane library, Reproductive health library, CINAHL and Popline databases. We also undertook manual searches of article bibliographies and web sites. Study inclusion was based on pre- specified criteria. We synthesised data by computing pooled relative risks (RR) using the Cochrane RevMan software.

Results: Fourteen randomized studies (292 256 live births) met the inclusion criteria. Meta-analyses showed that exposure to BPCR interventions was associated with a statistically significant reduction of 18% in neonatal mortality risk (twelve studies, RR = 0.82; 95% CI: 0.74, 0.91) and a non-significant reduction of 28% in maternal mortality risk (seven studies, RR = 0.72; 95% CI: 0.46, 1.13). Results were highly heterogeneous (I^2 = 76%, p < 0.001 and I^2 = 72%, p = 0.002 for neonatal and maternal results, respectively). Subgroup analyses of studies in which at least 30% of targeted women participated in interventions showed a 24% significant reduction of neonatal mortality risk (nine studies, RR = 0.76; 95% CI: 0.69, 0.85) and a 53% significant reduction in maternal mortality risk (four studies, RR = 0.47; 95% CI: 0.26, 0.87). Pooled results revealed that BPCR interventions were also associated with increased likelihood of use of care in the event of newborn illness, clean cutting of the umbilical cord and initiation of breastfeeding in the first hour of life.

Conclusions: With adequate population coverage, BPCR interventions are effective in reducing maternal and neonatal mortality in low-resources settings.

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Background

In spite of important progress towards attaining the Millennium Development Goals (MDGs), maternal and neonatal mortality continue to figure as major public health problems in developing countries [1,2]. Improvements in maternal health and reductions in maternal mortality have been slower than anticipated and – despite isolated successes – remain far from the MDG5 target of a 75% reduction in the maternal mortality ratio (MMR) from 1990 to 2015 [3]. Although child survival progress is accelerating [4], only 31 countries are on track to achieve the MDG4 target to reduce child mortality by two-thirds between 1990 and 2015 [2]. Moreover, over the period 2000–2010 decreases in mortality have been more rapid in the age group 1–59 months, such that the neonatal fraction of deaths has increased from 38.2% to 40.3% [4]. To achieve MDGs 4 and 5, the global community will need to focus attention and resources on effective strategies to reduce maternal and neonatal deaths, particularly in poor and underserved communities [5].

Developing countries have recently invested in behavior change and community mobilisation interventions to reduce maternal and neonatal risks following the concept of "Birth Preparedness and Complication Readiness" (BPCR), which comprises elements of antenatal, intrapartum, postpartum care and neonatal care [6]. BPCR programs generally include counselling for women and their families to: 1) encourage them to take decisions before the onset of labour and potential occurrence of obstetric complications; 2) inform them about the signs of complications so they will know and be able to react promptly if needed; 3) inform them about the locations of emergency services to make the care-seeking process more efficient; and 4) encourage them to save the money needed to pay for services and to plan their transportation to a health facility during labour and in case of emergency [6-9].

To aid in BCPR implementation, the Johns Hopkins Program for International Education in Gynecology and Obstetrics (JHPIEGO) has developed a BPCR matrix [6] that delineates the roles of policymakers, facility managers, providers, communities, families, and women in ensuring that women and newborns receive appropriate, effective, and timely care. The BPCR matrix outlines plans and actions that can be implemented by each group of stakeholders to build an enabling environment for normal and emergency care.

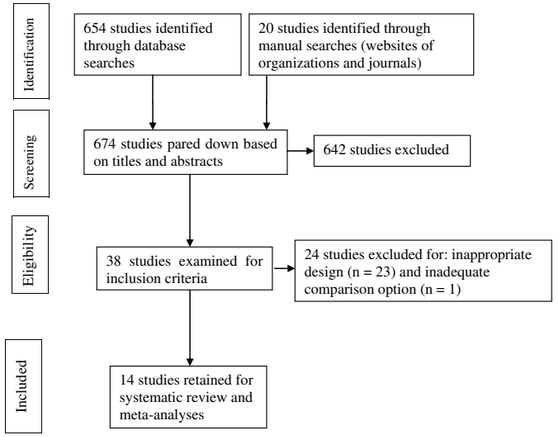

Figure 1 Flow diagram for the selection of studies

BCPR is a broad and integrative strategy; evidence related to its comprehensive implementation is scarce. However, components of the BPCR matrix have been implemented and evaluated in many settings [10-14]. BPCR components are included in the new World Health Organization (WHO) model for antenatal care as part of antenatal care education in clinic setting [15]. Based on critical primary research in India [16] and elsewhere, WHO and UNICEF [17] also now recommend antenatal and postnatal home visits to counsel mothers, provide newborn care and facilitate referral [18]. In addition to making use of formal health services, BPCR requires making effective use of community health workers and health promotion groups. A 2010 systematic review and meta-analysis of community-based intervention packages found a significant reduction in neonatal mortality (twelve studies, risk ratio 0.76, 95% CI 0.68, 0.84), but inconclusive evidence of reduction in maternal mortality (ten studies, risk ratio 0.77; 0.59, 1.02) [19]. Community mobilization through stakeholders such community health workers, or through participation in women's groups also forms part of the BPCR concept [20]. This component was recently evaluated in a Lancet systematic review and meta-analysis focussing on trials involving women's groups practising participatory learning and action [21]. Meta-analyses of seven trials showed that exposure to women's groups was associated with a 37% reduction in maternal mortality (odds ratio 0.63, 95% CI 0.32, 0.94), a 23% reduction in neonatal mortality (odds ratio 0.77; 0.65, 0.90).

This systematic review and metanalysis provides the first assessment of the full range of BPCR strategies on maternal mortality, neonatal mortality, and a variety of intermediate outcomes critical for maternal and child survival. It also aims to assess which components of the BPCR concept are most effective.

Objective of the review

The primary aim of this review was to evaluate the impact BPCR interventions in reducing maternal and neonatal mortality in developing country settings. We also examined the impact of BPCR interventions on process outcomes such use of skilled services, and hygienic practices in the home. Stratified analyses were used to examine program impact in relation to types of interventions and background neonatal mortality level.

Methods

Criteria for including studies in the review

Types of studies

We considered only randomized trials. The unit of randomization could be at the individual or cluster level.

Participants

Participants were pregnant women who received BPCR interventions and lived in developing countries as classified by the World Bank [22].

Types of interventions

These were intervention packages that included any component of the BPCR concept, individually or in combination. Interventions could take place in antenatal, intrapartum, postpartum and neonatal care periods; and at different levels of care (provider, facility, home, community). Specific approaches assessed included counselling of women in prenatal clinics, home visit strategies; and community mobilisation activities.

Comparator group

Women who received no experimental BPCR intervention defined by studied trial.

Outcome measures

Primary outcomes are maternal mortality and neonatal mortality. Secondary outcomes are institutional delivery, home delivery with skilled birth attendant, use of skilled care for neonatal illness, use of postpartum care, clean cutting of the umbilical cord, initiation of breastfeeding within the first hour of birth, knowledge of maternal and neonatal danger signs, and birth preparedness and complication readiness behaviours.

Language of publication

Only studies published in English or French were considered.

Search methods to identify studies

The search strategy was designed in conjunction with an information retrieval specialist and followed Cochrane collaboration guidelines [23]. We searched the PubMed, Embase, Cochrane library, Reproductive Health library, POPLINE and CINAHL databases. The date of search was December 17th, 2012, updated December 5th 2013. The search strategy combined the terms "Birth preparedness", "antenatal education", "home visits", "Community mobilisation", "women's groups" "maternal mortality", "neonatal mortality" "facility-based childbirth" and "developing countries" (Additional file 1 presents a sample search strategy). To supplement the electronic searches, we also hand-checked bibliographies of review papers and related articles [21], international agency websites (WHO, UNFPA, JHPIEGO, USAID and CARE) and two scientific journals specialized in maternal and neonatal health: BMC Pregnancy and Childbirth and International Journal of Gynaecology & Obstetrics.

Selection of studies

Two authors (DS and MJ) reviewed titles, abstracts and keywords of all articles retrieved by the search strategy. Studies

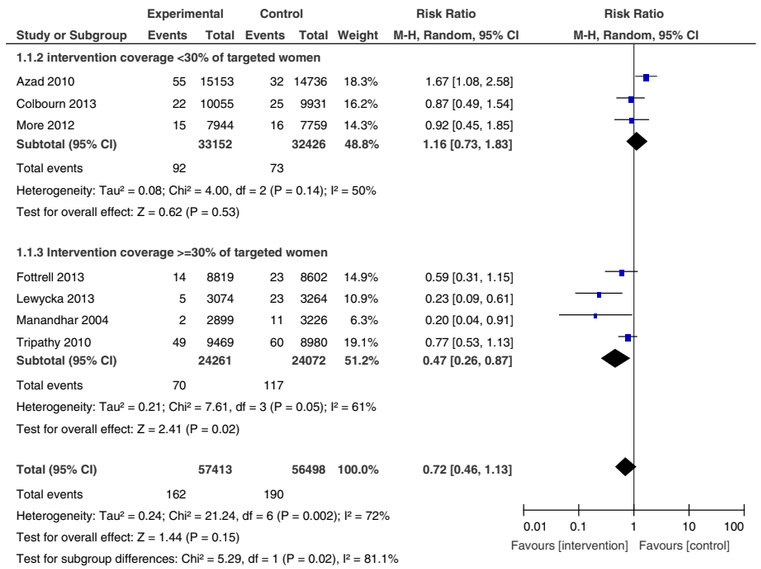

Figure 2 Maternal mortality, overall results and stratification by studies coverage.

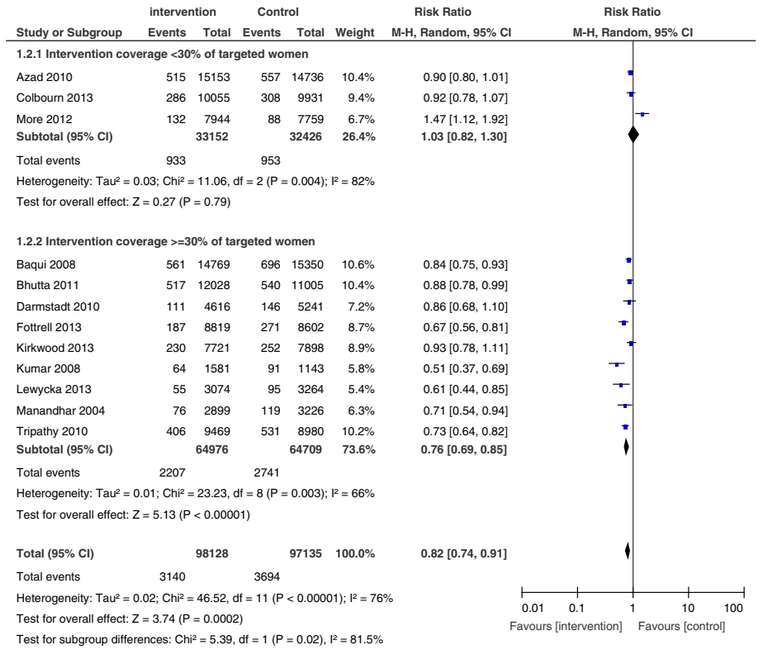

Figure 3 Neonatal mortality, overall results and stratification by studies coverage.

that did not meet criteria related to type of study, participants, intervention, and study country were excluded. The full texts of candidate studies were then examined; those that did not meet inclusion criteria were discarded.

Data extraction

Two authors (DS, MJ) extracted data on the interventions, participants, outcomes and findings, as well as on indicators of methodological quality (randomization, blinding methods, losses to follow-up, etc.). Authors jointly determined study inclusion on the basis of their individual assessments and discussion.

Assessment of methodological quality

Three authors (DS, MJ and LG) assessed the methodological quality of the included studies. We established nine criteria for methodological quality based on the recommendations of the Cochrane Collaboration [24] and the McMaster Quality Assessment Tool for Quantitative Studies [25]. Each dimension was rated adequate, inadequate, or unclear, based on the information reported.

1. *Randomization.* The method used to generate the allocation sequence was rated adequate if the procedure used was genuinely random (random number table, software, etc.), inadequate if the procedure was not random, or unclear if the information was missing.
2. *Concealment of the allocation sequence.* Adequate methods to prevent selection bias are, for example, centralized randomization and the use of opaque and sealed numbered envelopes.
3. *Blinding of evaluators* was rated adequate if the study used independent evaluators who were blind to the intervention.
4. *Contamination* was rated adequate if the steps taken to prevent the control group from receiving the intervention were described.
5. *Co-intervention* was rated adequate if the article mentioned the absence of any additional intervention in the intervention or control groups.
6. *Coverage.* In the trial conducted by Azad et al. [26], the authors considered a participation rate in group sessions of at least 30% of pregnant women as the minimum necessary to achieve desired results. Thus, we considered coverage above a threshold of 30% as adequate.
7. *Quality of implementation.* This component refers to measures taken to ensure that the intervention was administered as planned (i.e., training of educators, use of practice guidelines, supervision, etc.). This component was rated adequate if the article mentioned specific training for the implementation staff or the use of practice guidelines for the education sessions.
8. *Losses to follow-up.* For individual trials, this component was rated adequate if at least 90% of the participants completed the study. For cluster trials, an adequate rating meant that no cluster was lost.
9. *Analysis based on "intention to treat" (ITT).*

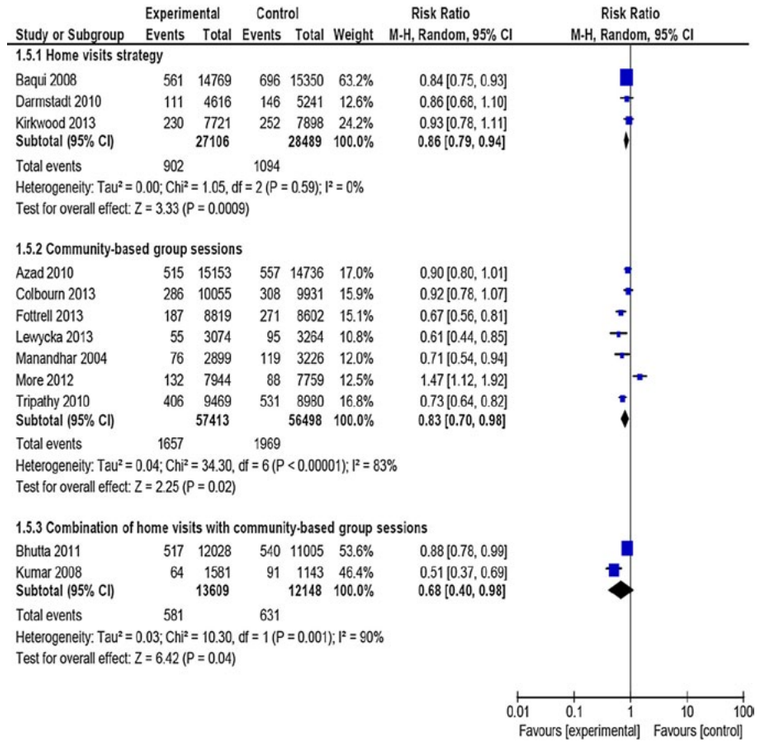

Figure 4 Neonatal mortality, subgroup analysis by type of intervention.

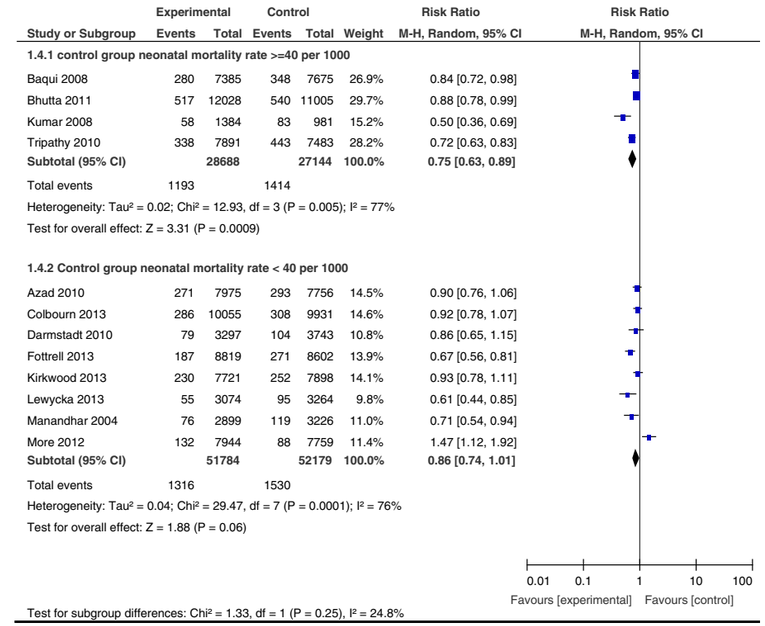

Figure 5 Neonatal mortality, subgroup analysis by level of mortality in control group.

Quality assessments did not influence inclusion of studies in the meta-analyses. However, these assessments later served as criteria for subgroup analyses, and were used in interpreting results.

Data synthesis

We performed meta-analyses to combine relative risks (RR) comparing intervention groups with control groups. Meta-analyses used a random effects model due to important variations in populations and in interventions. Combined RRs and 95% confidence intervals (CIs) were calculated for outcomes measured in the same way by at least two studies. All were binary variables. The number of studies contributing to the meta-analyses ranged from two to 12. Data were re-analyzed based on the ITT principle and baseline differences in outcomes were assumed to have little influence. Combinations were carried out using the Mantel-Haenszel method in the Cochrane Review Manager software [27]. For results reported as cluster averages, the number of events for each group was estimated using the formula N*cluster average/100.

To adjust for cluster effects, for each study randomized in clusters we divided the original number of participants by the cluster effect, whose value was 1 + (M-1)*ICC, where M was the average cluster size and ICC, the intraclass correlation coefficient [24].

Finally, we prepared a description of the reported results for outcomes not included in the meta-analyses, such as knowledge of maternal and neonatal danger signs and birth preparation behaviours.

Investigation of heterogeneities and subgroup analyses

To investigate heterogeneities we calculated the I^2 statistic, which describes the percentage of total variation among studies due to heterogeneity rather than to chance [28]. An I^2 value of 50% or more indicates significant heterogeneity among studies.

Subgroup analyses were planned on the basis of factors identified a priori as potential sources of heterogeneity. These were: methodological quality of the trials; place of intervention (i.e., prenatal clinic, home or community); intervention approach (i.e., clinic-based counselling, home visit strategy, community mobilization led by stakeholders and women 'groups participatory sessions); participants' living environment (i.e., rural or urban); baseline or control group neonatal mortality rate

(i.e., ≤ 30‰; > 30‰ to < 40‰; ≥ 40‰); baseline or control group facility-based delivery rate (i.e., <30%; ≥ 30% to < 50%; ≥ 50% to < 70%; ≥ 70%); components of the intervention (i.e., only prenatal education, both prenatal and postnatal education); and involvement of people from the woman's social network (i.e., husband, other family member, or member of the community). However, there were not enough studies to cover the different subgroup modalities and only intervention type, background neonatal mortality rate and women's participation rate could ultimately be analysed.

Results

Results of the initial search strategy

Electronic and manual searches identified 654 potentially useful reports, after elimination of duplicates (see Figure 1). We examined titles and abstracts of these 654 studies and 38 reports were retained for full text review.

Description of studies included in the review

The Additional file 2 describes the 14 randomized studies retained. Two studies [29,30] used individual randomized units. The other 12 were cluster trials with geographic entities (villages, administrative unions or neighbourhoods) as the randomization units.

Study settings were Indi, Nepal , Bangladesh, Ghana, Malawi, Pakistan and four Latin American cities (Rosario in Argentina, Pelotas in Brazil, Havana in Cuba, and Mexico City in Mexico).

Characteristics of the interventions

Objectives. To assess the impact of educational interventions and community mobilization on neonatal mortality [31,32]; to test the impact of the husband's involvement in prenatal education on the use of maternal care services and birth preparation [29]; to measure the effectiveness of the women's groups program in addressing maternal and neonatal care [33]; and to show whether an intervention providing education and psychological support to pregnant women could change health behaviours and service utilization [30].

Participants. For all interventions, the target population consisted of pregnant women. Belizan's study [30] selected prenatal care attendees presenting at least one of eight predefined risk factors. In addition to pregnant women, studies included husbands [29], persons close to the women [30], other women of reproductive age in the community [20,26,33], or community leaders [32].

Type of interventions. The 12 randomized cluster studies evaluated a whole series of interventions including prenatal and postnatal components. Only in the two individual trials assessing individual counselling in prenatal clinics were the interventions purely prenatal. Three studies considered a home visit strategy. Seven studies involved participation in women's groups engaged in action-learning cycles. Two studies combined community mobilisation with home visits.

In the women's groups approach, the implementation workers acted as facilitators and organized monthly meetings with each group, set up on the basis of neighbourhood proximity. In these meetings, the facilitators guided the women through the four phases of the action-learning cycle: identifying and prioritizing problems, planning strategies, implementing strategies and evaluating the effects. In this way, the women were encouraged to develop actions based on their perceptions of maternal and neonatal issues. Each group was free to implement its own combination of action [20].

Outcomes measured

The Additional file 2 provides an overview of the outcomes measures reported in the 14 studies. All studies measured multiple outcomes. Neonatal mortality was the main outcome measured in 12 cluster-randomised trials. Maternal mortality was assessed in seven studies.

Methodological quality of the retained studies

As a whole, the methodological quality of the studies was acceptable (see Additional file 3). In all studies, randomization, co-intervention, quality of implementation, losses to follow-up, and analysis based on intention to treat (ITT) were rated as adequate. Evaluator blinding was rated inadequate in all studies, except for three [30,32,34] that used evaluators with no prior knowledge of the intervention. Coverage of the target population (pregnant women) by the intervention was inadequate in three studies.

Intervention impact

Fourteen randomized studies involving a total of 307 018 women participants, with 292 256 live births, were included in the meta-analyses. Combined relative risks (RR) were calculated.

Maternal mortality was measured in seven studies. When the results were combined, the reduction in maternal mortality was non-significant in the intervention groups (RR = 0.72; 95% CI: 0.46, 1.13). In addition, the seven results were heterogeneous (I^2 = 72%, p = 0.002) (Figure 2).

A subgroup analysis of studies in which at least 30% of targeted women participated in interventions showed a 53% significant reduction in maternal mortality risk (four studies, RR = 0.47; 95% CI: 0.26, 0.87); with less heterogeity (I^2 = 61%, p = 0.05).

Neonatal mortality was measured in 12 studies. Their pooled results suggested a significant reduction of 18% neonatal mortality risk (RR = 0.82; 95% CI: 0.74, 0.91). But results were highly heterogeneous (I^2 = 76%, p < 0.001) (Figure 3). A subgroup analysis of nine studies in which at least 30% of targeted women participated in interventions showed a statistically significant and greater reduction of up to 24% of neonatal mortality risk (RR = 0.76; 95% CI: 0.69, 0.85). However results remained heterogeneous (I^2 = 66%, p = 0.003).

Stratified analyses suggested that the effects of the interventions differed depending on type of interventions. Two trials that combined home visits with community-based group sessions showed higher impact (RR = 0.68; 95%CI: 0.40, 0.98) than did those with either only home visits strategy (RR = 0.86; 95%CI: 0.79, 0.94) or only community-based group sessions (RR = 0.83; 95% CI: 0.70, 0.98) (Figure 4).

In addition, the impact of the interventions fluctuated depending on the level of neonatal mortality observed in the control group (see Figure 5). In four trials in which the group registered a neonatal mortality rate of at least 40 per 1,000, the impact of the interventions was more marked, with a 25% significant reduction in risk of death (RR = 0.75; 95% CI: 0.63, 0.89). On the other hand, the reduction in risk was only 14% (RR = 0.86; 95% CI: 0.74, 1.01) in the other eight trials and did not reach statistical significance, where the neonatal mortality rate was under 40 per 1,000.

Facility-based delivery. Six studies were included in this analysis [26,30,33-36]. The aggregate result showed only a slight increase in the probability of facility-based delivery that was not statistically significant (RR = 1.16; 95% CI: 0.92, 1.45).

Home delivery with skilled birth attendance. Four studies measured the use of skilled birth attendance in home deliveries [20,26,32,33]. The combined effect of the interventions on this outcome was not statistically significant (RR = 1.06; 95% CI: 0.61, 1.85).

Use of postpartum care. This process outcome was measured in the two individual trials [29,30] conducted in urban settings. The effect of intervention was not significant.

Conditional use of care in newborn illness. Four studies evaluated this outcome [20,31-33]. The combined results indicated a substantial improvement in the probability of using skilled services among the reported cases of newborn illness (RR = 1.66; 95% CI: 1.23, 2.25). Stratified analysis showed no significant difference in relation to the educational strategy used.

Clean cutting of the umbilical cord. The use of sterile materials to cut the umbilical cord was measured for home deliveries in six studies [18,20,31-33]. The combined result showed a moderately statistically significant positive impact on this endpoint (RR = 1.33; 95% CI: 1.14, 1.55).

Initiation of breastfeeding within one hour after birth. This practice was also measured for home deliveries in four studies [18,31-33]. The aggregate effect of the interventions was positive, statistically significant and substantial in size (RR = 1.79; 95% CI: 1.27, 2.51).

Knowledge of maternal and neonatal danger signs / birth preparedness and complications readiness. We did not combine results for these two outcomes, because they were measured differently in the studies. Knowledge of danger signs was measured by two trials [30,31], and birth preparedness and complication readiness behaviours were also measured in two trials [29,32]. All studies showed improvements in measured outcomes.

Discussion

We undertook this systematic review and meta-analysis to investigate the effectiveness of Birth Preparedness and Complications Readiness interventions in reducing maternal and neonatal morbidity and mortality and in improving process outcomes contributing to maternal and newborn survival. Fourteen randomized studies were selected for synthesis. The methodological quality of the studies was generally adequate except for criteria related to blinding of evaluators, since only three studies used evaluators who were blinded to the intervention.

Key results of the review

The meta-analysis of 14 randomized studies showed that BPCR interventions were associated with significant reductions in neonatal mortality. Positive but statistically non-significant effects were shown for maternal mortality. Significant improvements in some process outcomes associated with child survival (i.e., use of care in the event of newborn illness, clean cutting of the umbilical cord, and breastfeeding within the first hour after birth) were also shown.

In addition, two trials reported improvements in knowledge about danger signs, and two others [30,34] indicated that women in intervention groups were more likely to carry out birth preparedness and complication readiness activities than were their peers in the control groups.

Interventions coverage of target population

Variation in the proportion of women reached by the interventions was an important factor in explaining heterogeneity of findings [21].

Home visits versus women's group sessions

Home visits and community-based women's group sessions are both strategies that can potentially reduce the risk of neonatal mortality. However, subgroup analyses suggested that combining the two strategies would have a greater impact than would either one alone. While the number of studies may be insufficient to draw definitive conclusions, this observed tendency is logical as the two strategies are complementary. Home-based individual counselling is more personalized and appropriate for developing the mothers' personal skills related to sanitary care practices. Community-based activities are still needed to support decision-making, because in traditional settings, decisions are more often taken by the community than by the individual. In practice, the choice of one strategy or another will depend on the social context and resource availability. Future studies that take into account cost parameters will be useful for comparing the different options.

Regions with very high neonatal mortality rates

Subgroup analyses showed that reductions in neonatal mortality varied significantly depending on the neonatal mortality rate in the control group. The neonatal mortality risk decreased by 25% (RR = 0.75; 95% CI: 0.63, 0.89) in trials where the mortality rate in the control group was greater than 40 per 1,000. However, the decrease was not statistically significant in studies where the control group mortality rate was below 40 per 1,000. This result corroborates the hypothesis that educational interventions are more useful for preventing and managing infections [35]. In regions with high neonatal mortality (more than 40 per 1000), the cause of death structure is dominated by infectious diseases due to poor sanitation [16,35]. These conditions can be improved by implementing appropriate educational interventions that promote simple preventive measures [36]. On the other hand, in contexts where the neonatal epidemiological structure is dominated by non-infectious diseases (e.g. prematurity), educational interventions would seem to be less effective [31].

Limitations of the review

The main limitation of this review was the small number of studies that were relevant for the investigation of our research questions. Subgroups analyses were undertaken with few studies. Several planned subgroup analyses could not be carried out because there were not enough studies covering the different modalities defined.

Furthermore, the results we obtained included important heterogeneities (expressed by the I^2 statistic). Significant heterogeneities persisted in most of the subgroups for the stratified analyses.

Interpretation of findings in the light of the scientific literature

Our results are consistent with those from two earlier reviews, while adding important complementary information. A 2010 review by Lassi and colleagues showed that community health workers and other health promotion agents could successfully implement important BPCR strategies such as home visits [19]. They found conclusive evidence of a reduction in neonatal mortality but inconclusive evidence of an effect on maternal mortality. A 2013 systematic review by Prost and colleagues focussing on the effects of women's groups practising participatory learning and action found evidence of significant reductions in both neonatal and maternal mortality [21]. Our study confirms and extends these general findings in three ways. First, the BPCR concept is broader and more encompassing than the interventions studied in previous reviews, enabling consideration of a larger number of studies. As BPCR is widely used by governments, international agencies, and funding bodies, consideration of this broader concept is especially relevant for policy and practice. Second, this review was able to provide the first comparison of the relative value of specific BPCR components such as home visits, community mobilisation, and combined strategies. Third, our review is the first to examine results by level of neonatal mortality, providing insights into underlying mechanisms of disease causation and intervention effect. Together, these three systematic reviews underscore the potential value of several BPCR components in reducing maternal and neonatal mortality.

Conclusions

Implications for practice

There is evidence to support implementation of BPCR interventions to improve maternal and neonatal health in developing countries. Neonatal and maternal risks can be significantly reduced if home visits and/or women's group sessions reach a high proportion of pregnant women. Decision-makers could support these approaches in settings where healthcare facilities are inadequate, where healthcare utilization is low, and where the burden of neonatal mortality is high. Sufficient resources should be mobilized for widespread implementation of these interventions and to ensure their quality, through ongoing training of educators/facilitators, provision of practice guidelines, and regular field supervision.

Implications for research

Additional primary studies are needed to consolidate the results of our review. In particular, it will be important to conduct randomized trials of BPCR interventions in other regions with high maternal and neonatal risks. This is particularly important in francophone West and Central Africa, where no similar studies have as yet been conducted and the rates of neonatal and maternal mortality are among the highest in the world. It would be interesting to conduct trials of educational programs in certain areas where health facilities are sufficiently available but underused by the population [37].

The main methodological weakness that should be corrected in future trials relates to the blinding of evaluators.
Blinding introduces special considerations in the context of cluster randomised trials [38]. Given that participants and implementation workers cannot generally be blinded to these types of interventions in cluster-randomised trials, it is important to use independent investigators to evaluate the outcomes. Cost-effectiveness analyses are also needed to provide direction to decision-makers on the most efficient strategies to adopt. In addition, WHO has published prenatal standards of care, including prenatal education, with updates regarding developing birth and emergency plans to be applied in maternal services in developing countries [39]. It would be important to investigate the effectiveness of birth preparedness programs offered in routine prenatal clinics, where there is little control over the behaviours of the implementation workers or of the beneficiaries.

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Early Feeding of Fortified Breast Milk and In-Hospital Growth in Very Premature Infants: A Retrospective Cohort Analysis

Christoph Maas, Cornelia Wiechers, Wolfgang Bernhard, Christian F Poets and Axel R Franz

Abstract

Background: Fortified human milk may not meet all nutritional needs of very preterm infants. Early transition from complementary parenteral nutrition to full enteral feeds might further impair in-hospital growth. We aimed to investigate the impact of the cumulative intake of fortified human milk on early postnatal growth in a cohort of very low birth weight infants after early transition to full enteral feeds.

Methods: Retrospective single-centre observational study. Data are presented as median (interquartile range).

Results: N = 206 very preterm infants were analysed (gestational age at birth 27.6 (25.6-29.6) weeks, birth weight 915 (668-1170) g). Full enteral feeds were established at postnatal day 8 (6-10) and adequate postnatal growth was achieved (difference in standard deviation score for weight from birth to discharge -0.105(-0.603 - -0.323)). Standard deviation score for weight from birth to day 28 decreased more in infants with a cumulative human milk intake >75% of all enteral feeds (-0.64(-1.08 - -0.34)) compared to those with <25% human milk intake (-0.41(-0.7 - -0.17); p = 0.017). At discharge, a trend towards poorer weight gain with higher proportions of human milk intake persisted. In contrast, we observed no significant difference for head circumference growth.

Conclusions: Our current standardized fortification of human milk may not adequately support early postnatal growth.

Background

Human milk feeding reduces the risk of necrotizing enterocolitis [1,2] and is associated with improved long-term outcome in very preterm infants [3,4]. On the other hand, several reports show an association of maternal milk feeding with early postnatal growth restriction in very preterm infants even if human milk was fortified [5,6]. This is most probably caused by intra- and inter-individual variability of human milk composition resulting in deficits in macro- and micronutrient supply in some infants [7]. These negative effects on growth may be particularly relevant to very preterm infants receiving expressed breast milk early on.

We consequently investigated the relationship between the proportion of cumulative total enteral feeding volume administered as breast milk and early postnatal growth in a cohort of very preterm infants after early transition to full enteral feeds.

Methods

This retrospective, non-consecutive three year cohort analysis was performed at Tübingen University Children's Hospital. The ethics committee at the University of Tübingen, Faculty of Medicine, approved this retrospective evaluation and waived the need for parental consent, hence parental consent was not asked for.

Study population

We evaluated all inborn infants with a gestational age (GA) <32 weeks at birth and a birth weight (BW) <1500 g, born in 2006, 2007 and 2010. The initial study [8] aimed at evaluating the effect of accelerated enteral feeding advancement on the time to full enteral feeds. As there was a transitional period (2008/09) after implementation of the new feeding guidelines, data was collected for two cohorts: infants born in 2006/07 and in 2010.

Data collection

Exact nutritional intakes and anthropometric data were determined daily by detailed chart review for the first 28 days of life, then weekly, until discharge.

Nutrition policy

A standardized feeding protocol was applied that defined feeding increments, handling of feeding difficulties, and complementary parenteral nutrition. Feeding of expressed breast milk of the infant's own mother was encouraged. Because donor milk was not available, supplemented breast milk was complemented with preterm formula (Beba preterm formula, Nestlé) if necessary to meet the prescribed enteral feeding volume.

The feeding policy in 2006/07 was to start enteral feeds on the first day of life with 10-15 ml/kg/d of preterm formula (Beba preterm formula, Nestlé). As soon as possible, preterm formula was replaced by breast milk. Daily feeding advancements were scheduled at increments of 15-20 ml/kg/d. Supplementation with a multicomponent fortifier (FM 85, Nestlé; 1.0-1.5 g protein and 18-27 kcal per 100 ml) was started when enteral feeds reached 150 ml/kg/d.

In contrast, in 2010, enteral feeds were initiated with 20 ml/kg/d and advanced by 25-30 ml/kg/d. Breast milk fortification was started at a feeding volume of 100 ml/kg/d.

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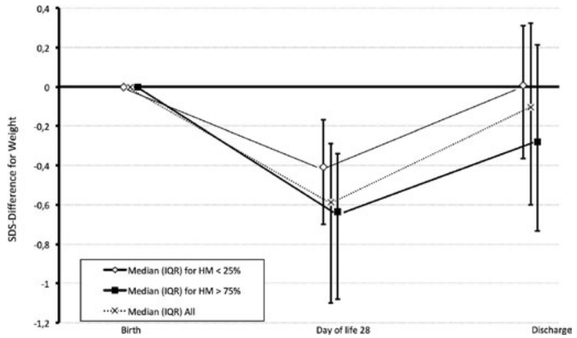

Figure 1. Change in SDS-differences for weight during hospitalisation (median and interquartile range). Box and whiskers is point estimate and interquartile range; horizontal line cutting y-axis in zero representing no differences in SDS for weight.

In cases of fluid restriction (total fluid intake < 150 ml/ kg/d), the dosage of the multicomponent fortifier was increased up to 7.5% (equal to 1.5 g protein and 27 kcal per 100 ml) in both periods. At discretion of the attending neonatologist, the dosage of multicomponent fortifier was also augmented in infants showing persistently faltering growth.

Assumptions and definitions

For calculation of macronutrient supply, we assumed a protein and energy content of 1.4 g/100 ml and 67 kcal/ 100 ml in human milk.

Full enteral feeding was defined as ≥140 ml/kg/day of milk feeds actually administered for more than 24 h.

Further details of the study population, exclusion criteria, nutrition policy and macronutrient supply have been reported previously [8].

Measures of growth

From birth to discharge, weight was measured daily with electronic scales and frontooccipital head circumference (HC) weekly with a measuring tape.

Standard deviation scores (SDS) for weight and HC were computed using LMSgrowth (version 2.14; http://www.healthforallchildren.com/?product=lmsgrowth). The reference population was the British 1990 growth reference [9,10] fitted by maximum penalized likelihood as described before [10]. To account for the impact of intrauterine growth restriction, SDS-differences ($SDS_{discharge} - SDS_{birth}$) and ($SDS_{d28} - SDS_{birth}$) were calculated to illustrate in-hospital postnatal growth.

Data on linear growth were not reported due to the poor reliability of length measurements in the routine neonatal intensive care.

Statistical analyses

Data are presented as median (interquartile range). Comparisons between cohorts were performed using the Wilcoxon/Kruskal-Wallis test or Fisher's exact test. Statistical significance was assumed at $p < 0.05$.

Results

206 of 240 inborn infants with a GA <32 weeks and a BW <1500 g had complete data sets and were analysed. GA at birth was 27.6 (25.6-29.6) weeks and BW 915 (668-1170) g. Full enteral feeds were established at postnatal d8 (6-10). A total of 197/206 infants (96%) received at least some breast milk. The proportion of cumulative total enteral feeding volume provided as breast milk was 86% (41%-95%) at d28 and 81% (33%-94%) at discharge.

122/206 (d28) and 112/206 infants (discharge) received >75% human milk, whereas the proportion of human milk was <25% in 37/206 (d28) and 40/206 (discharge) infants, respectively. SDS-difference for weight from birth to d28 was significantly more negative with >75% cumulative human milk intake in comparison to the group receiving <25% human milk (Figure 1, p = 0.017). Comparing infants with >75% cumulative human milk intake versus those with <25% human milk intake, GA, BW, SDS for weight at birth (-0.995(-1.64- -0.27) vs. -1.28(-2.11- -0.64), p = 0.17), proportion of infants with SDS for weight at birth < -2 (9/37 vs. 25/122, p = 0.65), gender distribution, Clinical Risk Index for Babies (CRIB) and cumulative energy intake were similar (see Table 1). There was, however, a slightly lower calculated cumulative protein intake until d28 in the group receiving >75% human milk (3.86 (3.67-4.02) vs. 3.98 (3.77-4.26) g/kg/d; p = 0.023). The incidence of necrotizing enterocolitis was 3.6% in the group receiving > 75% human milk and 5% in the group receiving < 25% human milk (difference not significant, p = 0.33).

SDS-difference for weight persistently tended to be lower until discharge with >75% vs. <25% cumulative human milk intake (SDS-difference for weight -0.28 (-0.74- +0.21) vs. +0.01(-0.37- +0.31); p = 0.07). SDS-differences for weight during hospitalisation for all study infants and the two subgroups are displayed in Figure 1.

SDS-differences for HC were similar, both at d28 (-0.75 (-1.48 - +0.06) vs. -0.58(-1.31 - +0.26); p = 0.2) and at discharge (0.1(-0.56- +0.76) vs. 0.52(-0.77 - +1.14); p = 0.24).

Discussion

Following early transition to full enteral feeds with predominantly fortified human milk, we observed a significant drop in SDS for weight and a non-significant trend towards lower HC during the first four postnatal weeks, with the majority of infants returning to their growth trajectories until discharge (Figure 1). The latter was true most notably for infants receiving a cumulative human milk intake <25%. During the first four weeks of life a cumulative human milk intake >75% was associated with a significantly more severe decline in SDS for weight compared to children receiving <25% human milk (Figure 1). This difference persisted as a trend until discharge. These results are in line with previous reports [5,6] yet with remarkably better overall postnatal weight gain (median SDS-difference for weight of -0.28 at discharge with >75% human milk in this study, compared with -0.5 in the study by Colaizy et al. [6]).

In contrast to the observed differences in weight gain, no significant difference was observed in HC growth with different proportions of cumulative human milk intake, both, at d 28 and at discharge. Better HC growth than overall weight gain in predominantly human milk fed preterm infants is consistent with the previously delineated "breastfeeding paradox" in very preterm infants describing better neurodevelopmental outcome in spite of suboptimal initial weight gain [4].

Most likely the differences in weight gain can be attributed to intra- and inter-individual variability of human milk composition, particularly the early decline in protein content of human milk during lactation [11], resulting in insufficient protein

Table 1 Patient characteristics and outcome variables in relation to cumulative human milk intake until d 28

	> 75% human milk	< 25% human milk	p-value by Wilcoxon test
Number of infants [n/N] (m/f) [n/n]	122/206 (48/74)	37/206 (21/16)	
Gestational age at birth [weeks] median (IQR) (range)	27.6 (25.5-29.7) (23.0-31.7)	28.6 (25.6-30.5) (23.7-31.9)	p = 0.3
Birth weight [g] median (IQR) (range)	925 (665-1175) (290-1490)	846 (705-1160) (340-1490)	p = 0.9
CRIB-score median (IQR)	4 (1-7)	4 (1-6)	p = 0.42
Incidence of necrotizing enterocolitis [n/N]	3/122	2/37	p = 0.33 (Fisher's exact)
Day of life when full enteral feeds were attained median (IQR)	8 (6-10)	8 (6-10)	p = 0.68
Cumulative energy intake (*) [kcal/kg] first four weeks of life median (IQR)	3431 (3219-3601)	3438 (3356-3562)	p = 0.58
Cumulative protein intake (**) [g/kg] first four weeks of life median (IQR)	105 (101-110)	109 (105-116)	p = 0.002
SDS-difference for weight (SDSd28 – SDSbirth) median (IQR)	-0.64 (-1.08-0.34)	-0.41 (-0.7-0.17)	p = 0.017
Postmenstrual age at discharge [weeks] median (IQR)	38.1 (36.5-40)	38.3 (36-40.3)	p = 0.48
Age at discharge [days] median (IQR)	72 (48-98)	69 (44-93)	p = 0.41

IQR = interquartile range.
(*) = assuming human milk energy content of 67 kcal/100 ml.
(**) = assuming human milk protein content of 1.4 g/100 ml.

supply in some infants predominantly receiving human milk if current standardized fortification is applied [7]. The variability in nutrient content of human milk is reflected in the wider (interquartile) ranges for SDS-difference for weight at d28 and discharge observed in infants receiving >75% human milk compared with those receiving <25% (Figure 1).

Future studies are required to show whether this potential protein deficit is best prevented by standardized supplementation with more protein given to all infants fed human milk, or via individual fortification of human milk after milk analysis.

Furthermore, optimization of the micronutrient content of human milk and formula to the needs of very preterm infants may be required for further improvement of growth [12].

Strengths of this study include the meticulous documentation of exact nutrient intakes along with anthropometric data expressed as SDS-changes during hospitalisation in early enterally fed very preterm infants. Additionally, the cohort included a high proportion of extremely immature infants who are at the highest risk of faltering postnatal growth. Limitations consist in the retrospective, observational, and single-centre design of the study. The fact that we do not report linear growth data because of potential poor reliability and that non-consecutive years were evaluated may also be perceived as limitation.

Conclusions

Although adequate early postnatal growth can be achieved in early enterally fed very preterm infants, our current standardized fortification of human milk does not meet the needs of all infants. To prevent the observed small yet persisting growth deficit in predominantly human milk fed very preterm infants, special attention to intra- and inter-individual variability of protein content in human milk may be required.

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Intelligent Neonatal Monitoring Based On A Virtual Thermal Sensor

Abbas K Abbas, Steffen Leonhardt

Abstract

Background: Temperature measurement is a vital part of daily neonatal care. Accurate measurements are important for detecting deviations from normal values for both optimal incubator and radiant warmer functioning. The purpose of monitoring the temperature is to maintain the infant in a thermoneutral environmental zone. This physiological zone is defined as the narrow range of environmental temperatures in which the infant maintains a normal body temperature without increasing his or her metabolic rate and thus oxygen consumption. Although the temperature measurement gold standard is the skin electrode, infrared thermography (IRT) should be considered as an effortless and reliable tool for measuring and mapping human skin temperature distribution and assist in assessing thermoregulatory reflexes.

Methods: Body surface temperature was recorded under several clinical conditions using an infrared thermography imaging technique. Temperature distributions were recorded as real-time video, which was analyzed to evaluate mean skin temperatures. Emissivity variations were considered for optimal neonatal IRT correction for which the compensation vector was overlaid on the tracking algorithm to improve the temperature reading. Finally, a tracking algorithm was designed for active follow-up of the defined region of interest over a neonate's geometry.

Results: The outcomes obtained from the thermal virtual sensor demonstrate its ability to accurately track different geometric profiles and shapes over the external anatomy of a neonate. Only a small percentage of the motion detection attempts failed to fit tracking scenarios due to the lack of a properly matching matrix for the ROI profile over neonate's body surface.

Conclusions: This paper presents the design and implementation of a virtual temperature sensing application that can assist neonatologists in interpreting a neonate's skin temperature patterns. Regarding the surface temperature, the influence of different environmental conditions inside the incubator has been confirming.

Background

Recently, the rapid improvement in medical thermography technologies in various clinical fields has promoted the use of thermography imaging as a contactless physiological sensor. In particular, neonatal intensive medicine is a clinical field in which infrared thermography may play a future role in non-invasive monitors.

Initially, Clark et al. [1] performed the first clinical trials using direct thermography measurement in neonates, which was dated back to 1980. To perform non-invasive skin temperature measurements, the setup included a hole in the roof of the incubator and the assistance of a mirror system; these additions [1,2] allowed for real-time measurements of thermal reputation.

Adams et al. [3] achieved successful direct thermography imaging in the earliest minutes of life by using a long-wave infrared (LWIR) system. In that project, continuous thermal monitoring of the neonate was accomplished at intermittent intervals ranging between 20 and 30 minutes at the initial stage. Then, a modified protocol was defined to monitor preterm infants inside a convective incubator, kangaroo mother care, and open radiant warmer. The results were compared with values obtained from multiple weighted measurements of resistance temperature device (RTD) sensors.

Pavlidis et al. [4-6] developed a tracking system for infrared thermography as part of an augmented computer vision system. This development was based on a coalitional tracking approach in which a distinct region of interest (ROI) was defined over the neonate's face and its position was tracked over numerous infant motion planes.

Recently, Abbas et al. [7] developed a concept for non-contact respiration monitoring in infants based on IR thermography (IRT). This technique also tracks the nostrils' thermal signature to detect the infant's breathing rate at a distance, and it provides an insightful analysis of possible error sources within the neonatal IRT (NIRT) imaging technique. The need for a robust and intelligent temperature monitoring methodology has increased, which makes NIRT imaging a suitable candidate for contactless temperature measurement and observation inside neonatal intensive care unit (NICU) facilities [2,8].

The NIRT method demonstrates good outcomes for the real-time and continuous quantification of a neonate's surface and core temperatures; however, it lacks the ability to estimate the real temperature value on a neonate's body surface accurately. This lack of reliability is mainly due to the unknown emissivity,

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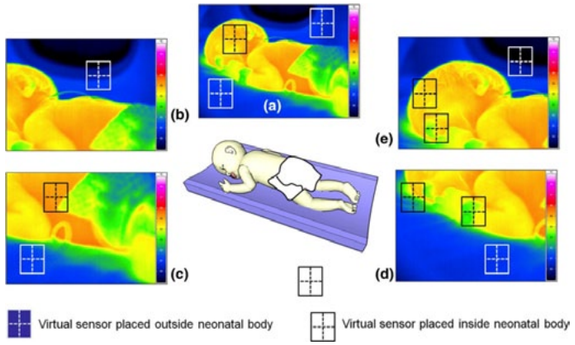

Figure 1 Positions of different possible locations of the virtual temperature sensor developed for NIRT. Directing from (A) initial position of black window (on face) as reference sensor and white windows as ancillary points showing spatial variation over (B, C, D and E) to register different temperature of the neonate and incubator.

ε. For reference, the experimenter could utilize an emissivity value ε for a known material surface or could utilize fabric supplies, such as a hand band or head caps, sutured with a material of known emissivity, such as copper, polished steel, or polyvinyle-flouride electrical tape (e.g. scotch-764). However, in such clinical study, it is impossible to use like material due to the hygienic and disinfection concern that roses within the utilization of these material inside infant incubators.

Thermal imaging

Radiation in the long wave infrared (LWIR) bands (8-14 µm) is important because the human body emits most of its thermal radiation, which encodes valuable physiologic information, in this region of electromagnetic spectrum. This vital information, if properly processed and analyzed, may be used in many biomedical applications, such as mean body temperature mapping and arterial pulse measurements [6,9,10]. A solid base that includes an understanding of the physics of image formation principles, the choice of imaging IR band, and instrumentation is crucial for successful biometrics signature processing. Such signatures include superficial vessel blood flow [11], forehead mean temperature, and nostril thermal patterns [4,12-14].

Possible IRT tracking and monitoring sites on a neonate's body are displayed in Figure 1; these spatial points will be the reference sites for virtual temperature sensing as the issue is discussed further in this paper.

Thermography imaging offers a high-quality concept for the observation and monitoring of different physiological processes [8,15,16]. Recently, we used IR thermal imaging to monitor and map the temperature distribution over the preterm infant's body [12,17,18]. We believe that this technique will become an alternative technique in the future to gold-standard technologies in neonatal temperature monitoring and control [19].

Methods

All measurements were performed using a VarioCAM hr head (InfraTec GmbH, Germany) IR camera (LWIR, 7 µm to 14 µm). The camera transferred the thermal map to a PC via the IEEE 1394 FireWire interface. The neonate's thermal images were taken inside a convective infant incubator (Caleo, Draeger AG, Germany) and converted to a 2D array containing temperature information within the LabVIEW software platform. Additionally,

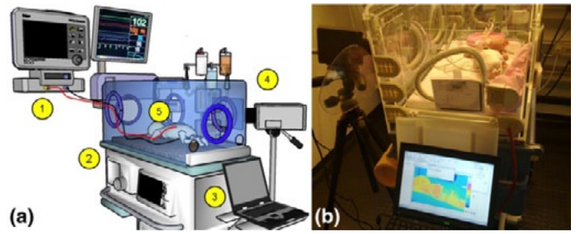

Figure 2 Experimental setup of the NIRT Clinical study by using thermography imaging technique in association with a clinical temperature measurement (a) 3D schematic for components and elements of the setup (1) patient monitoring system, (2) convective infant incubator unit, (3) analysis workstation, (4) IR camera and (5) infant with two skin electrodes connected. (b) Photograph of typical clinical setting.

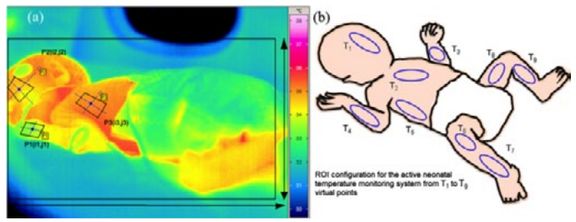

Figure 3 Virtual geometric profiles utilized in ROI tracking for NIRT images (a) and the corresponding profiles over the neonate's body (b), which will be tracked throughout all of the video frames (the perspective of the overhead ROI changes).

these data were used to test the algorithm software's ability to track the specified virtual temperature sensor points on a neonate's skin after motion. Figure 2 illustrates a typical setting for NIRT clinical study inside a convective incubator.

Thermography imaging experiment design

Only ten newborn infants were selected to participate in the clinical study, five of them were under radiant warmer therapy and the rest are placed inside convective incubator. A referential ground truth measurement was implemented by using skin temperature electrodes as gold standards. The accuracy of these clinical skin electrodes is (± 0.1 °C). The NIRT imaging and measurement was performed at the Department of Neonatology (RWTH Aachen University Hospital), and this has been approved by the medical ethics committee of the RWTH Aachen University Hospital, issued on 19 August 2009 with reference code (EK032/09). The acquired thermography datasets used for testing the tracking algorithm. Each dataset contained one measurement scene consisting of a newborn infant undergoing thermography inside a convective incubator or under a radiant warmer. The tracking time was approximately 20 minutes for each subject with a frame rate of 25 fps, and the measurements were conducted as a real-time imaging operation. In principle, a higher frame rate (up to 50 fps) could be achieved; however, a higher frame rate would increase the size of the thermography data to an out-of-memory level in many PCs.

Principally, the selected thermography datasets often included involuntary movements of the neonate during the 20 minutes of thermography acquisition time. The thermography data featured out-of-plane rotation of the facial tissue, hands, feet, and main trunk as the neonates rotated their heads left, right, up, down, or in a random motion. For covering all planes and geometry of the neonate, we configure and selected ROI over the neonate's skin

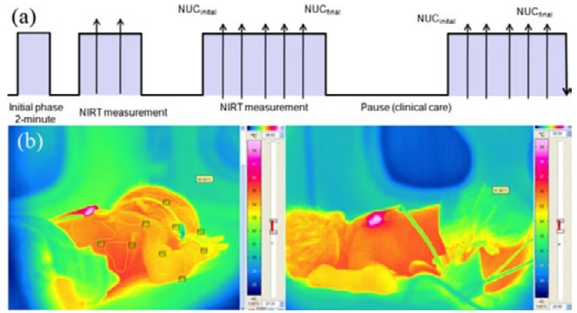

Figure 4 NIRT protocol used in the virtual sensor tracking (a). ROI profiles located over the neonate's skin (b) and an alternative layout of the neonate prior to NIRT imaging.

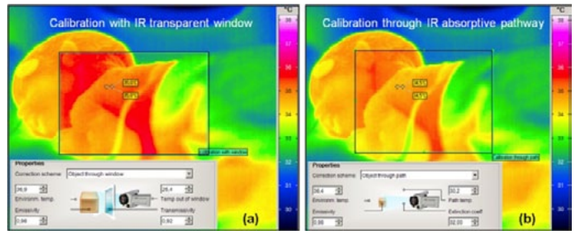

Figure 5 Two thermograms showing the effect of geometric correction of the neonate he neonate's skin (b) and an alternative layout of the neonate prior to NIRT imaging.

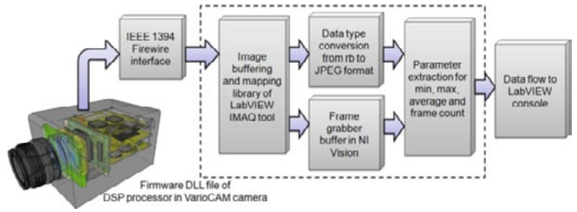

Figure 6 Architecture of thermography imaging acquisition within the LabVIEW platform for the virtual thermal sensor.

to guarantee effective temperature detection over examination time (Figure 3).

A ring-projection transformation was selected in the tracker hierarchy to be compared against the active ROI tracker. The calibration phase of the IR camera was performed directly throughout the measurement time. The typical NIRT protocol sequence used in this study explained in Figure 4, in which the NIRT measurement phase indicates different intervals throughout time.

IR thermal camera calibration setting

The calibration process of the thermal camera took place inside the NICU ward in synchronization with the NIRT measurement phases [20]. This process is called automatic non-uniformity calibration (ANUC), and the procedure compensates for temperature drift during measurements. In addition, the selected field of view (FOV) for the camera assured that there is no influence on thermography resolution during NIRT imaging despite the inclined side angle of the thermal camera within the allocated FOV. This was confirmed during analysis and modeling of heat fluxes dissipated from neonate within NIRT measurement [19].

Temperature and humidity variations inside the convective incubator are commonly considered the main factors that prevent accurate temperature calibration. Therefore, to avoid any incorrect temperature registration and physical related errors in NIRT imaging, the calibration process was implemented during the clinical measurement using the IRBIS Professional software of the IR camera. Objects of interest (OOIs) inside the acquired thermogram were selected and the environmental, incubator and object settings were performed through an IR transparent window (with 0.01 mm thickness) made of polyethylene (PE) material [3].

The transmission of IR radiation through the foil is between 0.92 and 0.94. Therefore, this transparent foil was chosen to block the opened incubator clapper while allowing the baby inside the incubator to be visualized because the Plexiglas material of the incubator hood is an IR-reflecting material with emissivity values reaching 0.97 [1,21].

A geometric correction was applied to the acquired thermography using selected region of interests (ROI) over the neonate's skin and setting the physical parameters (e.g., incubator air temperature, outside window temperature, humidity, IR transmission of PE thin-foil and body temperature) for optimal thermography correction. Figure 5 shows the difference in calibration setting between different thermography scenes where in scene (a) the thermography imaging performed through IR-transparent window and in scene (b) thermography imaging performed directly without interfering media [19].

Moreover, the data were registered against an emissivity equal to unity (considering neonatal skin as a typical blackbody radiator), although the actual value of emissivity was equal to 0.972 [22,23]. This correction strategy plays a vital role in accurate temperature mapping because any slight difference in the emissivity value will tend to add inaccuracies to the temperature reading from the IR camera.

Thermal virtual sensor architecture

The term "Virtual InfraRed SENSor" (VIRSENS) relates to a sensing method based on augmented visual or physical measurements. In this work, a virtual temperature sensor was developed wherein contactless temperature measurements essentially replace the clinical gold standards. Furthermore, virtual sensor tracking software was developed using LabVIEW Vision Assistance (National Instruments) as an integrated toolkit. This software allowed the thermal camera to be connected directly the LabVIEW console by using a native interface file provided by the manufacturer (Figure 6).

Thermography acquisitions began after IR camera calibration and were followed by the extraction of the thermal data from the color space of the image; this task formed a crucial step of the VIRSENS concept. Moreover, the selection of the ROI array was initiated afterward to set the tracking coordinates of the neonate's body regions to be implemented the image-processing loop and architecture (Figure 7).

Tracking technique

The key aspect for robust virtual sensing is the tracking method,

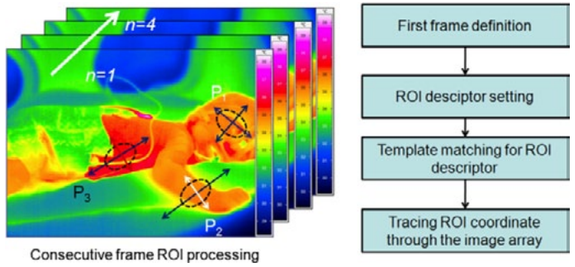

Figure 7 (Left): Successive thermography frame-by-frame definition and tracking of selected ROIs from the different body parts of a neonate, (Right): Simplified flow diagram for tracking method in the virtual sensor.

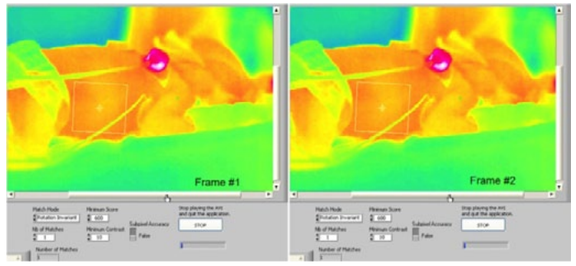

Figure 9 Two successive ROI tracking images used in the virtual sensing technique, were the ROI profile moves due to the neonate's body movements along relative coordinates.

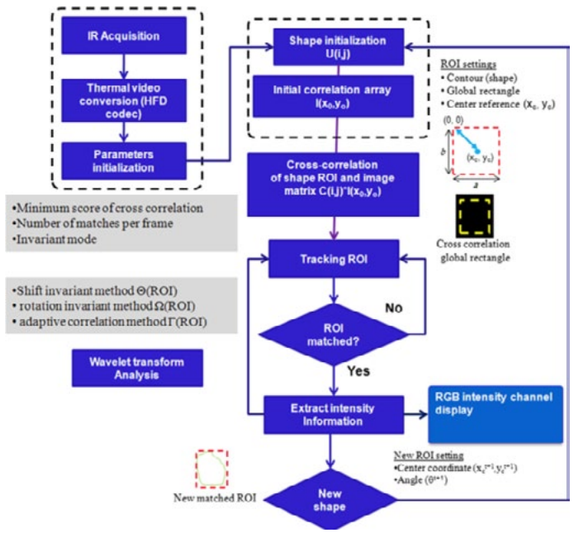

Figure 8 Fundamental steps of the ROI tracking algorithm for NIRT virtual thermal sensing, illustrating processing flow from thermal acquisition down to the surface temperature presentation.

which should accurately monitor the motion of the target surface even in the presence of partial occlusion or deformation [24]. This tracking system is applied to follow the motion of the target's outline (and not only superficial features) [25-28]. Generally, motion tracking is not a straight forward process; it depends on the proper definition of the tracked anatomical geometry and the ability to follow-up and mark the defined ROI over multiple thermography frames (Figures 7 and 8).

Primarily, the tracking algorithm can be divided into five main stages, as illustrated in Figure 8: IR thermography acquisition, ROI geometry profile definition, object coordinate tracking, information extraction, and sensor display. The manner in which the active ROI moves through the image frames is illustrated in Figure 9, where the yellow rectangle moves with the relative motion of the baby inside the camera's field of view (FOV).

When template matching, the ring projection template (RPT) process was used to address rotational variations within the thermography-imaging scene. The RPT reduces a 2D thermogram image into a 1D vector. In general, this task is used as a pre-processing step in the VIRSENS approach.

We define the initial template to be $T(x,y)$ of size $(M \times N)$. The RPT process begins by deriving a center point on the Template $T(x,y)$ that is denoted as (x_c, y_c). Subsequently, the Cartesian frame coordinate Template $T(x,y)$ is transformed into polar frame coordinates based on the following relations:

$x = r\cos\theta$ *(for horizontal reference)* , $y = r\sin\theta$ *(for vertical reference)*

where

$$r = (\text{int})\left(\sqrt{(x-x_c)^2-(y-y_c)^2}\right), r\in[0,R], \mathrm{R} = \min(\mathrm{M},\mathrm{N}) \quad (1)$$

Basically, the ring projection in the selected template $T(x,y)$ at radius r is denoted as $P_T(r)$ and is defined as follows:

$$P_T(r) = \frac{1}{S_r}\sum\nolimits_k T(r\cos\theta_k, r\sin\theta_k), \quad (2)$$

where S_r is the total number of pixels falling on the circle of radius $r = 0,1,2,\ldots,R$ and k denotes the number of correlation iterations in template matching kernel. Note that $P_T(r)$ is defined as the mean pixel intensity along a circle whose radius to the center of the template has equal order in the correlation computation.

Because the RPT is synthesized along circular rings of increasing radii, the derived 1D RPT on the thermography image is invariant to the rotation of its corresponding 2D image template. To effectively obtain the RPT computation along concentric circles, the method employs a look-up table (LUT) whose diameter is set to the size of the template in the ring projection process.

Finally, the RPT is obtained simply by summing up the pixel values along a concentric circle within the template results. For the matching process, the normalized correlation (NC) is adopted in the similarity measurement. Therefore, we consider the following:

$$\vec{P}_T \overset{\Delta}{=} [P_T(0), P_T(1), \ldots, P_T(R)] \quad (3)$$

and

$$\vec{P}_S \overset{\Delta}{=} [P_S(0), P_S(1), \ldots, P_S(R)] \quad (4)$$

Generally, the representations of the reference template ring-projection vectors ($\vec{P}_T$) and thermography scene subimage ($\vec{P}_S$)

$$\left\langle \vec{P}_T, \vec{P}_S \right\rangle = \frac{\left((R+1)\sum_{r=0}^{R} P_T(r)P_S(r) - \sum_{r=0}^{R} P_T(r)\sum_{r=0}^{R} P_S(r)\right)^2 \times 100}{\left((R+1)\sum_{r=0}^{R} P_T(r)^2 - \left(\sum_{r=0}^{R} P_T(r)\right)^2\right)\left((R+1)\sum_{r=0}^{R} P_S(r)^2 - \left(\sum_{r=0}^{R} P_S(r)\right)^2\right)} \quad (5)$$

are computed consecutively. The normalization correction (NC) process between the ring projection vectors $\vec{P}_T$ and $\vec{P}_S$ denoted by $\left\langle \vec{P}_T, \vec{P}_S \right\rangle$ is defined as

With this definition, the value is unaffected by rotational and linear changes (at constant gain and contrast offset in the thermal imaging) in the reference template and thermography scene subimage. In addition, the dimensional length of the ring projection vector is only (R + 1). This significantly increases the computational efficiency for the vector $\left\langle \vec{P}_T, \vec{P}_S \right\rangle$.

Parametric vector approach for template matching

The method proposed here is inspired by the PT method, which is characterized by a decrease in computational complexity when the thermography image involves a change of scale and rotation. Therefore, it is considered a robust solution for the large-scale image data generated in medical thermography [26,29,30]. To obtain rotation/scale invariance in the matching process, a simple approach using a $\mathrm{P_T}$ vector (template image) and a $\mathrm{P_S}$ vector (scene subimage) was proposed.

In the VIRSENSE approach, a PT vector $\vec{P}_T$ was constructed from a base-ring projection set ($\vec{P}_{t_0}, \vec{P}_{t_1}, \ldots, \vec{P}_{t_N}$) consisting of the RPTs and including the template image and differently scaled images as follows:

$$\vec{P}_{T_P} \overset{\Delta}{=} \frac{\vec{P}_{t_0}\omega_0 + \vec{P}_{t_1}\omega_1 + \ldots + \vec{P}_{t_N}\omega_N}{\left|\vec{P}_{t_0}\omega_0 + \vec{P}_{t_1}\omega_1 + \ldots + \vec{P}_{t_N}\omega_N\right|}, 0.0 \le \omega_i \le 1.0, \sum_{i=0}^{N}\omega_i = 1. \quad (6)$$

The NC between the scene subimage vector $\vec{P}_S$ and a PT vector $\vec{P}_{T_P}$ becomes $\left\langle \vec{P}_T, \vec{P}_S \right\rangle$; then, the problem under consideration can be solved by constrained optimization, that is,

$$\max_{\{\vec{\omega}\}}\left\langle \vec{P}_T, \vec{P}_S \right\rangle, \text{subject to } \sum_{i=0}^{N}\omega_i = 1. \quad (7)$$

Essentially, the Lagrangian multiplier (LM) method can solve this problem of difference optimization. The solution of $\vec{\omega}$ is given by

$$\vec{\omega} = \frac{L^{-1}\vec{F}}{\left(\vec{n}\bullet L^{-1}\vec{F}\right)}, \quad (8)$$

where

$$\vec{\omega} \overset{\Delta}{=} \begin{bmatrix}\omega_0\\ \vdots \\ \omega_{\mathrm{N}}\end{bmatrix}, \quad L \overset{\Delta}{=} \begin{bmatrix}\left\langle \vec{P}_{t_0}, \vec{P}_{t_0}\right\rangle & \cdots & \left\langle \vec{P}_{t_0}, \vec{P}_{t_N}\right\rangle \\ \vdots & \ddots & \vdots \\ \left\langle \vec{P}_{t_N}, \vec{P}_{t_0}\right\rangle & \cdots & \left\langle \vec{P}_{t_N}, \vec{P}_{t_N}\right\rangle\end{bmatrix},$$

$$\vec{F} = \begin{bmatrix}\left\langle \vec{P}_S, \vec{P}_{t_0}\right\rangle \\ \vdots \\ \left\langle \vec{P}_S, \vec{P}_{t_N}\right\rangle\end{bmatrix} \text{ and } \vec{n} \overset{\Delta}{=} \begin{bmatrix}1\\ \vdots \\ 1\end{bmatrix}$$

The next step of the algorithm is producing the scaling value sq estimation of the scene subimage, which initiates in terms of the following equation

$$sq = \sum_{i=0}^{N}\omega_i s_i, \quad (9)$$

where s_i for $0 \le \mathrm{i} \le \mathrm{N}$ denotes the different scaling values generated by scaling the template image. The approach enables fast matching in the ROI tracking algorithm. The computational efficiency is significantly increased because the RPT process reduces a 2D thermography image array into a 1D vector. Additionally, the correlation matrix (L) can be determined in the training phase while the optimal parameters $\vec{\omega}$, the scaling value obtained directly from the correlation vector $\vec{F}$, and the correlation matrix L are determined in the matching phase [30]. In fact, there is no iteration step involved in this tracking template-matching-based algorithm. Therefore, the computational time is considerably reduced.

Generally, this data description is appended to the input template image. During the matching phase, the template descriptor (the ROI descriptor, $P_{ROI}(x_T, y_T)$) is extracted from the template image and used to search the template in the inspection image [31-33].

The mathematical process of image cross-correlation is simple; the RPT is overlaid on the source thermogram image, and the intensity values for each corresponding pixel are multiplied individually. Additionally, all of the matched templates are summed to produce a single correlation value [32,33].

The correlation value matrix is then scanned for its peak value. This position generally conforms to the position in the source image that most closely matches the template [22,34,35]:

$$\vec{P}_T \equiv [P_T(0), P_T(1), \ldots, P_T(R)]^T . P(x,y) \quad (10)$$

where $P(x,y)$ is the reference template position on the thermography image. The correlation matrix can include several high values that correspond to several instances (events) of tracked templates in the source thermography image [36-38].

Scale (shift)-and rotation-invariant technique

One of the greatest flaws in cross-correlation is its inability to match objects in a source image that are either a different size or rotated compared to the reference template. These two template-matching mechanisms are used in the ROI descriptor tracking (corresponding to the projected template) in the frame matrix. The mathematical approximation of such a template inside a rectangular contour with $T_k(x_k,y_k)$ is as follows:

$$P_T(u) = \frac{1}{S_k}\sum\nolimits_k T(x_k, y_k), \quad (11)$$

To overcome and compensate for this issue throughout the NIRT data frames, the template must be rescanned over the thermography scene image using different rotations and sizes (variances in both the x-and y-axes). This process can be extremely time consuming; consider performing a cross-correlation 360 times just to perform a rotation-invariant match without even sub-degree precision [35,39,40].

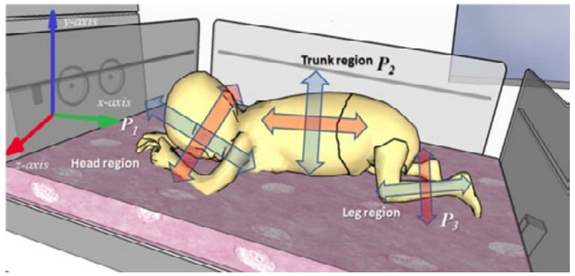

Figure 10 Imaging-plane layout of ROI tracking over a neonate's different body regions displaying the out-of-plane rotation coordinates that were used to develop an ROI tracking algorithm for medical IRT.

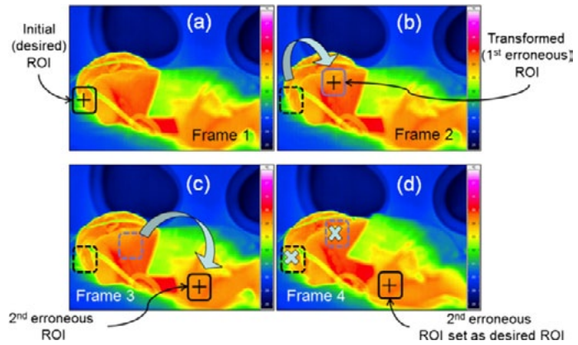

Figure 11 Setting of Erroneous ROI and tracking over a neonate's body regions displaying the desired ROI position changing by misallocation the coordinates in the tracking software.

If the tracked portion always has the similar size and no spatial distortion exists, then the virtual sensor does not scan for size variations [4,26,27,41]. The identical principle is applicable for rotation variance if the body part will be repeatedly positioned at the same orientation (Figure 10). In that case, the source thermography image is rescanned using a range of different angles (cross-correlation can typically detect object rotations of approximately ±5° without rescanning) is not necessary.

The detection of object rotations can be accomplished at up to ±12°-18° angle of rotation without rescanning and initializing the reference ROI template. However, the inability of cross-correlation to match objects in a source image that are either a different size or rotated compared to the template is still one of the shortcomings in the rotation-and shift (scale)•invariant method for the object detection system [26,30,42-44].

Results and discussion

In summary, the results obtained from the virtual sensor demonstrate its ability to accurately track different geometric profiles over the external anatomy of a neonate. Only a small percentage of the motion detection trials failed to track due to the lack of a properly matching matrix for the ROI descriptor under study (see Table 1).

The main clinical application of the presented virtual sensor approach is the continuous monitoring of patients without loss of the ROI due to unexpected movements or involuntary motions initiated by the patient. The VIRSENS approach offers the flexibility to perform stress-test infrared thermography, e.g., on treadmills, or to monitor unconscious patients (e.g., under intensive or critical care). Furthermore, this non-contact temperature monitor may become a tool in high-risk missions, such as for pilots or submarine staff [9,12,45], to provide online monitoring of respiration activity through convective heat-loss during expiration and inspiration [7,20,41,46].

To further advance the use of VIRSENS in neonatal medicine, we used embedded contactless temperature monitoring and regulation in a neonatal incubator closed-loop control system. This approach can reduce the need for skin temperature electrodes and the problems associated with their use, such as sensor dislocation, motion artifacts, calibration drift, wire crowding, false connections, and the possibility of infection for newborn infants.

Moreover, this tracking method requires additional validation tests and clinical trials to provide beside the proof-of-concept (POC) of this technology feasibility in the neonatal monitoring field.

In addition, the ability of VIRSENS to perform geometric identification of selected body parts (e.g., face, hands, legs, interscapular, and maxillary region) (see Additional files 1, 2 and 3) adds a crucial role in anatomical posture identification for neurological reflexes and postural control of neonates. Because the VIRSENS has several misallocated ROI over the neonate's geometry during the tracking process (Figure 11), which indicates that this method need further optimization and feasibility studies. This believed to be solved when more stable and precise tracking algorithms used in the VIRSENS architecture to become more stable monitoring technique.

Table 1 Comparison of scoring rate success for VIRSENS in NIRT imaging[1]

Frame no.	Success rate (%)	Data-over flow time (ms)	Tracked anatomical region	p = error rate	Correlation coeff.
1	82	1,200	Face-hand/belly	0.0037	0.235
2	74	1,403	Face-hand/belly	0.0022	0.171
3	80	1,227	Face-hand	0.0015	0.217
4	79	1,296	Face-hand/belly	0.0023	0.182
5	85	1,372	Face-hand	0.0012	0.302
6	86	1,214	Face-hand/belly	0.0031	0.319
7	87.2	1,306	Face/hand	0.0024	0.479
8	82	1,278	Face/hand/belly	0.0027	0.466
9	89.02	1,282	Face-hand/belly	0.0018	0.502
10	88.5	1,307	Face/hand	0.0023	0.412

The table also illustrates the correlation of the tracked ROI descriptor over the measurement scene with respect to a newly chosen position of the ROI descriptor.
[1]The table presents the comparison of different success rates for the virtual temperature sensor used within the NIRT imaging for illustrating the scoring percentage of fitted and tracked ROI over the misallocated ones.

Table 2 Comparison of different desired ROI locations of virtual temperature sensor[2]

NIRT datasets/infant	Tracked regions	Total desired ROI/region	Desired ROI (fitting and tracked)	False ROI (misallocated)	Scoring percentage %
Infant 1	Facial	4	3	1	75
	Abdominal	6	4	2	66.6
	Upper limb	4	3	1	60
	Lower limb	5	5	0	100
Infant 2 (radiant warmer)	Facial	4	2	2	50
	Abdominal	6	4	2	66.6
	Upper limb	5	4	1	75
	Lower limb	5	4	1	75
Infant 3 (radiant warmer)	Facial	4	4	0	100
	Abdominal	6	5	1	83.3
	Upper limb	5	5	0	100
	Lower limb	5	4	1	80
Infant 4 (radiant warmer)	Facial	4	3	1	75
	Abdominal	6	5	1	83.3
	Upper limb	5	4	1	80
	Lower limb	5	3	2	60
Infant 5	Facial	4	3	1	75
	Abdominal	6	4	2	66.6
	Upper limb	5	3	2	60
	Lower limb	5	4	1	80
Infant 6	Facial	4	4	0	100
	Abdominal	5	5	0	83.3
	Upper limb	5	3	2	60
	Lower limb	5	3	2	60
Infant 7	Facial	4	2	2	50
	Abdominal	6	3	3	50
	Upper limb	5	4	1	80
	Lower limb	5	3	2	60

[2]This table gives the quantitative index for the total numbers of fitted ROIs and missed ROIs over the total number of these selected ROIs for different spatial positions over neonate's body.

Table 2 provides some of quantitative analysis for performance measuring in different thermography datasets within NIRT study. This table showing the scoring of matches of tracked ROI per anatomical regions for seven infants participating in the study. As we can see from Table 2 that the higher success rate of this scoring occurs, in the facial, plane where there is a prominent landmark such as nose, orbital, forehead and maxillofacial regions. Therefore, this is highly discriminated from other anatomy such as hand, arms, legs and trunk can be use the facial tracking as referential template for tracking accuracy and validation procedure of virtual thermal sensor.

Conclusion

In this study, a thermal imaging tracking method was proposed and tested based on a template-matching algorithm. The developed method uses a spatially trained ROI tracker whose interactions are modeled using cross-correlations of the ROI template and a searchable IR image. The method's output provides pixel-level tracking accuracy even in the presence of multidimensional target transformation. The proposed tracking method was effectively tested in thermal and visual datasets featuring facial regions and other anatomical objects.

The thermography tracking system for neonatal monitoring was implemented and tested for clinical monitoring inside NICU unit. The main conclusion from this experiment is that the tracking can be robust over well-calibrated thermography frames and for lesser jerky movements of the neonate. In fact, thermography measurements performed at a distance are beneficial from a psychological viewpoint for both staff and the patient's relatives but produce challenges from the medical perspective. The tracking problem, which is pivotal in this study, was particularly challenging due to the functional nature of thermal IR imaging and its application in real-time operation.

Moreover, NIRT imaging depicts physiological changes; therefore, it is highly dynamic, non•linear, unpredictable in its uncertainties, and difficult to model. In addition, the estimation

of the emissivity value at certain tracking points requires further optimization and development before it can be included in prospective NIRT applications, such as the detection of respiration signatures with the IRTR method or evaluation of superficial blood perfusion over active metabolic regions (e.g. liver and brain). Because these applications would appear to be difficult tasks due to the slow hemodynamic activities of the superficial vessels, the method requires further development and improvement for clinical convention in contactless blood perfusion and hemodynamics parameters.

Furthermore, this physiological tracking application based on thermography might consider a good candidate for running on smartphones and other mobile communication devices. These applications can be a part of the widespread adoption and use of mobile and computing vision technologies is opening new and innovative ways to improve health care delivery. This in turn can transform a mobile platform into a regulated medical monitoring system.

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Preterm Birth By Vacuum Extraction and Neonatal Outcome: A Population-Based Cohort Study

Katarina Åberg, Mikael Norman and Cecilia Ekéus

Abstract

Background: Very few studies have investigated the neonatal outcomes after vacuum extraction delivery (VE) in the preterm period and the results of these studies are inconclusive. The objective of this study was to describe the use of VE for preterm delivery in Sweden and to compare rates of neonatal complications after preterm delivery by VE to those found after cesarean section during labor (CS) or unassisted vaginal delivery (VD).

Methods: Data was obtained from Swedish national registers. In a population-based cohort from 1999 to 2010, all live-born, singleton preterm infants in a non-breech presentation at birth, born after onset of labor (either spontaneously, by induction, or by rupture of membranes) by VD, CS, or VE were included, leaving a study population of 40,764 infants. Logistic regression analyses were used to calculate adjusted odds ratios (AOR), using unassisted vaginal delivery as reference group.

Results: VE was used in 5.7% of the preterm deliveries, with lower rates in earlier gestations. Overall, intracranial hemorrhage (ICH) occurred in 1.51%, extracranial hemorrhage (ECH) in 0.64%, and brachial plexus injury in 0.13% of infants. Infants delivered by VE had higher risks for ICH (AOR = 1.84 (95% CI: 1.09-3.12)), ECH (AOR = 4.48 (95% CI: 2.84-7.07)) and brachial plexus injury (AOR = 6.21 (95% CI: 2.22-17.4)), while infants delivered by CS during labor had no increased risk for these complications, as compared to VD.

Conclusion: While rates of neonatal complications after VE are generally low, higher odds ratios for intra- and extracranial hemorrhages and brachial plexus injuries after VE, compared with other modes of delivery, support a continued cautious use of VE for preterm delivery.

Background

Preterm birth is common [1] but still, the optimal mode of delivery of preterm infants is not known. Although neonatal outcomes in preterm infants delivered vaginally or by cesarean section (CS) [2-5] have been compared, there is no evidence to provide clear guidance on the method of choice [6]. Given the widespread assumption that assisted vaginal delivery could be harmful for fragile infants that are underweight and preterm, very few studies have addressed the use of vacuum extraction (VE) for preterm birth.

Delivery by VE is a common obstetrical procedure, and in many countries it has replaced the use of forceps. VE is used to terminate a protracted second stage of labor and as an intervention for fetal or maternal distress. VE requires vertex presentation, a fully dilated cervix and ruptured membranes [7]. A cesarean section, on the other hand, can be performed at any stage of labor and does not require prerequisites of this kind. Most clinical guidelines do not recommend VE before 34 gestational weeks [8-10]. These recommendations are not based on results of randomized controlled trials, but rely on the observation that preterm infants are more likely than term infants to develop ICH, and on extrapolations from studies of term infants showing that VE is associated with an increased risk of ICH and other neonatal complications [11-17]. Only three studies have previously investigated the use and outcomes of VE in preterm births. The first was undertaken over 40 years ago and showed increased mortality and morbidity among preterm infants delivered by VE as compared with term infants delivered by VE [18]. The second study compared neonatal morbidity in preterm infants delivered vaginally with (n = 61) or without VE (n = 122), and found no differences in neonatal morbidity between the two groups [19]. The last study compared VE and forceps for preterm delivery (n = 64) [20]; the neonatal outcomes were similar in both groups. The available data are clearly untimely and hampered by limitations in power and, therefore, current knowledge on safety of preterm vacuum-assisted birth is unsatisfactory.

The aim of this study was to 1) describe the use of VE and compare it to rates of CS during labor in preterm deliveries in Sweden from 1999-2010, 2) characterize the distribution of perinatal risk factors associated with each mode of delivery, and 3) compare rates of neonatal intra- and extracranial hemorrhages, as well as occurrence of brachial plexus injury after preterm delivery by VE or CS during labor, using unassisted vaginal birth as a reference.

Methods

This study was based on data from national data bases held by the Swedish National Board of Health and Welfare. The national registration number, assigned to each Swedish resident at birth, was used for individual record linkage. We used two registers: The Swedish Medical Birth Register (SMBR) that covers 99% of all births in Sweden, and The Swedish National Inpatient Register (IPR) that covers all public inpatient care. The SMBR includes prospectively collected information on maternal characteristics, reproductive history, and complications during pregnancy, delivery, and the neonatal period. The IPR includes data on each hospital admission and discharge.

Study population

During the period of 1999-2010, there were 75,296 (6.2%) preterm births in Sweden. We excluded deliveries by CS before the onset of labor (n = 17,306), forceps (n = 257), or performed with both VE and CS (n = 125). We also excluded stillbirths (fetal deaths occurring before labor or intra partum) (n = 1,839), multiple births (n = 11,088), and births in breech presentation (n = 3,917). Thus, the final study population was restricted to all live-born, preterm singleton infants with a non-breech presentation at birth, delivered after a spontaneous or induced onset of labor followed by CS, vacuum extraction (VE), or by unassisted vaginal delivery (VD) before gestational week 37 + 0 days (N = 40,764). CS during labor was defined as abdominal delivery after the onset of labor, either spontaneously, by rupture of membranes, or by induction.

A number of independent variables were collected; the maternal anthropometrics included: age, height, and body

Table 1 Neonatal outcomes studied in 40 764 preterm infants

Neonatal outcomes			
Outcome	**Main ICD-code**	**ICD-subgroup**	
Intracranial bleeding	P10 Intracranial laceration and hemorrhage due to birth injury	10.0	Subdural hemorrhage due to birth injury
		10.1	Cerebral hemorrhage due to birth injury
		10.2	Intraventricular hemorrhage due to birth injury
		10.3	Subarachnoid hemorrhage due to birth injury
		10.4	Tentorial tear due to birth injury
		10.8	Other intracranial lacerations and hemorrhages due to birth injury
		10.9	Unspecified intracranial laceration and hemorrhage due to birth injury
	P52 Intracranial non-traumatic hemorrhage of fetus and newborn	52.0	Intraventricular (non-traumatic) hemorrhage, grade 1, Subependymal hemorrhage (without intraventricular extension)
		52.1	Intraventricular (non-traumatic) hemorrhage, grade 2, Subependymal hemorrhage with intraventricular extension
		52.2	Intraventricular (non-traumatic) hemorrhage, grade 3, Subependymal hemorrhage with both intraventricular and intracerebral extension
		52.3	Unspecified intraventricular (non-traumatic) hemorrhage of fetus and newborn
		52.4	Intracerebral (non-traumatic) hemorrhage of fetus and newborn
		52.5	Subarachnoid (non-traumatic) hemorrhage of fetus and newborn
		52.6	Cerebellar (non-traumatic) and posterior fossa hemorrhage of fetus and newborn
		52.8	Other intracranial (non-traumatic) hemorrhages of fetus and newborn
		52.9	Intracranial (non-traumatic) hemorrhage of fetus and newborn, unspecified
Neonatal cerebral dysfunction	P90 Convulsions of newborn	P90	Convulsions of newborn
	P91 Other disturbances of cerebral status of newborn	P91.0	Neonatal cerebral ischemia
		P91.1	Acquired periventricular cysts of newborn
		P91.2	Neonatal cerebral leukomalacia
		P91.3	Neonatal cerebral irritability
		P91.4	Neonatal cerebral depression
		P91.5	Neonatal coma
		P91.6	Hypoxic ischemic encephalopathy of newborn
		P91.8	Other specified disturbances of cerebral status of newborn
		P91.9	Disturbance of cerebral status of newborn, unspecified
Extracranial bleeding	P12 Birth injury to scalp	12.0	Cephalhaematoma due to birth injury
		12.2	Epicranial subaponeurotic haemorrhage due to birth injury
Neonatal nervous injury	P14 Birth injury to peripheral nervous system	14.0	Erb paralysis due to birth injury
		14.1	Klumpke paralysis due to birth injury
		14.2	Phrenic nerve paralysis due to birth injury
		14.3	Other brachial plexus birth injuries

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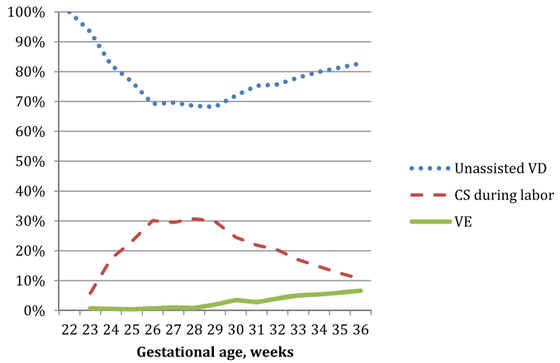

Figure 1 Mode of delivery in relation to gestational age. Figure 1 shows rates (%) of different modes of delivery in relation to gestational age (in completed weeks). The blue, dotted line represents unassisted vaginal deliveries, the red, dashed line represents cesarean sections performed after onset of labor, and the green line represents the vacuum extraction deliveries.

mass index (BMI). BMI was calculated from measured height and weight obtained at the first antenatal care visit, which occurred before the 15th week of gestation in more than 95% of the pregnancies. BMI was categorized into underweight (below 18.5 kg/m2), normal (18.5-24.9 kg/m2), overweight (25-29.9 kg/m2), obese (>29.9 kg/m2), or missing. Parity was categorized as primior multiparity. Information on complications during pregnancy and delivery were coded according to the International Classification of Diseases (ICD) Tenth Revision (1997 and onwards). The following pregnancy complications were included: diabetes—both gestational and types 1 and 2 (O24.0-9) preeclampsia—both hypertension, preeclampsia, and eclampsia (O10.0-O15.9). Labor-related risk factors or covariates included epidural analgesia (EA; yes/no), and induction of labor (yes/no). Indications for operative delivery were classified into four major groups: prolonged labor (O62.0-2, O63.0-9), signs of fetal distress (O68.0-O68.1-9), preeclampsia, and a non-occipitoanterior presentation of the fetus (all presentations except occipitoanterior and breech, registered at birth). Gestational age (GA) for preterm infants was divided into three periods according to the World Health Organization:

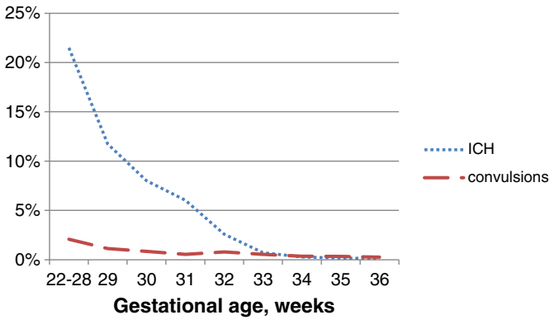

Figure 2 Proportion (%) preterm infants diagnosed with intracranial hemorrhage (ICH) or convulsions by gestational age. Figure 2 shows the proportions (%) of preterm infants diagnosed with ICH and neonatal convulsions in relation to gestational age (in completed weeks). The blue, dotted line represents intracranial hemorrhage (ICH) and the red, dashed line represents neonatal convulsions.

extremely preterm (before 28 weeks), very preterm (28-31 weeks) and moderately preterm (32-36 weeks). Furthermore, we also divided the preterm gestational period according to guidelines on instrumental delivery into either: less than 34 weeks (VE not recommended), and 34-36 weeks (VE may be used). GA was recorded in completed weeks, and was based on routine ultrasound dating performed at 17 to 18 postmenstrual weeks in 97-98% of all pregnant women. Infant birthweight was categorized as less than 1,500 grams, 1,500-2,000 grams, 2,001-2,500 grams, 2,501-3,000 grams, and 3,001-4,000 grams.

Outcome variables

Neonatal diagnoses were classified according to the International Classification of Diseases (ICD) Tenth Revision (1997 and onwards), and identified/collected in the SMBR or in the IPR. The following neonatal outcomes (ICD codes) were assessed: Intracranial laceration and hemorrhage due to birth injury (P10), intracranial non-traumatic hemorrhage of fetus and newborn (P52), convulsions of newborn (P90), other disturbances of cerebral status of newborn (P 91), subgaleal hematoma (P12.2), cephalhematoma (P12.0), and brachial plexus injury (P14.0-3). The definitions of outcomes are described in detail in Table 1.

Neonatal diagnoses of intracranial hemorrhages in preterm infants were mainly based on imaging of the brain using ultrasonography; however, some assessments of the brain at term-equivalent age were alternatively performed with CT and/or MRI. Imaging of the brain was performed on clinical indications only in cases born moderately or late preterm, whereas all very preterm infants (born before 32 weeks of gestation) were screened for intracranial lesions, even in asymptomatic infants. A diagnosis of convulsions included infants with clinical signs of convulsions and/or convulsions verified by EEG. Statistical analysis was performed using proportions and odds ratios (OR) with a 95% confidence interval (CI) for neonatal complications in relation to mode of delivery, using unassisted VD as the reference group (SPSS 20.0 for Windows software package). Three models were used to assess the relationship between the different modes of delivery and the risk for neonatal complications: one crude, and two adjusted (Models 1 and 2). The included covariates have been shown previously to be related to instrumental deliveries, and were related to the outcomes in cross tabulations. In Model 1, we adjusted for the following confounders or covariates: maternal age, height, BMI, and parity, as well as infant year of birth, birthweight and GA. In Model 2, we added the indication for operative delivery and preeclampsia. The year of birth was entered as a continuous variable in accordance with a linear secular trend, and all other variables were entered as categories. Furthermore, a separate logistic regression analysis was performed to investigate severe ICH in relation to mode of delivery. Here, intraventricular hemorrhages grades 1-2 were excluded and the analysis was adjusted for GA only. We also conducted separated analyses on potential relationships between sex and ICH in relation to mode of delivery. Missing data were entered as a separate category in the analyses. The study was approved by the Regional Ethical Review Board in Stockholm, Dnr 2008/1322-31.

Results

Use of VE in relation to gestational age

Among the 40,764 (54% of all) preterm deliveries included in this study, 2,319 (5.7%) preterm infants were delivered by VE, 5,505 (13.5%) by CS during labor, and 32,940 (80.2%) by VD. The rate of VE deliveries increased gradually with gestational age, Figure 1.

Table 2 Maternal, pregnancy, delivery, and infant characteristics by mode of delivery

	Total	Unassisted vaginal delivery	CS during labor	Vacuum extraction
	N = 40,764	n = 32,940%	n = 5,505%	n = 2,319%
Maternal age, yrs				
–19	1,063	85.0	10.3	4.7
20-24	6,130	85.6	9.3	5.0
25-29	12,845	82.2	11.6	6.2
30-34	12,767	79.8	14.2	6.0
35-39	6,380	76.4	18.6	5.0
>39	1,351	72.7	22.1	5.3
Missing	228	81.6	13.6	4.8
Maternal height, cm				
–155	2,481	75.6	18.0	6.4
156-160	6,538	79.9	14.3	5.8
161-165	10,336	81.0	13.0	6.0
166-170	10,129	81.8	12.5	5.7
>170	7,169	81.9	13.1	5.0
Missing	4,111	80.6	14.1	5.3
Maternal BMI				
Underweight	816	83.3	11.0	5.6
Normal	14,197	81.2	12.8	6.0
Overweight	6,124	79.0	15.2	5.8
Obese	2,944	76.4	19.4	4.1
Missing	16,683	81.7	12.6	5.7
Parity				
Primipara	18,120	80.0	11.6	8.4
Multipara	22,644	81.8	15.9	2.3
Preeclampsia				
Yes	1,833	64.2	28.3	7.5
No	38,931	81.6	12.8	5.6
Diabetes				
Yes	1,434	65.9	26.2	7.9
No	39,330	81.3	13.0	5.6
Induced labor				
Yes	6,372	73.8	19.9	6.3
No	34,392	82.1	12.3	5.6
EA				
Yes	8,894	80.9	7.3	11.8
No	31,870	80.8	15.2	4.0
Gestational age, weeks				
22-27	1,276	77.0	22.4	0.6
28-31	2,344	72.0	25.5	2.5
32-36	37,144	81.5	12.4	6.1
Infant birthweight, g				
< 1500	2,367	69.8	28.7	1.4
1501-2000	3,365	70.5	25.5	4.0
2001-2500	9,691	79.9	14.5	5.7
2501-3000	15,613	84.5	9.2	6.3
3001-4000	9,079	82.9	10.6	6.5
Missing	649	70.4	25.0	4.6

Population based cohort consisting of 40 764 preterm deliveries.
CS = caesarean section, BMI = Body Mass Index (weight in kilograms/height in meters^2), EA = Epidural Analgesia.

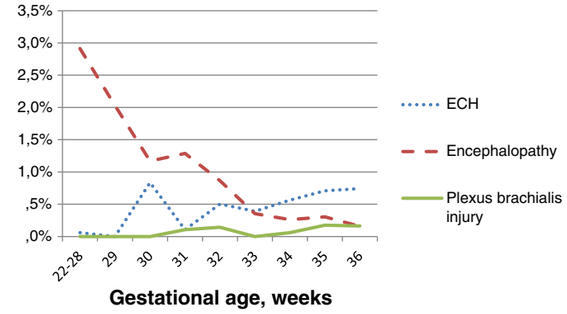

Figure 3 Proportion (%) preterm infants diagnosed with extracranial hemorrhage (ECH), encephalopathy and brachial plexus injury by gestational age. Figure 3 shows the proportions (%) of ECH, encephalopathy (ICD-code P91: other disturbances of cerebral status of newborn), and brachial plexus injury in relation to gestational age (in completed weeks). The blue, dotted line represents extracranial hemorrhage (ECH), the red, dashed line represents encephalopathy and the green line represents brachial plexus injury.

Distribution of risk factors or covariates in relation to mode of delivery

Table 2 shows maternal and perinatal characteristics of the study population in relation to mode of delivery. The VE rate decreased with maternal height and 80% of the women who delivered by VE were primiparae, compared with 48% of those who underwent CS during labor (not in table). More than 45% of the women who delivered by VE had received epidural analgesia during labor compared with 22% of women with VD, and 12% with CS during labor (not in table). Given the association between GA and VE, infants delivered with VE had higher birthweights.

The most common indication for VE was fetal distress (42%), followed by prolonged labor (25%). Having a non-occipitoanterior position (25%) or fetal distress (17%) were the most common indications for CS during labor, while only 3% in this group had a diagnosis of prolonged labor.

Neonatal outcome in relation to gestational age

The proportion of preterm infants diagnosed with an ICH varied more than hundred-fold in relation to GA. It decreased from 21.5% among preterm infants born at 22-28 weeks of GA to 0.1% among those born after 36 weeks of gestation. The rates of neonatal convulsions among preterm infants decreased from 2.0% at 22- 28 weeks to 0.25% among those born after 36 weeks of gestation, Figure 2. The proportion of preterm infants diagnosed with other disturbances of cerebral status (encephalopathy) decreased with GA, while proportion of infants with brachial plexus injuries or ECH increased slightly with GA, Figure 3.

Neonatal outcome in relation to mode of delivery

To report outcome in relation to mode of delivery, the study cohort was divided according to the current guidelines on the use of VE as either preterm births occurring between 34-36 weeks of gestation (VE may be used), or those occurring before 34 gestational weeks (VE not recommended). In our cohort, 33,202 (81.4%) of all preterm births occurred at 34-36 gestational weeks, and 7,562 (18.6%) before 34 weeks of GA.

In Table 3, neonatal outcomes before and after 34 + 0 weeks of gestation are presented in relation to mode of delivery. Overall, seven preterm infants were classified as having an ICH due to

Table 3 Neonatal outcomes in preterm infants by mode of delivery and gestational age

	Total		Unassisted vaginal delivery		Cesarean section during labor		Vacuum extraction	
	N = 40,764		n = 32,940		n = 5,505		n = 2,319	
	n	1/1000	n	1/1000	n	1/1000	n	1/1000
Intracranial hemorrhages								
All	617	15.1	486	14.8	105	19.1	26	11.2
<34 weeks	564	74.6	451	79.0	95	59.4	18	71.7
34-36 weeks	53	1.6	35	1.3	10	2.6	8	3.9
Convulsions								
All	169	4.1	109	3.3	45	8.2	15	6.5
<34 weeks	74	9.9	48	8.4	23	14.4	3	12.0
34-36 weeks	95	2.9	61	2.2	22	5.6	12	5.8
Other disturbances of cerebral status of newborn								
All	168	4.1	98	3.0	53	9.6	17	7.3
<34 weeks	97	12.8	66	11.6	24	15.0	7	27.9
34-36 weeks	71	2.1	32	1.2	29	7.4	10	4.8
Subgaleal and/or cephal hemorrhage								
All	259	6.4	166	5.0	10	1.8	83	35.8
<34 weeks	24	3.2	11	1.9	5	3.1	8	31.9
34-36 weeks	235	7.1	155	5.7	5	1.3	75	36.3
Brachial plexus injury								
All	53	1.3	37	1.1	2	0.4	14	6.0
<34 weeks	3	0.4	3	0.5	0		0	
34-36 weeks	50	1.5	34	1.2	2	0.5	14	6.8

birth injury, corresponding to a rate of 0.02%; and 612 infants were diagnosed with non-traumatic ICH, corresponding to a rate of 1.5%. Diagnoses of neonatal convulsions and other disturbances of neonatal cerebral status were rare, especially in infants at less than 34 weeks of GA, and occurred more frequently after VE and CS than after VD. Cephalic hematoma was the most frequent complication after VE of preterm infants (n = 72 or 3.1%), occurring much more often after VE than after CS (0.16%) and VD (0.49%). Subgaleal hemorrhage was less frequent, with a total of only18 cases. More than two thirds of those cases occurred in the VE group.

The ORs for convulsions were almost doubled in both the VE and CS groups after adjustments for the variables in Model 1. However, further adjustment for indication for operative delivery decreased the odds and made the associations statistically insignificant. Other disturbances of the neonatal cerebral status were significantly increased (two to three times higher) both among infants delivered by VE, and by CS during labor, although the OR was higher in the VE group.

A total of 53 infants were diagnosed with brachial plexus injury. Of these, 14 were born by VE, corresponding to a rate in the VE group of 0.6% and an OR of 6.21 (95% CI: 2.22-17.4) in the fully-adjusted model. In contrast, infants delivered by CS had no increased risk for this complication. Among infants with brachial plexus injury, there were 11 cases of shoulder dystocia (ICDcode O66.0), of which five occurred in the VE group

Discussion

In this large cohort study of singleton, non-breech preterm births after onset of labor, we identify three clinically important findings related to mode of delivery: First, VE was used in 5.7% of preterm births, and despite recommendations of no use, 3.3% of preterm infants born before 34 gestational weeks were delivered by VE.

Secondly, VE for preterm birth was used more frequently in shorter mothers, primiparae and among women treated with EA as pain relief during labor. Finally, and adjusting for potential confounders and co-variates, preterm infants delivered by VE had almost doubled OR for ICH, four times higher OR for extracranial hemorrhage, as well as a 6-fold risk for brachial plexus palsy compared with those delivered by VD. Exclusion of intraventricular hemorrhage grades I-II (the most common form of ICH in preterm infants) from the analysis increased the OR for ICH after VE, indicating that severe bleedings were more common among preterm infants delivered by VE.

Although VE was related to significantly increased rates of ICH, it is not clear whether the extraction as such causes the injury, or if there is an underlying common pathway for both VE-assisted delivery and ICH, i.e., that the relationship is confounded by indication. Since the ORs for ICH were significantly higher in the VE group compared with both the CS and unassisted VD groups, whereas the ORs for other disturbances of cerebral status were slightly higher in both the VE and CS groups as compared with VD, different mechanisms may be involved in the development of these two complications. The forces by vacuum extraction could lead to significant vertical stress, which might be avoided with CS. In a case report of MRI findings after birth injuries among infants delivered by VE [21], it was suggested that vertical traction on the skull and brain may produce tentorial lacerations and rupture of intracranial veins. Another explanation for our findings of different outcomes after VE and CS could be that infants delivered by VE may have been exposed to contractions

Table 4 Logistic regression (odds ratios) for intra– and extracranial hemorrhages, convulsions and other cerebral complications, and brachial plexus injury in preterm infants exposed to different modes of delivery

Mode of delivery	N	n	1/1000	Crude OR (95% CI)	AOR model 1 (95% CI)	AOR model 2 (95% CI)
				Intracranial hemorrhage		
Vaginal	32,938	486	14.8	1.0	1.0	1.0
CS during labor	5,507	105	19.1	1.30 (1.05–1.61)	0.73 (0.58–0.92)	0.76 (0.58–0.98)
VE	2,319	26	11.2	0.76 (0.51–1.13)	2.05 (1.34–3.15)	1.84 (1.09–3.12)
Total	40,764	617	15.1			
				Subgaleal– and/or cephalhematoma		
Vaginal	32,938	166	5.0	1.0	1.0	1.0
CS during labor	5,507	10	1.8	0.36 (0.19–0.68)	0.42 (0.22–0.81)	0.36 (0.18–0.70)
VE	2,319	83	35.8	7.33 (5.61–9.57)	5.89 (4.46–7.78)	4.48 (2.84–7.07)
Total	4,0764	259	6.4			
				Neonatal convulsions		
Vaginal	32,938	109	3.3	1.0	1.0	1.0
CS during labor	5,507	45	8.2	2.48 (1.75–3.52)	1.95 (1.36–2.79)	1.42 (0.92–2.17)
VE	2,319	15	6.5	1.96 (1.14–3.37)	2.51 (1.44–4.38)	1.48 (0.73–3.01)
Total	40,764	169	4.1			
				Other disturbances of neonatal cerebral status		
Vaginal	32,938	98	3.0	1.0	1.0	1.0
CS during labor	5,507	53	9.6	3.26 (2.33–4.55)	2.27 (1.60–3.23)	1.61 (1.06–2.45)
VE	2,319	17	7.3	2.47 (1.48–4.15)	3.84 (2.24–6.56)	2.15 (1.09–4.27)
Total	40,764	168	4.1			
				Plexus brachialis injury		
Vaginal	32,938	37	1.1	1.0	1.0	1.0
CS during labor	5,507	2	0.4	0.32(0.08–1.34)	0.29 (0.07–1.23)	0.29 (0.07–1.26)
VE	2,319	14	6.0	5.40 (2.92–10.00)	6.45 (3.32–12.5	6.21 (2.22–17.4)
Total	40,764	53	1.3			

CS = cesarean section, VE = vacuum extraction.
Model 1 is adjusted for year of birth, gestational age, parity, maternal age, height, BMI, and infant birthweight.
Model 2 is also adjusted for indications for operative delivery.

for a longer time than those delivered by CS. A protective effect of CS is indicated by lower ORs for ICH; however, the exposure to contractions as the sole explanation for the increased risks for ICH after VE is less likely, as the VD group—presumably the group exposed to the largest forces of labor—exhibited significantly lower odds for hemorrhagic complications compared with infants delivered with VE.

During the study period, the overall rate of ICH increased from 6% originally, up to 12% at the end of the period, most likely reflecting the increased access and use of ultrasonography among Swedish neonatologists in recent years. Improved ultrasound technology and image resolution may also have contributed to this development. Finally, we cannot exclude a contribution from misclassification: a large but normal choroid plexus could have been classified as a small subependymal hemorrhage by less experienced investigators. The finding that the diagnosis of small subependymal hemorrhage (without intraventricular extension; P52.0) increased most compared to other types of ICH during the study period (from 0.5% to 1.2%), supports these interpretations.

The overrepresentation of subgaleal hemorrhage and cephalhematoma after VE is less surprising, since earlier studies have stated the relation between these diagnoses and the use of VE. The risk of subgaleal hemorrhage seems to be unrelated to GA, as this study demonstrates rates similar to those in previous studies of infants born at term [12,13].

The present study showed that preterm infants delivered by VE had a 6- to 7-fold risk increase for injury to the plexus brachialis compared with unassisted VD. This injury is usually associated with large macrosomic infants and shoulder dystocia [22] and not to preterm birth. Our result emphasizes the importance of gentle maneuvers and avoiding application of excessive pressure or traction on the brachial plexus also when delivering the preterm infant, especially by VE.

The major strengths of this study were the large study population covering all preterm deliveries in Sweden during a period of twelve years, and the high quality of the registers, making it possible to analyze rare diagnoses and unusual events such as ICH in preterm infants delivered by VE. We were able to include data on risk factors, potential confounders, and outcomes collected independently from one another and without involving the study subjects, thus minimizing various types of bias (e.g., selection and recall bias). Moreover, antenatal and obstetric care is free of charge in Sweden, management routines as well as GA

determinations are standardized, and 99% of births are delivered in public hospitals. This minimizes the risk for confounding by unmeasured socio-demographic factors. Another advantage was the inclusion of the main indications for VE and CS, enabling us to address the question of confounding by indication.

A major limitation of this study is that the registers do not contain detailed information about many important factors during the VE deliveries. For instance the registry does not provide specific information about the type of VE instrument used, level, position, and attitude of the fetal head in the pelvis when applying VE, location of placement of the vacuum cup, traction work, skill of the obstetrician, pressure exposure (duration and force), and cup detachments. The register does not provide information about confounders such as use of oxytocin and application of fundal pressure.

There is a general recommendation not to use VE before a GA of 34 weeks. According to the Royal College of Obstetricians and Gynecologists, there is insufficient evidence to establish the safety on VE deliveries in gestations between 34 weeks + 0 days and 36 weeks + 0 days [9]. Our results show that the use of VE is related to rare, but serious complications also between gestational weeks 34-36.

Conclusion

The rates of serious birth injuries and complications are generally low, but preterm infants delivered by VE have higher odds ratios for intra- and extracranial hemorrhages and brachial plexus injuries than those delivered by CS during labor or by unassisted vaginal delivery. We therefore support a continued conservative/cautious use of VE in preterm deliveries. Furthermore, the possible causal relationship between mode of delivery and ICH needs to be further investigated.

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