Vol. 28 No. 3
Summer 2015

neonatal INTENSIVE CARE

The Journal of Perinatology-Neonatology

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1. American Academy of Pediatrics. Breastfeeding and the Use of Human Milk. Section on Breastfeeding. [originally published online February 27, 2012]. Pediatrics. DOI: 10.1542/peds.2011-3552

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neonatal INTENSIVE CARE

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DEPARTMENTS

ARTICLES

Editorial Advisory Board

In term and near-term neonates with hypoxic respiratory failure (HRF)...

When do you stop the cascade?

Early intervention with INOMAX® (nitric oxide) for inhalation upon confirmation of pulmonary hypertension may help:

- Avoid higher levels of supplemental oxygen
- Improve oxygenation[1]
- Potentially prevent the progression of HRF[2]

Learn more at www.inomax.com

Indication

INOMAX® is a vasodilator, which, in conjunction with ventilatory support and other appropriate agents, is indicated for the treatment of term and near-term (>34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, where it improves oxygenation and reduces the need for extracorporeal membrane oxygenation.

Utilize additional therapies to maximize oxygen delivery with validated ventilation systems.

Important Safety Information

- INOMAX is contraindicated in the treatment of neonates known to be dependent on right-to-left shunting of blood.
- Abrupt discontinuation of INOMAX may lead to increasing pulmonary artery pressure and worsening oxygenation even in neonates with no apparent response to nitric oxide for inhalation.
- Methemoglobinemia and NO_2 levels are dose dependent. Nitric oxide donor compounds may have an additive effect with INOMAX on the risk of developing methemoglobinemia. Nitrogen dioxide may cause airway inflammation and damage to lung tissues.
- In patients with pre-existing left ventricular dysfunction, INOMAX may increase pulmonary capillary wedge pressure leading to pulmonary edema.
- Monitor for PaO_2, methemoglobin, and inspired NO_2 during INOMAX administration.
- Use only with an INOmax DS_{IR}®, INOmax® DS, or INOvent® operated by trained personnel.

Please see Brief Summary of Prescribing Information on adjacent page.

INOmax® (nitric oxide) FOR INHALATION

References: 1. INOMAX [package insert]. Hampton, NJ: Ikaria, Inc.; 2013. **2.** González A, Fabres J, D'Apremont I, et al. Randomized controlled trial of early compared with delayed use of inhaled nitric oxide in newborns with a moderate respiratory failure and pulmonary hypertension. *J Perinatol*. 2010;30(6):420-424.

IKARIA® ADVANCING CRITICAL CARE

INOMAX® (nitric oxide) for inhalation
Brief Summary of Prescribing Information

INDICATIONS AND USAGE

Treatment of Hypoxic Respiratory Failure
INOMAX® is a vasodilator, which, in conjunction with ventilatory support and other appropriate agents, is indicated for the treatment of term and near-term (>34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, where it improves oxygenation and reduces the need for extracorporeal membrane oxygenation.

Utilize additional therapies to maximize oxygen delivery with validated ventilation systems. In patients with collapsed alveoli, additional therapies might include surfactant and high-frequency oscillatory ventilation.

The safety and effectiveness of INOMAX have been established in a population receiving other therapies for hypoxic respiratory failure, including vasodilators, intravenous fluids, bicarbonate therapy, and mechanical ventilation. Different dose regimens for nitric oxide were used in the clinical studies.

Monitor for PaO_2, methemoglobin, and inspired NO_2 during INOMAX administration.

CONTRAINDICATIONS
INOMAX is contraindicated in the treatment of neonates known to be dependent on right-to-left shunting of blood.

WARNINGS AND PRECAUTIONS

Rebound Pulmonary Hypertension Syndrome following Abrupt Discontinuation
Wean from INOMAX. Abrupt discontinuation of INOMAX may lead to worsening oxygenation and increasing pulmonary artery pressure, i.e., Rebound Pulmonary Hypertension Syndrome. Signs and symptoms of Rebound Pulmonary Hypertension Syndrome include hypoxemia, systemic hypotension, bradycardia, and decreased cardiac output. If Rebound Pulmonary Hypertension occurs, reinstate INOMAX therapy immediately.

Hypoxemia from Methemoglobinemia
Nitric oxide combines with hemoglobin to form methemoglobin, which does not transport oxygen. Methemoglobin levels increase with the dose of INOMAX; it can take 8 hours or more before steady-state methemoglobin levels are attained. Monitor methemoglobin and adjust the dose of INOMAX to optimize oxygenation.

If methemoglobin levels do not resolve with decrease in dose or discontinuation of INOMAX, additional therapy may be warranted to treat methemoglobinemia.

Airway Injury from Nitrogen Dioxide
Nitrogen dioxide (NO_2) forms in gas mixtures containing NO and O_2. Nitrogen dioxide may cause airway inflammation and damage to lung tissues. If the concentration of NO_2 in the breathing circuit exceeds 0.5 ppm, decrease the dose of INOMAX.

If there is an unexpected change in NO_2 concentration, when measured in the breathing circuit, then the delivery system should be assessed in accordance with the Nitric Oxide Delivery System O&M Manual troubleshooting section, and the NO_2 analyzer should be recalibrated. The dose of INOMAX and/or FiO_2 should be adjusted as appropriate.

Heart Failure
Patients with left ventricular dysfunction treated with INOMAX may experience pulmonary edema, increased pulmonary capillary wedge pressure, worsening of left ventricular dysfunction, systemic hypotension, bradycardia and cardiac arrest. Discontinue INOMAX while providing symptomatic care.

ADVERSE REACTIONS
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from the clinical studies does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Controlled studies have included 325 patients on INOMAX doses of 5 to 80 ppm and 251 patients on placebo. Total mortality in the pooled trials was 11% on placebo and 9% on INOMAX, a result adequate to exclude INOMAX mortality being more than 40% worse than placebo.

In both the NINOS and CINRGI studies, the duration of hospitalization was similar in INOMAX and placebo-treated groups.

From all controlled studies, at least 6 months of follow-up is available for 278 patients who received INOMAX and 212 patients who received placebo. Among these patients, there was no evidence of an adverse effect of treatment on the need for rehospitalization, special medical services, pulmonary disease, or neurological sequelae.

In the NINOS study, treatment groups were similar with respect to the incidence and severity of intracranial hemorrhage, Grade IV hemorrhage, periventricular leukomalacia, cerebral infarction, seizures requiring anticonvulsant therapy, pulmonary hemorrhage, or gastrointestinal hemorrhage.

In CINRGI, the only adverse reaction (>2% higher incidence on INOMAX than on placebo) was hypotension (14% vs. 11%).

Based upon post-marketing experience, accidental exposure to nitric oxide for inhalation in hospital staff has been associated with chest discomfort, dizziness, dry throat, dyspnea, and headache.

OVERDOSAGE
Overdosage with INOMAX will be manifest by elevations in methemoglobin and pulmonary toxicities associated with inspired NO_2. Elevated NO_2 may cause acute lung injury. Elevations in methemoglobin reduce the oxygen delivery capacity of the circulation. In clinical studies, NO_2 levels >3 ppm or methemoglobin levels >7% were treated by reducing the dose of, or discontinuing, INOMAX.

Methemoglobinemia that does not resolve after reduction or discontinuation of therapy can be treated with intravenous vitamin C, intravenous methylene blue, or blood transfusion, based upon the clinical situation.

DRUG INTERACTIONS
No formal drug-interaction studies have been performed, and a clinically significant interaction with other medications used in the treatment of hypoxic respiratory failure cannot be excluded based on the available data. INOMAX has been administered with dopamine, dobutamine, steroids, surfactant, and high-frequency ventilation. Although there are no study data to evaluate the possibility, nitric oxide donor compounds, including sodium nitroprusside and nitroglycerin, may have an additive effect with INOMAX on the risk of developing methemoglobinemia. An association between prilocaine and an increased risk of methemoglobinemia, particularly in infants, has specifically been described in a literature case report. This risk is present whether the drugs are administered as oral, parenteral, or topical formulations.

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1. Centers for Disease Control and Prevention. (2003) Guidelines for Environmental Infection Control in Health-Care Facilities. Recommendations of CDC and Healthcare Infection Control Practices Advisory Committee (HICPAC). MMWR, 52(RR10):1-42.

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News

☐ Summer 2015

Agreement Reached on Audiometric Hearing Test Devices

MAICO Diagnostics and Interacoustics have announced that an agreement has been recognized to offer a full line of hearing testing medical devices to the affiliate hospitals in the buying group. MAICO Diagnostics has been serving hearing healthcare professionals with screening devices since 1937. The agreement includes several of the company's screening and impedance products. Noteworthy is the MB 11, ABR newborn hearing screening device. The device uses patented CE-Chirp stimulus, which significantly reduces test times. Re-usable electrodes and an integrated earphone, means there are virtually no disposables. This significantly reduces medical waste and saves thousands in costly disposables. Interacoustics is the worldwide leader in diagnostic testing equipment. The Titan, otoacoustic emissions, impedance, and ABR device, offers a space saving hand held design that can be customized to meet hospital needs. The members served by Novation (including members of VHA Inc., UHC, Children's Hospital Association and Provista) will be able to purchase a wide variety of audiometric medical devices from MAICO and Interacoustics effective immediately.

FDA clears Invictus Medical's GELShield for market launch

Invictus Medical, the San Antonio, Texas-based medical device company, has received Food and Drug Administration (FDA) clearance to begin marketing its GELShield extracranial pressure relief device. The FDA cleared the GELShield with an indication to alleviate extracranial pressure due to prolonged immobility. The device has undergone a comprehensive safety validation study at the nationally recognized Baylor University Medical Center in Dallas. The center oversees approximately 4,200 births annually and operates an 83-bed, level III neonatal intensive care unit (NICU) providing the highest level of care for small and fragile newborn babies. Long-term, Invictus Medical's technology interest focuses on combating deformational plagiocephaly (DP), a cranial deformity exhibited in infants resulting from repeated external pressure to one area of the head. Studies have found a significant rise in the incidence of plagiocephaly since the early 1990s. In addition to being a cosmetic issue, DP has been associated with heightened risk for developmental delays in infants and toddlers, according to a study published in Pediatrics in 2013. To date, Invictus Medical has successfully raised $5 million. The company is in the process of securing an additional $4.5 million in Series B funding to support the commercialization efforts of the GELShield.

Rapid Whole-Genome Sequencing In Critically Ill Infants

A study presented at the annual Pediatric Academic Societies Meeting reveals the early results of the clinical usefulness of rapid whole-genome sequencing in neonatal and pediatric intensive care units (NICUs and PICUs). Children's Mercy Kansas City's STAT-Seq test helped diagnose a genetic disease in more than one half of 35 critically ill infants tested, compared to just nine percent with standard genetic tests. As a result of receiving a specific disease diagnosis, clinical care was refined in 62 percent of infants, including 19 percent who had a markedly favorable change in treatment, and palliative care was initiated in 33 percent. Lead authors of the study were Laurel Willig, MD, Josh Petrikin, MD, and Stephen Kingsmore, MB, ChB, BAO, DSc, FRCPath, of Children's Mercy Kansas City. Still a research protocol, STAT-Seq is the fastest whole-genome test in the world, taking less than 50 hours from test order to delivery of an initial report. STAT-Seq can identify mutations across the genome associated with approximately 5,300 known genetic diseases, and in some cases even identify previously unknown genetic diseases. In contrast, standard clinical practice calls for an array of genetic tests to be performed (94 standard genetic tests were ordered on patients in this study), which are time-consuming, costly and can only test for a limited set of disorders.

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The symptoms and signs of genetic diseases in neonates are often overlapping, making identification of a specific diagnosis difficult. Further, infants frequently show only a fraction of the full set of symptoms and signs of genetic diseases, further complicating timely diagnosis and specific treatment. STAT-Seq bypasses these difficulties by casting the widest net in defining the underlying etiology. These retrospective results underscore the importance of a larger, prospective, randomized study now under way: In September 2013, Children's Mercy became one of four pilot projects to explore newborn genomics through funding by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the National Human Genome Research Institute (NHGRI), both parts of the National Institutes of Health. Other projects include teams at Brigham & Women's Hospital at Boston Children's Hospital; University of California San Francisco and University of North Carolina Chapel Hill. Comprised of these four programs, the Newborn Sequencing In Genomic medicine and public HealTh (NSIGHT) program aims to explore, in a limited but deliberate manner, the implications, challenges and opportunities associated with the possible use of genomic sequence information in the newborn period.

PCV13 Works Well in Preemies Too

New research is showing that the 13-valent pneumococcal conjugate vaccine (PCV13) is immunogenic in preterm infants, with most babies mounting immunoglobulin G (IgG) antibody levels and functional antibody responses likely to protect them against invasive disease. Dr Federico Martinón-Torres from Hospital Clínico Universitario de Santiago de Compostela in Spain and his colleagues evaluated the immune response and safety profile of PCV13 in 100 healthy preterm and 100 healthy term infants in a phase IV open-label study. All of them received PCV13 at ages 2, 3, 4 months (infant series), and 12 months (toddler dose), together with routine vaccines. In a report in Pediatrics, the investigators report that immune responses were lower in preterm than term infants. However, the majority of babies in both groups achieved both pneumococcal serotype-specific IgG antibody levels after the infant series that surpassed the threshold of protection and functional antibody responses set by the World Health Organization. The researchers note that responses were "uniformly higher" after the toddler dose, which reinforces the importance of a timely booster dose. Both preterm and term infants tolerated PCV13 well regardless of gestational age.

Inhaled NO Used Despite No Benefit

Off-label use of inhaled nitric oxide (iNO) in premature infants continues despite an NIH consensus statement discouraging the practice, new data show. iNo was approved in 1999 for term and near-term babies for respiratory failure, but studies in preterm babies have not found a benefit. To assess the effect of the 2011 consensus statement urging that it not be used in preemies, data was reviewed from the Pediatrix Medical Group on 420,571 infants admitted to their NICUs from 2009 to 2013. During this interval, 5,676 infants (1.3%) were exposed to iNO, according to a Pediatrics report. The rate of iNO use in 23- to 29-week neonates increased by 23% (from 5.03% to 6.19%), whereas iNO use in 30- to 33-week and 34-week and over neonates did not change significantly. Of all neonates who received iNO therapy in 2013, 46% were <34 weeks' gestation and thus received it off label. Dr Neil N. Finer, from the University of California, San Diego, and Dr Nick Evans, from Royal Prince Alfred Hospital and Sydney University, Australia, wrote a commentary related to this report: "I think that changes in use will occur slowly. Neonatologists are using iNO for premature infants that they believe are not responding to maximal treatment and for whom there are few other treatment options."

Wide Variation Found in Antibiotics Prescriptions

Neonatal intensive care units (NICUs) in California registered a 40-fold variation in antibiotics prescribing practices, with half of intermediate-level NICUs reporting infection rates of zero while also reporting the highest use of antibiotics, according to a retrospective cohort study. Joseph Schulman, MD, from the California Department of Health Care Services, California Children's Services, Sacramento, and colleagues found NICUs traditionally have considered treatment of infection "a mainstay," and recent quality improvement efforts have targeted such hospital-acquired infections as central line–associated bloodstream infections. Antibiotics in this setting, however, are associated with increased risk for necrotizing enterocolitis, as well as mortality. The research team studied 127 California NICUs that admitted 52,061 infants during 2013 and analyzed their annual antibiotic use rate (AUR), the number of patient-days infants were given at least one antibacterial or antifungal agent per 100 patient-days. Overall, they found a 40-fold variation in AUR, ranging from 2.4% of patient-days to 97.1% of patient-days, with intermediate NICUs that treat less sick infants notching the highest, an almost 31-fold variation. The authors found no linkage between antibiotic use and proven infection, necrotizing enterocolitis, volume of surgeries, or mortality rate.

Birth Weight Impacts Discovered

The age of the medium used to culture fertilized embryos may affect eventual birth weight, a new study shows. Data were analyzed on fresh embryo transfers performed between 2008 and 2012 through IVF/intracytoplasmic sperm injection (ICSI) with one specific culture medium, the G-1 PLUS v5 (Vitrolife Sweden AB). Overall, the age of the medium did not affect embryo development, ongoing pregnancy, fertilization rate, early cleavage rate, and other factors. Age of the medium ranged from 35 to 113 days (median 79) at the time of arrival at the laboratory. However, using birth weight data from 372 of 396 (93.9%) live-born singletons, linear regression analysis showed a negative association between birth weight and age in days of the medium used for IVF (beta coefficient, -4.2 g / -0.15 oz, p=0.037). After adjusting for multiple confounders, including parental height and weight, gestational age, and gender, a significant association remained (-3.6 g / -1.3 oz, p=0.021). The study said companies should be "transparent about the exact composition of their embryo culture media, which will allow IVF clinics to further investigate the effects of the media or media components on the health of IVF children."

Managing Severe Infections

New research regarding severe infections has found a combination of intramuscular gentamicin or procaine penicillin with oral amoxicillin is effective for domiciliary treatment of severe infections in young infants, while oral amoxicillin alone can be used against chest infections. Serious bacterial infections, including pneumonia, meningitis, and sepsis are important contributors to morbidity and mortality among neonates and account for about 600,000 deaths per year, the researchers point out. A week of parenteral antibiotics in hospital is usually recommended, but is inaccessible to many due to transportation, social, or financial constraints. Two linked African Neonatal Sepsis Trial (AFRINEST) studies aimed to evaluate the role of oral amoxicillin alone or in combination for treatment of serious bacterial infections and pneumonia in young infants. Community health workers identified more than 7,000 young infants aged less than 60 days meeting the clinical criteria for serious infections. Study nurses reviewed the children, either at home or at the nearest health center, and 3564 infants enrolled with clinical features of possible serious bacterial infections whose parents were unable to access hospital care. Reduced feeding, lethargy, hypothermia, fever, and respiratory distress were the clinical signs the researchers looked for. Critically ill infants, defined as those who were unconscious, cyanosed, having seizures, severe congenital or surgical conditions, and low birth weights were excluded. Those with rapid breathing alone were enrolled into the second study.

Preemie Moms More Likely to Have Premature Births

The risk of preterm delivery is significantly higher in women who were preterm themselves, according to research from the Department of Paediatrics, Sainte-Justine University Hospital and Research Center, University of Montreal, Canada. The study compared infant gestation length among mothers born before 36 weeks of gestation with infant gestation length among mothers born at term. The researchers drew the study cohort of 7405 women born preterm, including 554 women born before 32 weeks of gestation, and 16,714 women born at term from women born between 1976 and 1996 in Quebec, Canada, who delivered at least once between 1987 and 2008. Among women born before 32 weeks of gestation, 14.2% delivered prematurely at least once, and 13.0% of mothers born at 32 to 36 weeks of gestation delivered prematurely at least once. In contrast, only 9.8% of women born at term delivered prematurely at least once. Instances of very preterm births (before 32 weeks of gestation) were also greater among mothers born very preterm. Among women born before 32 weeks of gestation, 2.4% delivered very preterm; 1.8% of those born between 32 and 36 weeks of gestation gave birth very preterm, and 1.2% of those born at term gave birth very preterm.

Glyburide Tied To Risks

In a study of more than 9,000 US women with gestational diabetes mellitus (GDM) who were covered by health insurance, infants whose mothers were treated with glyburide were more likely to be admitted to a neonatal intensive care unit (NICU), have hypoglycemia, and have respiratory distress than infants whose mothers received insulin. The study was published in JAMA Pediatrics. The data show that for every 1,000 women treated with glyburide rather than insulin, expected are 30 additional NICU stays of at least 24 hours, 14 additional newborns large for gestational age, and 11 additional cases of respiratory distress treated in the NICU. More research is urgently needed, according to the study authors.

Stressful Environments Can Have Long-Term Health Effects on Infants

Neonatal intensive care units (NICUs) can be stressful environments for infants due to bright lights, noisy alarms, and painful interventions like intravenous lines. Researchers have suggested that the stress associated with the NICU environment can have long-term health effects on brain development. The March/April 2015 issue of Journal of Obstetric, Gynecologic, &

Neonatal Nursing (JOGNN) from the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN) includes two articles in which the authors explore the effects of early stress on infant neurological development. In "Nurse Management of the NICU Environment Is Critical to Optimal Infant Development," Rosemary White-Traut summarizes the potential harm of stress on infant brain development and highlights a multisensory developmental intervention tool. The Auditory, Tactile, Visual, and Vestibular (ATVV) intervention offers developmentally appropriate sensory stimuli, including the mother's voice, moderate touch stroking, eye to eye contact with the mother, and vestibular stimuli via rocking. Rosario Montirosso, PsyD, and Livio Provenzi, PsyD, describe the physiological processing of stress in "Implications of Epigenetics and Stress Regulation on Research and Developmental Care of Preterm Infants." The early postnatal period is a sensitive time for development, especially for the brain and neurological system. During this time, the infant brain is especially sensitive and receptive to stimuli. Stressful stimuli (such as those experienced in the NICU) can negatively affect brain development, and early chronic exposure to painful stimuli has been associated with altered neurological and hormone responses and with long-lasting brain changes. These epigenetic alterations may be minimized by NICU practices designed to moderate the effect of the environment, minimize painful and stressful procedures, reduce parent-infant separation, and facilitate the parent-infant relationship. Nurses working in NICUs must provide necessary care in this environment and minimize stimuli that can be stressful to newborns and have the potential to negatively affect brain development. Some ways to mitigate the stress of the NICU environment include skin-to-skin contact between the infant and parent, dimming the lights, human milk feeding, and soothing touch. Extensive research demonstrates that caring touch and human social interaction aid the healthy growth of newborn infants. Supportive parenting can also act as a reliever of stress. In fact, more numerous or longer-length parental visits in the NICU are associated with less stress and more stable behavior in preterm infants.

Exercise and Reducing Heart Defects

New research that looked into the exercise habits of mice shows that it lessens the risk that a pregnant mother-to-be will give birth to offspring with serious heart defects. Scientists and cardiologists looking to halt or fix heart defects in babies, even in the womb, have begun looking at factors that may lower the risk of defects, including a focus on mothers. Researchers at the Washington University School of Medicine studied female mice that had been bred to have a genetically high risk of delivering pups with holes between the chambers in their hearts. Half of the mice were young. The other half were old, by mouse reproductive standards, approaching menopause. The scientists then simply transplanted young ovaries, containing young eggs, into the older mice and old ovaries into the young mice and impregnated all of the animals. The age of the ovaries and eggs turned out to play effectively no role in the mothers' risk of delivering pups with heart problems. Young mice had a low risk, even if their ovaries and eggs were old. Old mothers had a much higher incidence of pups with heart defects, even if their ovaries and eggs were youthful.

Seizures Studied in Neonatals

A near-infrared spectroscopy (NIRS) study out of the University of Michigan has found that cerebral oxygen metabolism increases during neonatal seizures and decreases with phenobarbital administration. There is still debate about if neonatal seizures harm the developing brain or reflect abnormal cerebral physiology. Some are wonder if phenobarbital being used to treat these seizures could induce abnormal neuronal cell death and cognitive impairment. NIRS has been shown to reflect cerebral blood flow, but its utility as a monitor for infants at risk for neonatal seizures remains unclear. Researchers used NIRS to assess the impact of neonatal seizures and their treatment with phenobarbital on cerebral oxygen metabolism in 20 infants who received 61 doses of phenobarbital. Eleven infants had 40 individual seizures. Cerebral regional oxygen saturation (rSO2) declined during neonatal seizures, reflecting increased oxygen metabolism. Fractional tissue oxygen extraction (FTOE) levels were highest during seizures, another reflection of increased oxygen metabolism. It is hoped that these results will push others to study the issue.

Parents Put In Charge

A multi-site study is putting parents in charge for at least eight hours a day of taking care of their babies in the neonatal intensive care unit, or NICU to mine the positive benefits parents can bring to their babies. The study, being conducted at 20 hospitals in Canada and 10 in Australia and New Zealand, follows a pilot program at Toronto's Mount Sinai Hospital that involved 42 premature newborns. The outcome: Preemies cared for by their parents gained 25% more weight and were nearly twice as likely to be breastfeeding when they went home as those taken care of primarily by nurses. Infections, 11% in the nurse group, fell to zero in the parent group. Doctors hope the study will verify the pilot program's positive results. They suggest that mothers and fathers get to know their babies better than nurses do and that physical contact with the parents may be beneficial while the infant's immune system is developing. About one of every nine newborns is premature, or born more than three weeks before the normal 40 weeks of gestation. Medical advances have improved survival rates of the youngest preemies, and today, newborns as young as 22 weeks are being given care. About 75% of infants born before 29 weeks survive to go home with their parents.

Assessment Tool's Effectiveness Questioned

An assessment tool for measuring infant and toddler development is not strongly predictive of future impairment in very preterm infants, according to a new study. For children born before 30 weeks' gestation, scores on the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) at two years of age had low sensitivity for predicting cognitive functioning two years later, said researchers at Monash University in Melbourne, Australia. But sensitivity improved when the researchers used cut-points based on reference data from local term-born infants.

Jaundice Meter Introduced

Dräger has announced the release of its next-generation Jaundice Meter – the JM-105, a non-invasive bilirubinometer that provides fast, accurate, cost-effective and pain-free jaundice screenings for newborns. JM-105 can be used on children as young as 35-weeks' gestational age. According to the Centers for Disease Control and Prevention, approximately 60 percent of full-term infants will develop jaundice within a few days of birth. While it is relatively common, jaundice is a serious issue that can lead to permanent brain damage if not treated. Traditionally, hospitals would use visual screenings and painful heel-stick

Continued on page 45…

The Benefits of Early Enteral Feeding

In this feature, Neonatal Intensive Care interviews clinicians and healthcare providers about the actual application of specific products and therapies. Participating in the interview is Olivia Mayer, RD, Clinical Dietitian, NICU Specialist from Lucile Packard Children's Hospital, Stanford.

Lynne Russo: Infants are being fed at 24 weeks gestational age, are their guts mature enough to accept enteral feeding?
Olivia Mayer: Yes, they are! The organ formation of the gastrointestinal tract is complete and intact at 12 weeks of gestation. Swallowing is detectable at 16-17 weeks of gestation. Amniotic fluid flows through the GI tract, in utero, which contains substances such as epidermal growth factors, carbohydrates, protein and fat, which stimulates the maturation of the organ. The absorptive process is only partially available at 26 weeks gestation; however, the composition of the enteral feeding (human milk vs. cow's milk based) also impact the absorption and tolerance of the feeds. At 36 weeks gestational age, the gastrointestinal tract should achieve mature motility - baring any surgical or ischemic injury.

LR: How do you define "early feeding"?
OM: Early feeding is more 'medicinal' than nutritional. I define it as using human milk within 24-72 hours of life, starting 10-30 mL/kg/day. It is to stimulate gut hormone maturation, gut hormone release, induce gut motility, continue to stimulate the microvilli of the GI tract.

LR: What are the measurable benefits of early enteral feeding?
OM: Decreased Necrotizing Enterocolitis, decreased days on parenteral nutrition, decreased cholestatic jaudice, decreased IV line days, decreased late-onset sepsis, likely achieve full feeds faster, regain birth weight faster, improved bone mass, and improved mental outcomes at 24 months corrected age. All good things.

LR: Are there any circumstances during which you shouldn't feed these infants early?
OM: If there is a major abdominal defect, such as an omphalocele or gastroschisis, or a gastrointestinal tract perforation, or a trachoesophageal fistula — or other anatomic limitation. If the baby is not hemodynamically stable and requiring aggressive resuscitation including dopamine.

LR: There has been debate about the speed of advancement of feeding, what is your view on this?
OM: I am of the 'slow and steady' mindset. I think in these extremely fragile infants, starting slow and advancing in a steady fashion is prudent. Watching the baby's tolerance very closely is key as well. If their feeds are advancing, and they start to show increased abdominal distention, emesis, etc. I would prefer to hold the feeds at the current volume — or even back off a few mLs per feed — at least for a day or two, instead of pushing through those signs.

LR: Is there a particular juncture where the start of enteral feeding outweighs the risk of developing NEC?
OM: This is a great question. Assuming the baby is relatively stable, and no anatomic malformations or pharmacologic therapies that may impede blood flow to the GI tract — I believe trophic feeds should be started within the first 24 hours of life. Now, the second part of this is the availability of mom's own milk vs. feeding with banked breast milk. Many feel very strongly that the very first feed(s) should be that infant's mother's own milk; however, mothers who deliver prematurely experience a delay in Lactogenesis II — or a delay in her milk 'coming in' — so it may be 3-4 days before mom is able to produce and express her own milk. Banked breast milk can 'bridge that gap'; however, the concern for some is that the baby is not being colonized with adequate/specific immunoglobulins and probiotics. Its true that there is some degradation of immunoglobulins in the pasteurization process of banked breast milk; however, there are still properties that survive that are unable to be replicated in formula. The other reality is that there are still NICUs without access to or budget for banked breast milk. If banked breast milk is not available, I believe the waiting for mom's own milk outweighs the risk of starting enteral feeds with formula.

LR: There is a difference of opinion about needing to hold feeds while treating PDA, what is your opinion on this?
OM: This is also a great question. There are several studies that looked at trophic feeding during indomethacin treatment for PDA and actually found their NEC rate decreased. As far as I know, this is still not widely practiced. In my opinion, I do think trophic feeds should be continued when treating PDAs. I completely understand the hesitation with feeding through treatment and the very real concern and risk of NEC/spontaneous intestinal perforation; however, I think a compromise might be to decrease the volume and/or frequency (i.e. if the baby was at 30 or 40 mL/kg/day and feeding Q 3 hours, maybe decreasing to 20 mL/kg/day &/or feeding every 4-6 hours).

LR: How important is it to have standard feeding protocols across any particular NICU?
OM: A standardized protocol can lead to improved nutritional outcomes, decreased rates of major morbidities and better

Input on questions was provided by Lynne Russo. If you would like to participate in this feature, as a company or healthcare provider, please contact Steve Goldstien at s.gold4@verizon.net.

growth for VLBW infants. In a unit, like a NICU, where the attending physicians and nurse practitioners rotate on and off service, the standardized feeding protocol promotes more consistent care with less variability. It facilitates improved communication and the continuity of care across all members of the medical team. The major aims of the LPCH protocol were to (1) advance enteral feeds in a safe, standardized manner; (2) advocate the use of human milk as the definitive first choice for feeds; and (3) use colostrum, by oral administration, to promote immunological protection and intestinal colonization and maturation in neonates.

LR: Your hospital (LCPH) did a study looking at feeding protocols, what did you find?
OM: Data were analyzed on 147 VLBW infants who received enteral feedings, 83 before ('Before') and 64 subsequent to ('After') feeding protocol initiation. We found improved nutritional outcomes, decreased rates of major morbidities and better growth for VLBW infants. The outcomes in the ELBW infants were even more pronounced.

LR: Did you see a difference on any of these things:
OM: *Nutrition* – Excluding those with weight <3rd percentile at birth, the proportion with weight <3rd percentile at discharge decreased significantly after protocol initiation (35% Before vs 17% After, P=0.03).

- *NEC rates* – Necrotizing enterocolitis decreased in the After group among VLBW (15/83, 18% Before vs 2/64, 3% After, P=0.005) and ELBW infants (11/31, 35% Before vs 2/26, 8% After, P =0.01).
- *Late onset sepsis* – Late-onset sepsis decreased significantly in the After group (26/83, 31% Before vs 6/64, 9% After, P = 0.001).
- *Reaching full feeds faster* – Extremely low birth weight (ELBW) infants in the After group attained enteral volumes of 120 ml/kg/day (43.9 days Before vs 32.8 days After, P=0.02) and 160 ml/kg/day (48.5 days Before vs 35.8 days After, P=0.02) significantly faster.
- *Decreased TPN days* – received significantly fewer days of parenteral nutrition (46.2 days Before vs 31.3 days After, P=0.01).

LR: How have you incorporated an exclusive human milk diet (EHMD) into your feeding protocols at your hospital?
OM: We have used banked breast milk in our hospital for a very long time. In 2010, we started using the human milk based, human milk fortifiers added to human milk feeds — mom's milk, or banked breast milk. We incorporated them into our standardized feeding pathways, so that when a baby is ordered to receive enteral feedings at a total of 100 mL/kg/day, the human milk based, human milk fortifiers are automatically ordered to start.

LR: What outcomes have you seen as a result of implementing an EHMD?
OM: Greatly improved tolerance to feeds, less stopping and holding of feeds, shorter time to reach full feeds, less number of days on parenteral nutrition, continued lower NEC rates.

LR: Have you seen a difference in growth weight rates?
OM: We have actually seen a steady, consistent increase in our growth rates. We have made many improvements to our unit's nutrition strategies including early parenteral nutrition, standardized feeding pathways for our VLBW infants, and use of an exclusive human milk diet in our less than, or equal to 1250 gm birthweight babies.

LR: Do you attribute to early feeding, EHMD or both?
OM: I attribute improved outcomes to both early, trophic feeding and utilizing an exclusive human milk diet. I think it is a synergistic relationship where by each strategy is enhanced by the other.

Helping Mothers Meet Their Lactation Goals: Strategies for Success

Irene Murphy Zoppi, RN, MSN, IBCLC

Introduction

What influences a woman's decision to cease breastfeeding earlier than she desired or expected? Stopping breastfeeding before meeting personal lactation goals may cause feelings of lasting regret. Regardless of the cause, earlier-than-expected cessation of breastfeeding should be a concern to health care professionals. This article is written for all health care providers who provide care to women desiring to breastfeed their infants. It examines the impact of not meeting lactation goals and identifies prenatal support strategies that may prevent the premature cessation of breastfeeding. It also explores implementation of in-hospital, evidence-based strategies and technologies to help combat insufficient milk supply that plays a major role in mothers not attaining their lactation goals.

US Breastfeeding Data

In 2014, the Centers for Disease Control (CDC) reported the breastfeeding initiation rate among American women continued its rise. The most current data identifies 79.2% of American women initiate breastfeeding (The United States Breastfeeding Report Card 2014). This continued increase in initiation rate is encouraging and reflects the continued work of multiple national and local campaigns. The data tell us that mothers want to initiate breastfeeding. They have heard the messages described by their health care providers and these campaigns. Unfortunately, the data also demonstrate only 40.7% of women are exclusively breastfeeding their infants at 3 months. More than one-half of US mothers don't achieve their intended breastfeeding goals supplementing their infants very early in the post-birth period with infant formula or stopping completely earlier than they planned.[1,2] Odom[3] reported that 60% of mothers who initiated breastfeeding did not continue to breastfeed for as long as they intended.

Mothers cite a variety of reasons for not continuing breastfeeding, many related to infant health concerns - including concerns about the lactation process and breastfeeding challenges. The perception of insufficient milk supply is cited by mothers as the major reason to supplement with infant formula and often complete weaning.[3-5] This early cessation of breastfeeding can negatively impact both the mother and the infant; the infant does not receive the health benefits of exclusive breastmilk feeding and the mother may encounter emotional distress by not meeting her lactation goals.[6]

Health care providers need to consider the emotional cost for mothers who prematurely stop breastfeeding. Author Stephanie Casemore's posting of a short article, 'Breastfeeding Failure' As An Oxymoron' began a series of blog postings from multiple mothers who did not meet their lactation goals. (www.bestforbabes.org accessed from google.com 3/5/2015) Mothers cited feelings of self-blame, sadness, shame, loss, trauma and embarrassment at having to stop breastfeeding. The emotional scars they suffered had lasting effects for many of these women.

Self-confidence and prenatal education

The literature substantiates breastfeeding self-confidence as a significant predictor of breastfeeding initiation, duration, and exclusivity for mothers.[7-10] Increasing a woman's confidence in her ability to breastfeed and prenatal education about the breastfeeding process play a vital role in aiding successful breastfeeding. Dennis describes a mother's breastfeeding confidence (self-efficacy) as a mother's confidence in her ability to breastfeed her infant.[11]

One approach to increase a mother's confidence about her breastfeeding abilities is through education. Chezem and colleagues demonstrated breastfeeding knowledge was strongly correlated with breastfeeding confidence.[12] Kingston et al.,[13] and Noel-Weis et al.,[14] further substantiated that providing breastfeeding education in the prenatal period increased breastfeeding self-confidence as well as improved breastfeeding outcomes. Breastfeeding prenatal education helps to increase mothers' knowledge about normal breastfeeding behavior, as well as develop positive attitudes toward breastfeeding.

Breastfeeding education occurs in multiple settings, such as hospital-based group classes, peer-to-peer education and online web-based programs. Clinicians should consider each of these settings as valuable methods for prenatal breastfeeding education. Becoming increasingly popular are web-based education programs. Huang's research[15] suggests that web-based breastfeeding education may contribute to both breastfeeding knowledge and attitude that improves breastfeeding rates. Women of child-bearing age, the 'Millennials' are accustomed to this type of digital learning. They learn using a combination of strategies and are accustomed to accessing information anywhere, at any time.[16] This means using digital

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phones, computers, and iPads. Providing web-based prenatal breastfeeding education may be preferred as information is easily attainable at the desired time by the consumer. Pitts suggests using technology-based education programs as an effective method in providing breastfeeding information and guidance.[17] Medela, Inc. designed a web-based breastfeeding education program to meet the needs of these consumers. "All About Breastfeeding" is a program of 10, 8-10 minute classes, offered in both English and Spanish describing the process and experience of breastfeeding.

Off to a Good Start: Initiation

Helping a mother meet her lactation goals begins prenatally through education, setting realistic expectations and by helping to increase her confidence about her breastfeeding abilities. It continues in the post-birth period by ensuring breastfeeding initiation is well-established. Any delay in the initiation of lactation may affect subsequent milk production and volume. It is important that bedside clinicians understand the physiology of lactation and intervene with evidence-based methodologies and technology when actual or potential interruptions in this process take place.

Healthy infants are physiologically capable to begin breastfeeding right after delivery. The WHO/UNICEF Baby Friendly Hospital Initiative recommends that healthy infants initiate breastfeeding within the first thirty to sixty minutes of life. Adequate amounts of colostrum are readily available to the infant after birth due to the process of Secretory Differentiation (Lactogenesis I) begun many weeks prior to delivery. The sucking infant accomplishes both feeding of colostrum and the initiation stimulation beneficial for triggering Secretary Activation (Lactogenesis II). The infant's continued breastfeeding at a frequency of 8-12 times in 24 hours during the first few days post-birth achieves ingestion of small amounts of colostrum[18] and continued breast stimulation. In the absence of pathology, the frequent and continued sucking of the healthy, term infant will drive milk synthesis, producing copious volumes of breastmilk — ~500mL/day — usually by 36 and 96 hours after birth.[19] With minimal assistance, the healthy, sucking infant and his mother will experience a successful lactation.

The first two weeks post-birth represent a critical period in lactation for all breastfeeding mothers.[20,21] Due to the complex endocrine, anatomic and biochemical changes occurring during this first two-week period, breastfeeding needs to get off to a good start, but also continue in the pattern of 8-12 times/day described above in order to build an adequate milk volume. Failure to provide adequate breast stimulation and expression techniques could seriously affect milk volumes.

Several risk factors have been identified that also pose a risk for delayed Secretory Activation.[22-25] Risk factors such as diabetes mellitus, preterm labor, pregnancy-induced hypertension, excessive maternal blood loss, prolonged bed rest, maternal stress during labor and delivery, an unscheduled Cesarean delivery, obesity, and the use of selective serotonin re-uptake inhibitors (SSRIs) are potential enemies for initiating an adequate volume of milk in any breastfeeding mother.

Some infants may not exhibit a robust start at breastfeeding. They may have difficulty latching or be ineffective at removing milk. Many late preterm infants appear disinterested in breastfeeding due to their excessive sleepiness. Consequently, these infants may not be breastfeeding in the frequency or vigor to properly stimulate the initiation of an adequate milk supply. These mothers require the same breast stimulation to produce adequate volumes of milk but are handicapped by the breastfeeding behavior of their infants. If the infant is not capable or does not produce adequate breast stimulation to help trigger the onset of Secretory Activation, alternative interventions should be employed. Thus, insufficient milk supply that occurs later in lactation may be avoided with early intervention. The following paragraphs describe evidence-based strategies that may impact a difference.

Evidence-based strategies

Bedside assessment of breastfeeding should occur multiple times during the immediate post-birth period. Clinicians should watch breastfeeding to ensure correct latch and breastfeeding behaviors are taking place. It shouldn't be assumed that a healthy infant will successfully breastfeed. To augment less-than-desirable infant breastfeeding behavior, the mother should begin regular and frequent milk removal as soon as possible.

Hill demonstrated correlation of early breast expression and milk volumes during 2-5 days postpartum.[26] A pilot study of mothers who delivered premature infants and began milk expression within 1 hour of delivery produced significantly more milk during the first 7 days after birth and throughout the entire six-week study period than mothers who initiated milk expression between 1 and 6 hours after delivery.[27,28] The use of a hospital-grade, double electric breast pump has been recommended for pump-dependent mothers to help them achieve adequate volumes of breastmilk and should be utilized when lactation assistance is needed in other populations.[29-32] Mothers should be instructed to pump at the same frequency that duplicates the breastfeeding frequency of a healthy term infant. This frequency is required to drive continued milk production. Spatz[29] and Rodriquez et. al.,[33] recommend mothers pump every 2 to 3 hours each day when pump-dependent. Walker[34] suggests pumping eight or more times in 24 hours. Participants in Parker's study[27,28] were instructed to pump at least eight times in 24 hours. Milk expression studies conducted within the dairy industry have revealed greater initial and subsequent milk volumes when milking commenced early and frequently.[35]

Hospital-grade electric breastpumps that mimic the bi-phasic sucking behavior of healthy infants during established breastfeeding are thought to be as effective and more comfortable than single-phase electric breastpumps.[36] The Medela (McHenry, IL) Symphony® breast pump, Preemie+™ pattern, incorporates the sucking pattern utilized by healthy-term infants during the first few days post-birth. This initiation pattern has effectively demonstrated a greater daily milk production of milk between days 6-13 post-partum in pump dependent mothers of premature infants.[37] Recently, Torowicz et. al.,[38] demonstrated support of this initiation pattern in mothers of term infants unable to breastfeed due to congenital heart disease.

Mothers should be instructed to double pump when using an electric breast pump. In addition to decreasing the time spent pumping, several studies[39-41] have identified increased milk volumes while double pumping. Prime[41] reported a higher caloric content of expressed milk and an additional milk ejection when mothers double pumped.

Hand expression has been mentioned as an alternative to using an electric breastpump in the initial stages of lactation. Morton[42] demonstrated greater volumes of colostrum in mothers who performed hand expression 5 times a day combined with use of a double, electric breast pump more than five times a day in the first few days after birth. Slusher[43] however reported a decrease in milk volumes using hand expression compared to using an electric breast pump in the first several days post-birth. Different expression options should be offered to mothers.

Assessment of breastshield fit should be considered whenever mothers utilize a breast pump. Breastshields, that portion of the breast pump collection kit that comes in direct contact with the mother's breast, nipple and areola areas, should be frequently evaluated to ensure they correctly fit. An incorrect fit may result in incomplete breast emptying, leading to the down regulation of milk volume and subsequent insufficient milk volumes.

Summary

Breastfeeding initiation rates continue to rise for mothers within the US. Yet many mothers begin early supplementation with formula and fail to reach their personal breastfeeding goals. Health care professionals have an obligation to assist mothers in meeting their lactation goals. This means intervening early prenatally with strategies to assess breastfeeding self-confidence and intervene with prenatal education and counseling programs when warranted. This also means early intervention in the initial post-birth period with in-hospital, evidence-based lactation strategies if the infant is unable to adequately demonstrate appropriate breastfeeding behavior, or if the mother is at risk for lactation failure. Mothers should leave the hospital knowing the signs of effective and ineffective breastfeeding behavior, and know when they need additional lactation assistance. Every mother deserves the best opportunity to successfully breastfeed and the best chance to meet her personal lactation goals. Not achieving one's breastfeeding goals is a sadness that may last her a lifetime.

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Hospital Noise Environments – An Interview

Chris Campbell

Since 1991, Mandy Kachur has worked as an acoustics and noise control engineer and is currently a principal and partner at Soundscape Engineering LLC, Ann Arbor, Michigan (www.soundscapeengineering.com). She has worked on over 300 architectural projects, including inpatient, outpatient and residential healthcare facilities.

Ms. Kachur has been active with the Facility Guidelines Institute (FGI) in providing technical input for the Guidelines for Design and Construction of Hospitals and Outpatient Facilities and the Guidelines for Design and Construction of Residential Health, Care and Support Facilities, used as the primary source for healthcare building design by architects, engineers and planners. She is a Board-Certified Member of the Institute of Noise Control Engineering (INCE) and currently serves on its Board of Directors. She is an adjunct professor at Lawrence Technological University, and has been published in the peer-reviewed American Journal of Nursing, at INCE conferences, and at Acoustical Society of America meetings.

Last year, Ms. Kachur was invited by the National Academies of Engineering to speak at the 2014 Japan-America Frontiers of Engineering (JAFOE) Symposium held in Tokyo, Japan, on the topic Noise Control Engineering in Healthcare Environments. She will also be speaking at the 2015 American Society of Healthcare Engineering annual conference in Boston.

Why is noise a concern?

Healthy soundscapes are paramount to the missions of hospitals: patients need to sleep and heal without environmental stressors; staff, patients, and family need to communicate accurately but privately; staff need to be able to localize alarms and calls for help. Mounting evidence indicates that poor hospital soundscapes can be detrimental to occupants. For example, noise in hospitals has been suggested to increase patient risk for cardiovascular response, pain, intensive care delirium, fragmented sleep, and reduced recuperation.

What causes noise in healthcare environments?

Hospitals are unique and complex acoustic environments filled with numerous noise sources, including staff and patient conversations and noise, movement of people and equipment, alarms, paging systems, telephones/mobile devices, building systems noise such as ventilation, and site noise.

In a large study comprising a variety of patient care units in two hospitals, voices were perceived as most bothersome by both patients and personnel followed by carts in the corridors, footsteps in the corridors and cardiac monitor alarms, overhead pages and pulse oximeter alarms. In an operation theatre the most frequent noise sources of distraction or interruption were conversation, work environment problems, telephone calls and medical equipment.

What is the effect of noise on patients and staff?

The effects of noise on patient healing and sleep strongly suggest that noise exposure has a negative effect on both. If average sound levels are over 50 dBA, a study found that patient heart rate increased 22%, respiratory rate increased 47%, systolic blood pressure increased 63% and diastolic blood pressure increased 44%. A Harvard sleep study found that sleep arousal rates were highest for sounds meant to alert people, such as telephone rings, medical alarms and paging. These caused a much higher probability of arousal than transportation noise, even if the aircraft and traffic noise was louder.

Evidence exists that high sound levels contribute to stress and staff burnout. One study of 133 ICU nurses found that noise-induced occupational stress was associated with burnout and emotional exhaustion. Another study in an ICU, comprising 47 nurses, found that they generally perceived noise to contribute to stress, and that 91% found that noise negatively affected them in their daily work.

Errors in drug name confusion are alarmingly high, resulting in death in many cases, and noise can contribute to these speech intelligibility issues. Also, one study indicates that more medications were required for surgical patients in recovery when the sound levels present were high (over 60 dBA). Documented results from several other studies have shown delays in wound healing in animals (mice and rats) when noise is present.

What determines an effective hospital noise environment?

Studies show that effective hospital soundscapes require a complex choreography of architectural layout, acoustic design, medical alarm prioritization, and administrative processes that is only beginning to be fully understood.

Guidelines set by The World Health Organization (WHO) for background noise in patient rooms recommend average background levels not exceeding 35 dBA during the day and 30

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dBA at night, with transient maximums not exceeding 40 dBA. Other common design metrics commonly used by engineers target a range of approximately 32 to 39 dBA for average background sound levels. The NICU literature ranges widely, with recommended level limits between 30 and 50 dBA. Most case studies, especially the recent data, show that noise levels inside hospitals are much higher than the guideline values. For example, the quietest measured noise levels in sampled ICU and NICU start at 50 dBA and increase from there.

Since the 1960's, the noise levels inside hospitals have generally increased by an average of 0.38 dBA (daytime) and 0.42 dBA (nighttime) per year, and today are well above the recommended ranges. To counter this trend, organizations must take active steps to reduce noise and new facilities should be designed with noise reduction as part of the programming directives.

What has been the approach for ensuring acceptable noise environments?

Noise engineers and medical personnel generally had been working separately on noise issues, with limited progress and implementation of their findings. With the new urgency for improvement, multidisciplinary teams have been formed to produce actionable research and evidence based design initiatives. This collaboration between medicine and engineering has produced data on physiological responses, healthcare outcomes, and economic impact, which all have more influence on policy making than the historic assumption that noise is nothing more than an annoyance.

While progress has been made in the built-environment, changing healthcare worker behavior and the healthcare culture has proven to be more challenging. When sound levels become unacceptably high in sound sensitive areas, providing a visual alert to hospital staff, patients, and visitors has proven to be effective at reminding people to limit the noise they make. One such system is SoundEar (offered by Scantek, Inc., http://scantekinc.com/brands/soundear/noise-alert-systems/soundear).

Patient surveys and medical research have provided valuable input for guiding the healthcare and architecture industries on the importance of reducing noise. The results have driven improvements in building codes and guidelines along with operational changes among staff.

Concerning patient survey scores, which one(s) address noise?

The Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) surveys have brought increased focus on noise control engineering for healthcare environments. This survey asks a series of questions to recent hospital patients, and the scores have a direct impact on the facilities rating and the government reimbursements for medical services.

The HCAHPS survey has one question on noise; "how often was the area around your room quiet at night?" This question does not lend itself well to normal noise control design metrics or mitigation design considerations. This has led designers, researchers and engineers to explore the connections between patient experience, the noise control impacts that lead to improved scores, medical outcomes, and performance. This question requires a balance between psychoacoustic and effective noise control design to optimize healthcare environments and patient health.

What is the history of noise in US healthcare environments?

Noise control in US healthcare environments has grown as a priority after the publication of landmark papers in 2004 which documented the detrimental rise in worldwide hospital noise levels since 1960 and the resulting noise-related medical errors. Consequently, noise in healthcare environments is becoming recognized as a serious health issue, increasing staff stress and absenteeism, hindering patient healing, and causing patient injury and fatalities.

In the US, new regulations and financial incentives have been put in place in the last five years. Since October 2013, government reimbursement to hospitals is adjusted based on the scores of a standardized patient assessment survey, on which noise is consistently rated worse than any other category. Also, the Joint Commission, an independent, not-for-profit organization that accredits and certifies healthcare facilities, has made alarm safety a national patient safety goal starting in 2014, signaling that hospitals must give it top priority.

Regarding the built-environment, the 2010 and 2014 editions of the FGI Guidelines, a document used as code or referenced in 42 American states and is of interest in 60 countries, has a greatly expanded acoustics section covering a wide range of topics from acoustical finishes and sound isolation to paging systems and noise-related safety risk reduction.

A Book & A Study that is Giving Preemies – A Voice Decades Later

Deb Discenza

As the parent of a 30-week preemie now, 11.5 years old, I am often connected with other parents of preemies who are older and I get a sense of how life has turned out for them. For anyone that is involved in premature birth, be it a parent, a professional or the preemie him/herself, these stories give little nuggets of information about the future but not always the full picture.

So in hearing about Saroj Saigal, MD FRCP (C) at McMaster University, her decades long follow-up studies and her forthcoming book Preemie Voices, I was incredibly curious. What have the results shown and what can we learn from the past to help the future? I talked with Dr. Sagail and found the insights very enlightening not to mention the book a real help in giving concrete insight into the lives of preemies after they leave the NICU.

Deb Discenza: Tell us a bit about your background and how you have been involved with preemies over the years.
Saroj Saigal: I did my medical degree and Pediatric training in India. Subsequently I trained in neonatology in Edinburgh, Scotland, as a resident, and as a neonatal fellow in Montreal (McGill University), and at Hamilton (McMaster University). I joined the faculty at McMaster University in 1973, as a neonatologist, and Director of the Neonatal Follow-up Program. I have been a professor of Pediatrics since 1984, and I am currently Professor Emerita, and still involved in follow-up care and research.

DD: Your follow-up of dozens micro-preemies for 30+ years is quite a project. What did you personally believe would be the fate of these micro-preemies so many years later? And how is that the same/different than now? Any surprises?
SS: The 1970s were the early days of neonatal intensive care with improved survival of very premature infants. We started the follow-up program as a clinical service for parents of premature infants. Not much was known about the outcomes of these infants beyond a couple of years at that time. We started to follow a cohort of 169 survivors who weighed less than 1000g or 2.2 pounds at birth, and 149 normal birthweight infants. We initially followed them to school age, and reported that a significant proportion had school difficulties. Subsequently, we recalled them every few years, as we were curious to see how they were doing. However, we had never planned to follow them into their 30s! Had follow-up not been performed to adulthood, we would never have known the extent of the resilience and recovery shown by them. Although survival of these tiny infants has improved to unprecedented levels in the last decade, disability rates have not improved concomitantly. Nevertheless, it is important to recognize that disability rates have not increased either, despite the fact that the infants today are more immature. With better care and nutrition, one hopes that the longer-term outcomes of the current survivors will be better. Further follow-up is important.

DD: You took this incredible study and have written an educational and inspiring book for professionals, for families and for the public, Preemie Voices. What amazes me is that you had the micro-preemies themselves telling their own stories. Reading them for the first time and having known these now adults for their entire life, what was that like for you?
SS: We knew from our studies to adulthood that the majority of these premature infants had made good recovery. They were very proud of having met the challenges and transitioned well into adulthood. When I suggested whether they would be willing to write about their lives so future parents of preemies might find encouragement, they were very enthusiastic. However, I did not expect such beautifully written, candid letters that were also extremely moving. I am so proud of them all!

DD: You also created a special video on the book's website (www.PreemieVoicesBook.com) from a number of those same micro-preemies. What was their feeling in making such a documentary? What was your feeling?
SS: It seems that the young people today are not at all inhibited by technology and social media. So they did not hesitate in agreeing to be filmed. They are very happy to share their lives with the world, as they are indeed the pioneers of modern day survival of tiny preemies. Also, we felt that seeing is believing, and the video complements the book very well.

DD: What has the response been to your book by professionals? By the families? The public?
SS: The book has been received extremely well by parents, preemies, and medical staff, both nationally and internationally. To date (April 2015), the video has been viewed by over 4,000 individuals in 65 countries, and many people have said that it is most remarkable. In fact, the video provides us all a unique opportunity to learn from our former patients.

Deb Discenza is the mother to a 30-weeker premature baby now almost 12 years old. Ms. Discenza is the head of PreemieWorld, LLC and the co-author of "The Preemie Parent's Survival Guide to the NICU" available at www.PreemieWorld.com.

Value Analysis Metrics for the Assessment of Donor Milk Vendors

Elena Taggart Medo

Hospital value analysis has evolved from what was a simple exercise in optimization of resources to today's more comprehensive model which includes a range of analytical touch points including quality, safety, infection control, reimbursement, cost, sourcing, and health outcomes, including technological and procedural evaluations. As hospitals seek products that provide the best clinical and financial value, new or expanding product offerings require more extensive scrutiny and evaluation. Donor human milk is one such product area experiencing a sharp increase in usage driven by the growing evidence of patient benefits. But donor milk from different sources are not equal since procedures for donor testing and qualification, milk quality and safety testing and milk processing methods differ greatly and often lack validation or verification. Hospital decision makers may not be aware that basic food safety guidelines are sometimes not followed by small processors simply because they lack technical capacity and the equipment necessary to take such measures. For example, small processors have been known to thaw frozen milk at room temperature and lack the cleaning, safety processes and expertise needed to avoid biofilm formation on equipment. Although not required by law, donor milk processors should look to relevant parts of the Pasteurized Milk Ordinance for guidance or adopt other suitable global standards that require pre-process microbiological screening.

Modern hospital based value analysis teams have the capacity themselves to bring much greater insight into all aspects of safety relating to human donor milk products that are supplied to them. A variety of stakeholders contribute to this process, keeping clinical quality and safety at the center and focusing on improved patient outcomes. The team includes clinicians with patient and product knowledge, personnel with financial analysis skills and contracting expertise to reduce overall cost while maintaining or improving quality. For a donor milk value analysis team, members should now be expanded to include personnel with experience in risk management, infection control, and food safety, regulatory and patient safety. As with other value analysis committees, care must be taken to assure that no conflicts of interest are inherent in any individual's participation. As milk banking grows, so does the population of NICU employees who hold board seats or consulting positions with local milk banks. Because the milk banks are non-profit, hospital employees sometimes do not think of those milk banks as vendors to the hospital and their involvement as a potential conflict of interest.

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Hospital risk management must take measures to ensure that loyalty to a local non-profit is not putting preterm infants at risk due to lower standards or failure to thoroughly conduct value analysis.

Value has been defined as the ratio of function to cost. It is a challenge to assess the value of donor milk when many vendors fail to provide even a basic nutrition facts label and often lack transparency about the most basic safety and quality features of their processes and products. As with other products, vendors refusing to provide vital information necessary to conduct a thorough value analysis should be disqualified from supplying donor milk to the hospital. Vital information should include donor testing and requalification protocols, thawing protocols, raw milk quality and safety testing data including protocols for sampling raw and processed milk, process validation and registration with the FDA low acid foods division, and detailed information about the management and detection of b. cereus, s. aureus, e. coli and the heat stable toxins that result from contamination with these potential pathogens. Vendors should be able to provide data about rejected incoming milk, allowable limits of known pathogens, percentage of incoming milk rejected for quality/safety and a complete list of all tests conducted before and after processing.

Historically, the lack of such information may have been tolerated since there were few sources of donor human milk. Before the abundance of evidence to support the widespread use of human donor milk, there was limited demand. But a growing body of clinical evidence is now driving many hospitals to pursue the goal of exclusive use of human milk in special care nurseries. Many hospitals are also starting to use donor milk for full term babies who are hypoglycemic, since mother's own milk is normally not available until the third or fourth day.

Small volume donor milk suppliers are increasingly unable to meet the growing demand, resulting in rationing at the hospital, with only the smallest and sickest babies qualifying to receive their small portion of the scarce supply. Rationing has led to an increase in informal milk sharing and this practice complicates matters further for hospitals as new moms of hospitalized babies with a low milk supply are tempted to procure milk from others and bring this milk to the hospital for her own baby to consume. Even when mother is bringing her own milk to the hospital for her fragile infant, hospitals

struggle with the decision on whether to test her milk for bacterial contamination or drugs of abuse. Infant nutrition, once the domain of infant formula companies is now a complicated world for hospitals to navigate.

What are the issues to consider when conducting an evidence based value analysis of the various commercially available donor breast milk products?

All of the standard metrics apply when assessing sources of donor milk, including process definition, differentiation, patient safety, operational impact and cost. But for donor milk, additional metrics and subcategories should include risk management, infection control, product waste, shipping costs, staff requirements for preparation, facility requirements (such as freezers for frozen products), procurement time and any additional charges including handling and dry ice. Many hidden expenses increase the per ounce cost to a much larger effective cost of use.

Process definition: Pasteurization or sterilization?

What kind of thermal process is used? If it is pasteurized using the Holder method which calls for a cook time of 130F for 30 minutes with at least 20 minute warmup time and a 20 minute cool down time, the donor milk is not commercially sterile. The bio-burden of potential pathogens is lower than the pre-process raw milk, but heat stable spores such as bacillus cereus may remain. Ask about raw milk testing which should be required prior to thermal treatment. If no raw milk testing is done, ask how they avoid the risk of heat stable toxins remaining after pasteurization if the level of bacteria in the raw milk is unknown. B. cereus vegetative cells and spores are difficult to detect in raw milk and Holder pasteurization cannot eradicate it. Ask the milk bank about how they prevent b. cereus contaminated milk from being processed. Commercial sterilization calls for a higher temperature but the milk is subjected to heat for a much shorter period of time (250F for <8 minutes with an 8 minute warm up time and a 5 minute rapid cooling cycle).

Differentiation: Ask the vendors how they differentiate their donor milk product from other competing products. Some vendors boast that they sell "preterm" milk but are not able to provide a uniform definition or any evidence that infants have better outcomes when fed "preterm" milk. Ask for the evidence behind all claims. Most donor milk is pasteurized and frozen. Ask about the shelf life in the freezer and after thawing. Commercially sterile donor milk can be stored for up to 3 years at room temperature, unopened and for 7 days after opening in the refrigerator. Is the milk homogenized? If not, there can be as much as 30% fat loss when infant is being fed through an NG tube.

Patient safety: In years past, there was no such thing as a commercially sterile donor milk. Non-sterile infant formula was eliminated from the NICU after babies became sick from bacteria remaining in the formula after processing. Now, only commercially sterile, liquid infant formula is recommended for use in the NICU, due to the immune compromised condition of the preterm infants. The recommendations by the World Health Organization and the Codex Alimentarius were made to protect vulnerable infants from potential pathogens including E. sakazaki, salmonella, bacillus cereus, clostridium botulinum, c. dificile, c. perfringens, listeria monocytogenes, staphylococcus aureus, Enterobacteriaceae and other bacterial spores. It should be noted that many of these potential pathogens have been found in donor milk after Holder pasteurization. The Brazilian milk banking network is one of the largest and most developed in the world. In 2001, the Ministry of Health established the criteria for the microbiological control of human milk for milk banking. A 2003 study done by a major Brazilian university found that potential pathogens were identified in over 50% of pasteurized donor milk and concluded "that…. a lower degree of initial contamination would be necessary for pasteurization to be an efficient means of microbiological control." Additionally, the researchers noted, "Taking into consideration the results obtained, the authors believe that efforts should be made to improve the microbiological control of expressed human milk, including the milk which is going to be pasteurized. In this sense, more rigorous measures for monitoring the quality of human milk are indispensable so as to guarantee safe feeding for neonates." Each hospital and their infection control departments must determine whether the risk of non-sterile donor milk is one they want to take or if donor breast milk should meet the same safety criterion as infant formula. Additional safety issues to consider include whether there is repeated testing of milk donors or if they are only tested once, what is the protocol for testing the raw milk prior to pasteurization and whether the milk is tested for drugs, alcohol or adulteration.

Operational impact: How does the type of donor milk used impact internal operations at the hospital? What is the procurement process? How long does it take each week to ensure a supply of donor milk is continuing to arrive? With the short shelf life on frozen donor milk, how much can be stockpiled without risking expiration? If using frozen products, a freezer is required and most often it cannot be the same freezer in which mother's own milk is stored. What is the impact of maintaining the freezer, responding to freezer monitoring alarms and what is the protocol for using partially thawed donor milk? How many FTEs are required for the thawing and preparation of the milk? What is your thawing process and is it validated? Thawing at room temperature is unsafe because bacterial growth occurs fastest at room temperature. Is your hospital required to assist in collecting milk in order to assure a steady supply? If so, assess the cost of staff time and facility space as well as potential liability associated with acting as a collection site. Risk management personnel should assure that the donor milk vendor has a formal recall method that could effectively notify all hospitals of any need to hold or withdraw a batch of donor milk at any given time.

Cost: There are several aspects to consider when calculating the cost of donor milk to your institution.

- The cost per ounce will range from $3.75-$15.00. Find out what the major differences are between the most expensive cost per ounce and the least expensive.
- Is the shipping cost included in the price per ounce or is it an additional cost? For frozen product, overnight shipping is mandatory. For commercially sterile donor milk, shipping by ground provides an affordable alternative.
- Are there additional costs added? Some hospitals pay as much as $120,000 per year in overnight shipments of donor milk. Due to administrative processes, the shipping cost is sometimes not visible to the neonatal unit and they are unaware.
- An assessment of waste is part of the cost equation. Frozen products have a short shelf life after thawing, requiring disposal after 24 hours. Assigning responsibility for making sure that expired breast milk is not fed to a baby is vital to prevention of potential harm to an infant.

Assessment of current vendors

As with many value analysis projects, a decision to standardize or add more qualified vendors is often a result of disappointing performance by one or more existing vendors. If your hospital is currently using donor milk, an assessment of the current vendor relationship(s) should be part of the value analysis.

For donor milk, some of the common complaints include:

- Lengthy backorders or shipping only partial orders
- Inability to ship product on a timely basis
- Lack of nutritional information or incorrect nutritional labeling
- Receiving milk in glass bottles that have been broken during shipment
- Receiving a shipment of milk that has thawed during shipment
- Foreign objects/hair in donor milk
- FDA recalls due to a variety of reasons
- No formal recall system and inability to track milk from donor through processing and to the recipient hospital

Inspection Visit

A visit to your donor milk vendor is highly recommended and provides an ideal opportunity to ask any questions that have not been supplied to the hospital previously. Ask to see copies of Standard Operating Procedures, donor records, proof of traceability and recall procedures and schedule your visit to fall on a processing day so that all operations may be observed.

Summary

With professional, high volume processing of donor milk available, it is now feasible to conduct a wider array of safety and quality testing. Donor milk vendors should be able to provide the same quality and safety data as professional food processors. In an industry that is primarily self-regulated, failure to demand such data could potentially risk the safety and well-being of the smallest, most vulnerable patients as well as expose the hospital to potential liability.

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Remifentanil Patient-Controlled Analgesia for Labor – Monitoring of Newborn Heart Rate, Blood Pressure and Oxygen Saturation During the First 24 Hours After Delivery

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Abstract

Introduction: There is no available information about the effects of remifentanil labor analgesia on newborns' vital signs in the first hours after delivery. The aim of the study was to assess changes in the heart rate, blood pressure and oxygen saturation during the first 24 h of neonatal life after using remifentanil patient-controlled analgesia (PCA) for labor analgesia.

Material and methods: Forty-four full-term neonates, 23 from intravenous PCA remifentanil labor anesthesia 0.2 µg/kg, repeated not more frequently than every 2 min, and 21 born to mothers without any pharmacological forms of analgesia, were studied. Heart rate, oxygen saturation, and systolic (SBP) and diastolic blood pressure (DBP) were monitored using a Nellcor Oxi Max monitor N5500 (Tyco Healthcare), and recorded at 1 h, 6 h, 12 h and 24 h.

Results: No significant differences in heart rate ($p = 0.54$; $p = 0.26$; $p = 0.60$; $p = 0.83$), oxygen saturation ($p = 0.21$; $p = 0.27$; $p = 0.61$; $p = 0.9$) and DBP ($p = 0.98$; $p = 0.31$; $p = 0.83$; $p = 0.58$) between the groups at 1 h, 6 h, 12 h and 24 h. Newborns from the remifentanil group had lower SBP at 1 h of life (59 mm Hg vs. 68.5 mm Hg) but the difference was just on the borderline of statistical significance ($p > 0.06$). There were no significant differences in SBP between the groups at 6 h ($p = 0.65$), 12 h ($p = 0.11$), and 24 h ($p = 0.89$) of life.

Conclusions: Remifentanil PCA analgesia during labor does not significantly modify the oxygen saturation, heart rate and blood pressure in infants during the first day of their life. Therefore, further studies are needed to explain the observed trend for arterial hypotension in the first hour of life in infants born to mothers treated with remifentanil.

Introduction

Remifentanil is a rapid-acting synthetic µ-opioid receptor agonist with a very short half-life, that is quickly metabolized by plasma and tissue esterases, regardless of any hepatic or renal impairment, or age-related differences in half-life [1-3].

For a decade, anesthesiologists have used the unique properties of remifentanil in the settings of surgical anesthesia, sedation and postoperative analgesia since its introduction into labor analgesia. However, remifentanil is not licensed to be administered to pregnant women. As it stands remifentanil is the best opioid for obstetric use so far. Proper informed consent, appropriate monitoring of the mother and the newborn, one-to-one nursing or midwifery care, as well as the availability of an attending physician experienced in neonatal resuscitation and an anesthesiologist with experience in the use of remifentanil, are important to ensure that this method retains its credit for obstetric analgesia [4].

Remifentanil rapidly and extensively crosses the placenta (umbilical vein/maternal artery ratio 0.88) in term pregnancies [5]. It is believed that although remifentanil crosses the placenta, it is eliminated quickly in neonates by rapid metabolism or redistribution. However, because of different duration of labor, pain severity and subjective feeling, total doses of remifentanil transferred during patient-controlled analgesia to the fetus/newborn may differ significantly. The phenomenon of the individual sensitivity to the drug and accumulation in some patients should also be taken into consideration. In general, the pharmacokinetics of opioids during fetal life and in newborns is guided by maturational aspects of absorption, distribution, metabolism and elimination of these drugs. In this age range, important factors such as gestational age, body composition, weight, liver maturation and impaired renal function result in considerable individual variability in the pharmacokinetics of the majority of drugs [6, 7].

There are limited studies about the safety of remifentanil use as a bolus in induction of general anesthesia for caesarean delivery [8–11]. In very few studies maternal and neonatal side-effects of remifentanil patient-controlled analgesia in labor are described [4, 11–14]. Cardiovascular instability and respiratory depression immediately after birth were noticed in some cases. In papers published up to now only Apgar score results, umbilical blood gas analysis or muscle rigidity during the first 10 min after birth were used as indicators of newborn wellbeing after remifentanil labor analgesia. In one study performed by Draisci et al., neonates were observed in the nursery with SpO2 monitoring removed at 3 h after birth [11]. None of the papers reports monitoring of the heart rate, oxygen saturation and blood pressure performed for at least 24 h after birth.

The aim of the study was to assess changes in the heart rate, blood pressure and oxygen saturation of hemoglobin during

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Table I. General characteristics of participants

Variable	Remifentanil group	Control group	Statistical analysis
Number of patients	23	21	NS
Female sex	7 (30.43%)	11 (52.38%)	NS
Male sex	16 (69.57%)	10 (47.62%)	NS
Duration of pregnancy [weeks]*	35–41 (39.04 ±1.74)	37–41 (38.9 ±1.28)	NS
Birth weight [g]*	2550–4180 (3324.8 ±443.4)	2400–4000 (3366.7 ±416.1)	NS
5' Apgar score, median (range)	9 (8-10)	10 (9-10)	$p < 0.001$

**Values are presented as ranges and mean ± standard deviation*

Table II. Comparison of oxygen saturation by pulse oximetry values (ScO_2) recorded in newborns from the remifentanil and the control group at 1 h, 6 h, 12 h and 24 h of life

Group	Life [h]	*N*	Median ScO_2	Minimum ScO_2	Maximum ScO_2	Q25%	Q75%	Value of *p**
Remifentanil	1	23	97.0	90	100	96	100	0.20796
Control	1	21	98.0	90	100	97.5	98.5	
Remifentanil	6	23	98.0	94	100	96	98	0.27885
Control	6	21	98.0	92	100	97	99	
Remifentanil	12	23	98.0	96	100	97	99	0.61449
Control	12	21	99.0	94	100	97	100	
Remifentanil	24	23	98.5	96	100	97	100	0.86997
Control	24	21	98.5	96	100	97.5	99.5	

**Statistical analysis – Mann-Whitney U test: differences between groups not significant*

the first 24 h of life in neonates born after using remifentanil PCA for labor analgesia in comparison with neonates born after labor without any pharmacological analgesia.

Material and methods

Patients

The study included 44 infants born at the Department of Obstetrics and Gynecology, and then hospitalized at the Department of Neonatology, Pomeranian Medical University in Szczecin, Poland. All infants were from uncomplicated pregnancies and after a normal spontaneous vaginal delivery.

Enrollment in the study was as follows: Remifentanil PCA for labor was suggested to pregnant women with no known obstetric complications and contraindications to epidural analgesia or in cases when the mother rejected the idea of regional analgesia. Neonates from the mothers who accepted remifentanil analgesia comprised the study group, while neonates from mothers who refused any pharmacological method of analgesia constituted the control group.

Inclusion criteria for the remifentanil group:
- written informed maternal consent for labor analgesia with the remifentanil PCA method obtained before enrollment of the newborn;
- no complications during pregnancy;
- healthy pregnant women;
- term pregnancy.

Inclusion criteria for the control group:
- written informed maternal consent for refusal of labor analgesia with remifentanil PCA method obtained before enrollment of the newborn;
- no pharmacological agents of labor pain release used during labor;
- no complications during pregnancy;
- healthy pregnant women;
- term pregnancy.

Exclusion criteria for both groups:
- major congenital malformations (cardiac, central nervous system, respiratory tract, chromosomal abnormalities and all lethal malformations);
- early onset sepsis (recognized up to 72 h of life based on clinical symptoms, laboratory test and bacterial culture results).

The remifentanil group consisted of 23 newborns of mothers who received intravenous remifentanil anesthesia using the method of analgesia controlled by the patient (PCA – patient-controlled analgesia) at the dose of 0.2 µg/kg repeated not more frequently than every 2 min. No background infusions of remifentanil were used. The control group comprised 21 infants born to mothers who did not use any pharmacological forms of anesthesia.

Methods

The study was designed as a prospective clinical controlled trial, conducted in compliance with the Declaration of Helsinki principles. The protocol and the parental informed consent forms were approved by the institutional review board (Ethical Committee of the Pomeranian Medical University, Szczecin, Poland). Written informed consent of the mother for examinations of the child was obtained in each study case.

All neonates were observed in the nursery for at least 48 h after birth with transcutaneous O2 saturation (ScO2) monitoring during 24 h after delivery. Measures of the heart rate (HR) and blood pressure (BP) of the newborns were recorded four times during the first day of life, at 1 h, 6 h, 12 h and 24 h. Vital

Table III. Comparison of the heart rate (HR) values in beats per minute (bpm) in newborns from the remifentanil and the control group obtained at 1 h, 6 h, 12 h and 24 h of life

Group	Life [h]	*N*	Median HR [bpm]	Minimum HR [bpm]	Maximum HR [bpm]	Q25%	Q75%	Value of *p**
Remifentanil	1	23	138.0	127	180	130	149	0.54557
Control	1	21	142.0	130	161	137	145.5	
Remifentanil	6	23	138.5	103	155	131	142	0.26242
Control	6	21	140.5	122	159	133.5	147	
Remifentanil	12	23	136.0	110	173	127	148	0.60566
Control	12	21	138.0	118	153	132	145	
Remifentanil	24	23	139.0	123	160	134	148	0.83050
Control	24	21	141.0	107	167	135	147.5	

**Statistical analysis – Mann-Whitney U test: differences between groups not significant*

Table IV. Comparison of systolic blood pressure (SBP) values in newborns from the remifentanil and the control group at 1 h, 6 h, 12 h and 24 h of life

Group	Life [h]	*N*	Median SBP	Minimum SBP	Maximum SBP	Q25%	Q75%	Value of *p**
Remifentanil	1	23	59.0	49	97	52	67	0.06949
Control	1	21	68.5	36	90	61	76	
Remifentanil	6	23	68.0	51	100	54	73	0.65591
Control	6	21	65.0	42	98	60	74	
Remifentanil	12	23	60.0	53	81	58	75	0.11315
Control	12	21	64.0	50	93	61	81	
Remifentanil	24	23	66.0	41	85	64	72	0.89497
Control	24	21	64.5	52	95	60	76	

**Statistical analysis – Mann-Whitney U test: differences between groups not significant*

Table V. Comparison of diastolic blood pressure (DBP) values in newborns from the remifentanil and the control group at 1 h, 6 h, 12 h and 24 h of life

Group	Life [h]	*N*	Median DBP	Minimum DBP	Maximum DBP	Q25%	Q75%	Value of *p**
Remifentanil	1	23	36.0	21	56	29	40	0.98683
Control	1	21	34.0	24	55	31	41	
Remifentanil	6	23	38.0	23	69	32	41	0.31411
Control	6	21	32.0	20	64	25	50	
Remifentanil	12	23	35.0	25	44	32	39	0.83013
Control	12	21	32.0	22	52	30	44	
Remifentanil	24	23	40.0	23	67	35	46	0.58605
Control	24	21	38.0	22	53	33	44	

**Statistical analysis – Mann-Whitney U test: differences between groups not significant*

signs such as the heart rate, transcutaneous O2 saturation of hemoglobin and blood pressure were monitored using a Nellcor Oxi Max monitor N5500 (Tyco Healthcare). Results of measurements of ScO2, HR and BP obtained at 1 h, 6 h, 12 h and 24 h of life were statistically analyzed.

Statistical analysis

The distribution of continuous variables was tested for normality by the Shapiro-Wilk test. The differences between newborns from the remifentanil PCA labor analgesia group and controls were tested by the Wilcoxon test or Mann-Whitney nonparametric U test as appropriate. Values were presented as mean and standard deviation or median and ranges, as appropriate. A value of $p < 0.05$ was considered statistically significant.

Results

General characteristics of the analyzed groups of newborns are presented in Table I. No significant differences regarding the number of patients enrolled, sex of newborns, gestational age and birth weight between newborns from the compared groups were found (Table I). However, 5-minute Apgar score was significantly lower in the remifentanil than in the control group (Table I).

Five newborns from the remifentanil group (21.7%) needed respiratory support with an oxygen bag and mask at the delivery room. Three of those demanded an oxygen hood also during the first hours of life, meaning that respiratory depression in newborns can develop after remifentanil used as a PCA method for labor analgesia.

There were no significant differences in ScO2 values recorded at 1 h, 6 h, 12 h, and 24 h of life between the compared groups of newborns (Table II).

There was no significant difference in the heart rate (HR) values recorded during the 24-hour monitoring of newborns at 1 h, 6 h, 12 h, and 24 h of life between newborns from the compared groups (Table III).

The neonates from the remifentanil group had lower systolic blood pressure in the first hour of life compared to the values found in newborns from the control group but the difference was only on the borderline of statistical significance ($p > 0.06$) (Table IV).

There were no significant differences in the diastolic blood pressure values recorded at 1 h, 6 h, 12 h, and 24 h of life between both groups of newborns (Table V).

Discussion

During childbirth, remifentanil offers hemodynamic stability for the mother, even during general anesthesia, but 50% of newborns may require ventilatory assistance because of respiratory depression. There is also a case report of generalized rigidity and apnea in a neonate immediately after birth following remifentanil administration during caesarean section to a high-risk mother [15]. Therefore, supervision and monitoring of both the mother and the infant are necessary [15].

To the best of our knowledge, this is the first published report on the biophysical monitoring of the heart rate, pulse oximetry and blood pressure during the first 24 h after birth in neonates born to PCA remifentanil labor analgesia mothers. We found no differences in the heart rate, pulse oximetry, or systolic and diastolic blood pressure values between the group of newborns born to remifentanil PCA labor analgesia women and the group of newborns born to control women, except for non-significant hypotension (systolic blood pressure below 60 mm Hg in the remifentanil group) at 1 h after delivery.

Despite a very short half-life in some adult patients, remifentanil was reported to possibly cause side effects even 1 h after stopping the infusion [16]. Based on the limited number of studies on newborns, one may consider that the varied process of birth (interruption of the mother-fetus metabolism), comorbidities, environmental factors (e.g. maternal smoking, use of medications) and polymorphisms contribute to the individual variability related to the pharmacokinetics of opioids, including remifentanil, in the neonatal period [6, 17].

Arnal et al. carried out a systematic review on the use of remifentanil in childbirth analgesia [18]. In the majority of cases, no serious side effects for either mothers or neonates in the delivery room conditions were noted. The authors concluded that intravenous remifentanil may be the drug of choice for childbirth analgesia when regional analgesia techniques are contraindicated [18].

Therefore, in papers published up to now, information about the effects of remifentanil labor analgesia on newborns' vital signs in the first hours after delivery is scarce.

Only in the study of Draisci et al. were neonates observed for at least 24 h after birth in the nursery, with SpO2 monitoring removed at 3 h if no episodes of desaturation had occurred [11]. Draisci reported significantly lower Apgar scores at 1 min and 5 min after birth and respiratory depression after using remifentanil 0.5 µg/kg as a bolus in cesarean section under general anesthesia [11]. They concluded that even at low doses remifentanil has the potential to cause respiratory depression. No other adverse effects during the first 24 h of neonatal life were observed in their study [11].

The ideal regimen for remifentanil infusion is yet to be established and further studies on maternal and fetal safety need to be carried out. During our study project, the dose of 0.2 µg/kg repeated not more frequently than every 2 min with no background infusion of remifentanil was used. Such doses seem to be safe from the fetal/neonatal point of view [4]. Additional information about the doses safe for neonates may be found in reports on the use of remifentanil in neonatal intensive care and anesthetic practice [6]. Lago et al. recorded the number of clinically significant desaturations, apnea and hypotension for the first 3 h after the infusion of remifentanil 0.03 µg/kg/min was over [1].

In a study by Wee et al., the starting rate of 0.025 µg/kg/min was considered preferable to avoid bradycardia and hypotension that were observed after administration of either a bolus of 1 µg/kg or an infusion rate of 1 µg/kg/min [19]. In a double-blinded, randomized and prospective study of Chambers, clinically insignificant bradycardia and mild hypotension (with no repercussion on peripheral perfusion) frequently followed administration of remifentanil 1 µg/kg/min or saline as a bolus over 1 min [20].

Davis et al., and Galinkin et al., among 60 patients with a mean rate of remifentanil infusion of 0.55 µg/kg/min, noticed the necessity of hypotensive treatment (systolic blood pressure < 60 mm Hg) in 11% of the patients [2, 3].

In a pilot study, INSURE, with remifentanil 2 µg/kg infused over 60 s, mean blood pressure decreased 5 min after remifentanil application, and usually normalized within 20-30 min after remifentanil infusion [21]. Hypothetically, remifentanil PCA labor analgesia may negatively influence the newborn condition even up to 30 min after birth. It should also be taken into account that higher remifentanil doses are associated with an increased risk of side effects. In the year 2010, Standing et al., published a study about the relationship between whole blood remifentanil concentration and its hypotensive effects in infants undergoing cranioplasty [22]. They concluded that remifentanil is effective in causing arterial hypotension.

Summarizing the above data and our results, hypotension after remifentanil infusion can occur. Further trials are needed to evaluate ideal dosing regimens and combinations of agents to be used with remifentanil in labor analgesia.

Our study has some limitations, chief among them the studied problem itself, whether or not to give labor analgesia. From an ethical point of view, a randomized, blinded study of used or not used labor analgesia is not accepted in pregnant women during labor. Also, it is commonly known that some pregnant women prefer to have natural labor without any pharmacological analgesia. Therefore, in our study the choice of whether to use labor analgesia or refuse it belonged to the mother and not to the researcher.

Secondly, the total dose of remifentanil varied depending on the length of labor and the number of applications provided by the mother. In the remifentanil-PCA method minimum interval between doses on the level of 2 min was specified, but the actual interval between successive doses in the method of PCA was dependent on the subjective perception of pain by the women giving birth. The time from the last dose of remifentanil to the moment of delivering the baby was also different, but in each case was longer than the half-life time of remifentanil. Taking into account that remifentanil has a very short half-life time, the listed limitations should not have any significant influence on our results and conclusions.

In conclusion, remifentanil PCA analgesia during labor in doses of 0.2 µg/kg, repeated not more frequently than every 2 min, does not significantly modify the hemoglobin oxygen saturation, heart rate and blood pressure in infants during the first day of life. Further studies are needed to explain the observed trend for arterial hypotension in the first hour of life in infants born to mothers treated with remifentanil.

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Risk-Adjusted Operative Delivery Rates and Maternal-Neonatal Outcomes as Measures of Quality Assessment in Obstetric Care: A Multicenter Prospective Study

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Abstract

Background: Although the evaluation of caesarean delivery rates has been suggested as one of the most important indicators of quality in obstetrics, it has been criticized because of its controversial ability to capture maternal and neonatal outcomes. In an "ideal" process of labor and delivery auditing, both caesarean (CD) and assisted vaginal delivery (AVD) rates should be considered because both of them may be associated with an increased risk of complications. The aim of our study was to evaluate maternal and neonatal outcomes according to the outlier status for case-mix adjusted CD and AVD rates in the same obstetric population.

Methods: Standardized data on 15,189 deliveries from 11 centers were prospectively collected. Multiple logistic regression was used to estimate the risk-adjusted probability of a woman in each center having an AVD or a CD. Centers were classified as "above", "below",or "within" the expected rates by considering the observed-to-expected rates and the 95% confidence interval around the ratio. Adjusted maternal and neonatal outcomes were compared among the three groupings.

Results: Centers classified as "above" or "below" the expected CD rates had, in both cases, higher adjusted incidence of composite maternal (2.97%, 4.69%, 3.90% for "within", "above" and "below", respectively; p = 0.000) and neonatal complications (3.85%, 9.66%, 6.29% for "within", "above" and "below", respectively; p = 0.000) than centers "within" CD expected rates. Centers with AVD rates above and below the expected showed poorer and better composite maternal (3.96%, 4.61%, 2.97% for "within", "above" and "below", respectively; p = 0.000) and neonatal (6.52%, 9.77%, 3.52% for "within", "above" and "below", respectively; p = 0.000) outcomes respectively than centers with "within" AVD rates.

Conclusions: Both risk-adjusted CD and AVD delivery rates should be considered to assess the level of obstetric care. In this context, both higher and lower-than-expected rates of CD and "above" AVD rates are significantly associated with increased risk of complications, whereas the "below" status for AVD showed a "protective" effect on maternal and neonatal outcomes.

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Background

Quality of care is an important topic in modern obstetrics of which risk-adjusted caesarean delivery (CD) rate is often used as an indicator, with the implicit assumption that low rates may reflect evidence-based intervention [1-8].

Although the evaluation of risk-adjusted CD rates is an important factor in quality assessment, it is just one of the elements to be considered in the process of labor and delivery auditing. In this regard, a comprehensive assessment should encompass both maternal and neonatal outcomes according to mode of delivery [4]. Several studies focused on the association between institutional adjusted CD rates and outcomes reporting controversial results. In their retrospective cohort study on 748,604 low risk singleton pregnancies, Gould et al. observed that neonatal morbidity (birth asphyxia and intensive care-therapeutic interventions) was increased both in low-and high-CD rate hospitals [5]. Bailit et al., considering the Washington State Birth Events Records for 1995 and 1996, showed that asphyxiated infants were likely to be delivered by caesarean in hospitals in which CD rates were above the predicted range [6]. In another study, the same authors showed a mixed picture for hospitals with CD rates above the expected, with some poorer and some improved maternal and neonatal outcomes [7]. Srinivas et al. evaluated both maternal and neonatal composite outcomes according to institutional adjusted CD rate in a population-based cohort from 401 hospitals. Their conclusion was that lower-than-expected risk-adjusted CD rates were associated with an increased risk of maternal or neonatal complications and that above than expected risk-adjusted CD rates did not result in improved outcomes [8].

All the above mentioned studies have however limited their attention to the CD rate. None of them has evaluated the association between the risk of adverse maternal and neonatal outcomes and the outlier status for both adjusted caesarean and assisted vaginal delivery rates (AVD) in the same obstetric population. Including the rate of assisted vaginal delivery in this analysis may be crucial in the assessment of quality of care. In fact, institutions with low frequencies of risk-adjusted CD rates might have, as a balance, high adjusted AVD rates, potentially

associated with adverse outcomes [9]. Limiting the evaluation of the obstetrics performance to the CD rates could therefore be misleading and not reflect the true outcomes of that center.

The aim of our study, carried out on more than 15,000 deliveries of 11 different centers of Friuli Venezia Giulia, a north-eastern region of Italy, was to determine the prevalence of adverse maternal and neonatal outcomes according to the mode of delivery. We tested the hypothesis that institutions with risk-adjusted AVD and CD rates above or below the expected would have higher and lower rates, respectively, of maternal and neonatal complications.

Methods

We prospectively collected data on all deliveries occurring in the 11 hospitals of Friuli Venezia Giulia in a period of 18 months between July 2006 and December 2007. Friuli Venezia Giulia is a region of North-Eastern Italy accounting roughly for 10,000 deliveries per year with one of the lowest overall regional CD rate in Italy (23.4% in 2010). Virtually all births of the region were included in the study, given the very low rate of home births and the absence of midwifery-led centers in the area. The Institutions of the region, referred to as A to M, are level one units, serving low risk pregnancies, with the exception of centers I and M that are level three units (range 369–1,810 deliveries/year/unit).

To eliminate the potential bias generated by different definitions and heterogeneous collection of data, we created a regional computerized database considering maternal characteristics (maternal age and pre-pregnancy body mass index-BMI), variables related to pregnancy (parity, gestational age at delivery, singleton or multiples, presence of previous CD), antenatal clinical risk factors, mode of delivery and short term neonatal and maternal outcomes. Data on pregnancies were prospectively collected at the time of delivery and before maternal/neonatal discharge and were systematically reviewed every month by the referent obstetrician of each center.

Special attention was devoted to completeness and accuracy of data. During the study period, two of the authors (GM and SA) organized periodical multicenter meetings to discuss the results and provide assistance. The study was approved by the institutional review board of the coordinating center (Institute for Maternal and Child Health – IRCCS Burlo Garofolo, Trieste, project 86/05 – February 28, 2007) and access to the data was approved by all hospital trust administrations. According to the Italian law on privacy, data were anonymized at every institution where each patient was assigned a unique identifier.

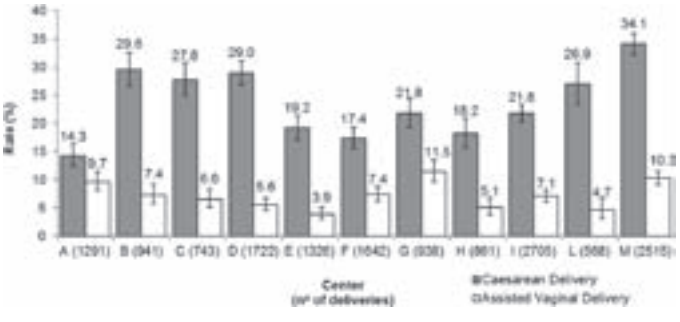

Figure 1 Institutional caesarean and assisted vaginal delivery rates (percentage). Centers are reported in capital letters.

Short term maternal and neonatal complications were analyzed both as single and combined complications (life threatening, non-life threatening and composite).

Life threatening maternal complications were defined as follow (criteria modified from McMahon [10]): 1. Major PPH (post-partum hemorrhage greater than 1000 mL or requiring blood transfusion) [11]; 2. Post-partum hysterectomy; 3. Obstetric wound hematoma requiring re-intervention; 4. Thromboembolic disease; 5. Uterine rupture. Non-life threatening maternal morbidities included: 1. Minor PPH (post-partum hemorrhage between 500 and 1000 mL) [11]; 2. III-IV degree perineal tears; 3. Asymptomatic wound dehiscence; 4. Endometritis or pyrexia needing antibiotic treatment; 5. Bowel or bladder injury; 6. Anaesthesiological complications; 7. Any other condition requiring admission to intensive care unit (ICU).

Life threatening neonatal complications (criteria modified from Fong [12]) included: 1. Mortality within 7 days of life; 2. Mortality within 28 days; 3. Abnormal neurologic status (encephalopathy as defined by Sarnat and Sarnat [13]), neonatal convulsions and intracranial hemorrhage (including all classes of intraventricular hemorrhage, epidural hemorrhage, and subdural hemorrhage). Non-life threatening neonatal morbidities were assessed as follow: 1. Pulmonary disorders, including transient tachypnoea of the newborn and respiratory distress syndrome, as defined by Hjalmarson [14]; 2. Bacterial infections including pneumonia and sepsis, diagnosed clinically with or without confirmation by blood cultures; 3. Umbilical artery cord pH at birth less than 7.00; 4. Umbilical artery cord base deficit greater than 12 mmol/L at birth; 5. Apgar score less than 7 at five minutes in term newborns; 6. Any other condition (birth trauma included) requiring neonatal intensive care (NICU) admission in term newborns for more than 24 hours (37–42 weeks/birth weight >2500 grams).

Incidence of complications was analyzed for all cases and divided into spontaneous vaginal (SVD), assisted vaginal (AVD), overall vaginal (VD) and caesarean deliveries (CD). Both women and newborns could have more than one complication, thus the total number of single complications is higher than the number of women or newborns with complications. In case of multiple pregnancies, if one of the newborns had a complication, this was considered as a neonatal complication. Only cases with complete data on all of the above indicated variables were included in the final analysis. Pregnancies complicated by antepartum stillbirths and/or life-threatening fetal congenital anomalies and deliveries with infants weighting less than 500 grams and/or below 24 weeks' gestation were excluded to avoid potential bias in the evaluation of the outcomes.

Associations between type of delivery (CD vs. SVD, CD vs. VD and AVD vs. SVD) and single or composite complications were analyzed calculating crude and adjusted risk ratios (RRs) and p values, resulting from log-binomial regressions [15]. Considering that we had approximately 50 comparisons, we adopted a conservative Bonferroni correction dividing the significance level of 0.05 by 50: thus we considered $p < 0.001$ as statistically significant.

CD and AVD rates were adjusted for maternal age (reference 20–24 years, <20 years, 25–29 years, 30–35 years, >35 years), maternal pre-pregnancy BMI (reference 18.5-24.9 kg/m2, <18.5 kg/m2,25 – 29.9 kg/m2, ≥30 kg/m2) [16], gestational age at

Table 1 Incidence of outcomes (individual and composite) by mode of delivery

	Overall	SVD	CD	AVD
	n = 15,189	n = 10,410	n = 3,638	n = 1,141
Maternal complications	***n (%)***	***n (%)***	***n (%)***	***n (%)***
Major PPH	61 (0.40)	30 (0.29)	20 (0.55)	11 (0.96)
Hysterectomy	8 (0.05)	3 (0.03)	5 (0.14)	0 (0.00)
Wound hematoma	49 (0.32)	30 (0.29)	9 (0.25)	10 (0.88)
TED	6 (0.04)	2 (0.02)	3 (0.08)	1 (0.09)
Uterine rupture	2 (0.01)	0 (0.00)	2 (0.05)	0 (0.00)
Life threatening composite	111 (0.73)	59 (0.57)	32 (0.73)	20 (1.75)
Minor PPH	369 (2.43)	232 (2.23)	90 (2.47)	47 (4.12)
III-IV degree tears	50 (0.33)	39 (0.37)	0 (0.00)	11 (0.96)
Wound Dehiscence	25 (0.16)	12 (0.12)	10 (0.27)	3 (0.26)
Endometritis	69 (0.45)	23 (0.22)	42 (1.15)	4 (0.35)
Bowel/bladder injury	4 (0.03)	0 (0.00)	4 (0.11)	0 (0.00)
Anaesthesiological	7 (0.05)	4 (0.04)	2 (0.05)	1 (0.09)
Other*	19 (0.13)	6 (0.06)	12 (0.33)	1 (0.09)
Non-life threatening composite	485 (3.19)	283 (2.72)	142 (3.90)	60 (5.26)
Overall composite	596 (3.92)	342 (3.29)	174 (4.78)	80 (7.01)
Neonatal complications	***n (%)***	***n (%)***	***n (%)***	***n (%)***
Mortality <7 days	17 (0.11)	3 (0.03)	13 (0.36)	1 (0.09)
Mortality <28 days	13 (0.09)	4 (0.04)	6 (0.16)	3 (0.26)
Neurologic symptoms	38 (0.25)	6 (0.06)	29 (0.80)	3 (0.26)
Life threatening composite	47 (0.31)	9 (0.09)	33 (0.91)	5 (0.44)
Pulmonary disorders	250 (1.65)	84 (0.81)	156 (4.29)	10 (0.88)
Bacterial infections	98 (0.65)	38 (0.37)	58 (1.59)	2 (0.18)
pH < 7.00	74 (0.49)	25 (0.24)	29 (0.80)	20 (1.75)
BD > 12 mmol/L	204 (1.34)	113 (1.09)	41 (1.13)	50 (4.38)
Apgar < 7	118 (0.78)	37 (0.36)	59 (1.62)	22 (1.93)
Other**	773 (5.09)	284 (2.73)	445 (12.23)	44 (3.86)
Non-life threatening composite	973 (6.41)	416 (4.00)	464 (12.75)	93 (8.15)
Overall composite	1,020 (6.72)	425 (4.08)	497 (13.66)	98 (8.59)

Footnotes: SVD, spontaneous vaginal delivery; AVD, assisted vaginal delivery; CD, caesarean delivery; VD vaginal delivery ; PPH, post-partum hemorrhage; TED, thromboembolic disease; BD, base deficit.
*Any other condition requiring Intensive Care Unit admission.
**Any other condition requiring Neonatal Intensive Care Unit admission in term neonates (37–42 weeks).

delivery (reference 37–41 weeks, <30 weeks, 30–36 weeks, >41 weeks) classification of pregnancy at risk (reference no risk, low/intermediate risk, high risk), parity (reference multiparous, nulliparous), gestations (reference singleton, twin), presentation (reference cephalic, other), presence of previous CD (reference no past CD, one, more than one) newborn birth weight (reference 2,5004,000 grams, <1,000 grams, 1,000-1,499 grams, 1,5002,499 grams, >4,000 grams). Pregnancy was classified as at low-intermediate or high risk on the basis of the following definitions: 1. Low risk: if no pre-existing or ante partum risk factor was identified; 2. Intermediate risk: presence of pre-existing maternal medical conditions complicating the pregnancy, but not representing per se an absolute indication to CD or induction of labor (e.g. chronic hypertension, pregnancy-associated hypertension, gestational diabetes, obstetric cholestasis, polyhydramnios and Rh-isoimmunization); 3. High risk: presence of pre-existing maternal diseases or other obstetric conditions suggesting the need for delivery, such as HIV infection, pre-existing diabetes, severe preeclampsia, placenta previa, oligohydramnios and intrauterine growth restriction defined as fetal abdominal circumference or estimated fetal weight less than the 10th centile [7]. In case of a multiple pregnancy, we considered the lowest newborn birth weight. Finally, given the acknowledged high risk of complications related to the delivery in the presence of impeding maternal and fetal compromise, the degree of urgency was also considered into the risk-adjustment (reference maternal and fetal compromise, no maternal and fetal compromise) [17].

Following these adjustments, we calculated for each of the 11 centers the expected AVD and CD rates.

According to the methodology adopted by Bailit et al., a logistic regression model was initially developed to generate the predicted probability of operative deliveries (CD and AVD) for each patient. Second, the probabilities of operative deliveries for all patients were added together for each center to obtain the predicted number of CDs and AVDs for that institution. We then

Table 2 Risk ratios for outcomes (individual and composite) by mode of delivery

	CD vs. SVD		CD vs. VD		AVD vs. SVD	
Maternal complications	***Crude RR***	***Adj RR***	***Crude RR***	***Adj RR***	***Crude RR***	***Adj RR***
Major PPH	1.91 (1.08-3.35)	0.81 (0.38-1.70)	1.55 (0.91-2.64)	0.52 (0.25-1.07)	3.35 (1.68-6.66)	2.41 (1.20-4.83)[§]
Hysterectomy	5.29 (1.27-22.13)	1.68 (0.27-10.54)	5.29 (1.27-22.13)	1.39 (0.44-8.16)	-	-
Wound hematoma	0.86 (0.41-1.81)	0.32 (0.07-1.48)	0.71 (0.35-1.47)	0.28 (0.07-1.14)	3.04 (1.49-6.20)	2.09 (0-97-4.51)
TED	4.29 (0.71-25.68)	0.31 (0.06-1.45)	3.18 (0.64-15.72)	0.45 (0.06-2.90)	4.56 (0.41-50.27)	2.10 (0.97-4.55)
Uterine rupture	-	-	-	-	-	-
Life threatening composite	1.57 (1.02-2.41)	0.61 (0.36-1.03)	1.30 (0.86-1.95)	0.49 (0.29-0.84)	3.18 (1.92-5.25)[§]	2.24 (1.46-.3.45)[§]
Minor PPH	1.11 (0.87-1.41)	0.66 (0.31-1.37)	0.71 (.129)	0.61 (0.28-1.32)	1.85 (1.36-2.51)[§]	1.41 (1.02-1.93)[§]
III-IV degree tears	-	-	-	-	3.47 (1.78-6.76)[§]	2.26 (1.13-4.52)[§]
Wound Dehiscence	2.38 (1.03-5.51)	1.15 (0.16-1.28)	2.12 (0.95-4.71)	0.97 (0.11-8.59)	2.28 (0.64-8.07)	2.14 (0.58-7.91)
Endometritis	5.22 (3.15-8.68)[§]	4.74 (2.53- 8.87)[§]	4.94 (3.05-8.00)[§]	4.33 (2.39-7.84)[§]	1.59 (0.55-4.58)	1.80 (0.79-4.08)
Bowel/bladder injury	-	-	-	-	-	-
Anaesthesiological	1.43 (0.26-7.81)	0.65 (0.16-2.55)	1.27 (0.25-6.54)	0.56 (0.12-2.46)	2.28 (0.26-20.39)	1.95 (0.21-18.03)
Other*	5.72 (2.15-15.24)[§]	1.59 (0.62-4.09)	5.44 (2.14-13.81)[§]	0.79 (0.40-1.55)	1.52 (0.18-12.62)	1.09 (0.12-9.76)
Non-life threatening composite	1.44 (1.18-1.76)[§]	0.85 (0.44-1.64)	1.32 (1.09-1.60)	0.92 (0.72-1.81)	1.96 (1.49-2.57)[§]	1.57 (1.11-2.23)[§]
Overall composite	1.46 (1.22-1.74)[§]	1.04 (0.61-1.80)	1.31 (1.01-1.56)	0.77 (0.39-1.53)	2.13 (1.69-2.70)[§]	1.67 (1.22-2.27)[§]
Neonatal complications	***Crude RR***	***Adj RR***	***Crude RR***	***Adj RR***	***Crude RR***	***Adj RR***
Mortality <7 days	12.40 (3.54-43.49)[§]	3.04 (0.65-14.31)	10.32 (3.37-31.63)[§]	2.50 (0.44-14.13)	3.04 (0.32-29.21)	3.61 (0.50-25.08)[§]
Mortality <28 days	4.29 (1.21-15.20)	0.68 (0.28-1.63)	2.72 (0.92-8.09)	0.51 (0.13-2.03)	6.84 (1.53-30.54)	7.12 (1.51-33.68)[§]
Neurologic symptoms	13.83 (5.75-33.28)[§]	2.34 (0.86-6.36)	10.23 (4.85-21.59)[§]	1.87 (0.64-5.43)	4.56 (1.14-18.22)	2.77 (0.69-11.06)
Life threatening composite	11.55 (5.53-24-10)[§]	3.30 (0.85-12.78)	8.20 (4.39-15.30)[§]	1.55 (0.35-6.97)	5.30 (1.78-15-78)	3.31 (1.59-6.90)[§]
Pulmonary disorders	5.31 (4.09-6.91)[§]	2.07 (1.17-3.66)[§]	5.27 (4.09-6.79)[§]	2.12 (1.17-3.84)[§]	1.08 (0.57-2.09)	0.81 (0.45-1.48)
Bacterial infections	4.37 (2.91-6.56)[§]	1.34 (0.57-3.14)	4.60 (3.08-6.88)[§]	1.43 (0.65-3.13)	0.48 (0.16-1.99)	0.42 (0.05-3.72)
pH < 7.00	3.32 (1.95-5.66)[§]	1.41 (0.54-3.69)	2.05 (1.29-3.26)	0.78 (0.31-2.00)	7.30 (4.07-13.10)[§]	7.02 (4.13-11.95)[§]
BD > 12 mmol/L	1.04 (0.73-1.48)	0.49 (0.24-0.97)	0.80 (0.57-1.12)	0.35 (0.16-0.77)	4.04 (2.91-5.60)[§]	3.28 (2.01-5.37)[§]
Apgar < 7	4.56 (3.03-6.87)[§]	2.06 (1.16-3.67)[§]	3.17 (2.22-4.55)[§]	1.01 (0.62-1.64)	5.43 (3.21-9.16)[§]	5.00 (2.60-9.61)[§]
Other**	4.48 (3.88-5.18)[§]	1.05 (0.81-1.36)	4.31 (3.75-4.94)[§]	1.99 (1.62-2.43)[§]	1.41 (1.04-1.93)	1.12 (0.79-1.57)
Non-life threatening composite	3.21 (2.83-3.65)[§]	0.94 (0.75-1.18)	2.92 (2.59-3.29)[§]	0.92 (0.73-1.17)	2.05 (1.65-2.54)[§]	1.78 (1.42-2.22)[§]
Overall composite	3.35 (2.96-3.79)[§]	0.95 (0.76-1.19)	3.01 (2.68-3.39)[§]	0.89 (0.70-1.12)	2.10 (1.70-2.60)[§]	1.92 (1.45-2.25)[§]

Footnotes: Risk ratios adjusted by maternal age, maternal body mass index, gestational age at delivery, pregnancy at risk, parity, fetal presentation, number of fetuses, presence of previous CD, neonatal birth weight, grade of urgency (e.g. maternal or fetal compromise requiring immediate delivery).
RR, risk ratios; SVD, spontaneous vaginal delivery; AVD, assisted vaginal delivery; CD, caesarean delivery; VD vaginal delivery; Adj, adjusted; PPH, post-partum hemorrhage; TED, thromboembolic disease; BD, base deficit.
*Any other condition requiring Intensive Care Unit admission.
**Any other condition requiring Neonatal Intensive Care Unit admission in term neonates (37–42 weeks).
[§]p < .001.

divided these predicted numbers of deliveries by the total number of patients who were delivered at that hospital to obtain the institutional expected caesarean and assisted vaginal delivery rates. Units were herein classified by evaluating the ratio of observed-to-expected rates and considering the 95% confidence interval (CI) around the ratio. If the 95% CI of the resulting ratio included 1, the center was classified as within the expected. If the 95% CI was above or below 1, the centers were respectively classified as above or below the expected [7]. Maternal and neonatal outcomes were thus analyzed according to the outlier status of the centers as within, above and below the expected rates. The incidences of maternal and neonatal complications were adjusted by maternal age, maternal BMI, pregnancy at risk (no, low, high), parity, fetal presentation, number of fetuses, presence of previous CD (no, one, more than one), gestational age at delivery and neonatal birth weight and delivery grade of urgency. Finally, given the potential influences of obstetric volume and the organization of newborn care on outcomes, complication rates were also adjusted by considering the number of deliveries per center (reference ≥1000 deliveries/year, <1000 deliveries/year) and the presence of a Neonatal Intensive Care Unit (reference available, non-available) [18-20]. Differences among adjusted outcomes were evaluated with the analysis of variance (ANOVA) with Bonferroni corrections for single comparisons between within vs. above and within vs. below the expected CD and AVD rates. Finally, considering we already had applied the correction to each outcome, we additionally corrected for the number of outcomes and considered as significant p values below 0.003.

All statistical analyses were performed using Stata/IC 11.2 software (StataCorp, College Station, TX, USA).

Results

From a total number of 15,726 pregnancies, we excluded from the analysis cases with life-threatening fetal congenital anomalies (18 cases), all antepartum stillbirths (16) and incomplete records, regarding maternal age (18), BMI (441),

Table 3 Adjusted outcomes (individual and composite) by caesarean delivery rates outlier status

	Caesarean delivery outlier		
	Within expected	Above expected	Below expected
Maternal complications	***% (95% CI)***	***% (95% CI)***	***% (95% CI)***
Major PPH	0.20 (0.20-0.21)	0.59 (0.57-0.62)	0.37 (0.35-0.39)
Hysterectomy	0.03 (0.03-0.04)	0.09 (0.07-0.11)	0.04 (0.03-0.04)
Wound hematoma	0.32 (0.31-0.33)	0.32 (0.31-0.33)	0.33 (0.32-0.33)
TED	0.07 (0.05-0.08)	0.03 (0.03-0.03)	0.03 (0.03-0.04)
Uterine rupture	0.01 (0.01-0.01)	0.01 (0.01-0.01)	0.01 (0.01-0.01)
Life threatening composite	0.53 (0.51-0.55)	0.92 (0.89-0.94)	0.71 (0.68-0.73)
Minor PPH	1.85 (1.81-1.89)	2.71 (2.65-2.77)	2.51 (2.47-2.56)
III-IV degree tears	0.28 (0.27-0.28)	0.35 (0.34-0.36)	0.34 (0.33-0.35)
Wound Dehiscence	0.17 (0.17-0.18)	0.16 (0.15-0.17)	0.16 (0.16-0.17)
Endometritis-Infection	0.44 (0.43-0.46)	0.52 (0.50-0.54)	0.42 (0.41-0.44)
Bowel or bladder injury	0.02 (0.02-0.03)	0.03 (0.03-0.03)	0.03 (0.03-0.03)
Anaesthesiological	0.05 (0.04-0.05)	0.05 (0.04-0.05)	0.05 (0.04-0.05)
Other*	0.09 (0.08-0.10)	0.16 (0.14-0.17)	0.12 (0.11-0.13)
Non-life threatening composite	2.46 (2.42-2.51)	3.82 (3.75-3.89)	3.20 (3.15-3.25)
Overall composite	2.97 (2.92-3.02)	4.69 (4.61-4.78)	3.90 (3.85-3.96)
Neonatal complications	***% (95% CI)***	***% (95% CI)***	***% (95% CI)***
Mortality <7 days	0.03 (0.03-0.04)	0.16 (0.14-0.19)	0.11 (0.09-0.13)
Mortality <28 days	0.05 (0.05-0.06)	0.13 (0.10-0.16)	0.08 (0.06-0.10)
Neurologic symptoms	0.06 (0.05-0.07)	0.40 (0.34-0.46)	0.21 (0.18-0.24)
Life threatening composite	0.13 (0.10-0.16)	0.53 (0.44-0.62)	0.23 (0.20-0.26)
Pulmonary disorders	0.66 (0.61-0.70)	2.24 (2.08-2.39)	1.60 (1.50-1.70)
Bacterial infections	0.46 (0.42-0.49)	0.94 (0.84-1.04)	0.58 (0.54-0.61)
pH < 7.00	0.66 (0.62-0.71)	0.35 (0.33-0.37)	0.48 (0.47-0.50)
BD > 12 mmol/L	1.22 (1.19-1.26)	1.30 (1.27-1.34)	1.41 (1.38-1.44)
Apgar < 7	0.59 (0.57-0.61)	0.99 (0.89-1.09)	0.70 (0.66-0.73)
Other**	1.74 (1.57-1.91)	8.20 (7.75-8.66)	4.71 (4.46-4.95)
Non-life threatening composite	3.56 (3.33-3.79)	9.08 (8.62-9.54)	6.13 (5.88-6.37)
Overall composite	3.85 (3.67-4.02)	9.66 (9.31-10.01)	6.29 (6.10-6.48)

Footnotes. Outcomes were adjusted by maternal age, maternal body mass index, gestational age at delivery, pregnancy at risk, parity, fetal presentation, number of fetuses, presence of previous CD, neonatal birth weight, grade of urgency (e.g. maternal or fetal compromise requiring immediate delivery) and cluster variables: centers with NICU and obstetric volume per center (number of deliveries/year).
PPH, post-partum hemorrhage; TED, thromboembolic disease; BD, base deficit.
*Any other condition requiring admission to Intensive Care Unit.
**Any other condition requiring admission to Neonatal Intensive Care Unit in term neonates (37–42 weeks).

classification of pregnancy at risk (10), neonatal complications (29) and maternal complications (5). Analyses were consequently carried out on 15,189 pregnancies.

Distributions of non-missing independent variables and CD/AVD rates were similar across the analyzed and the excluded records (data not shown).

CD and AVD rates by institution ranged from 14.3% to 34.1% and from 3.9% to 10.2% (Figure 1). Four hospitals (36.4%: B, D, L and M) had adjusted CD rates above the predicted confidence interval; four centers (36.4%: A, F, H, I) were below the interval and three centers (27.2%: C, E and G) fell within the interval for their patient population. With regard to AVD, two hospitals (18.3%: G and M) had adjusted rates above the predicted confidence interval; three (27.2%: E, H, L) were below the interval, and six (54.5%: A, B, C, D, F, I) were within the interval.

Analysis of maternal and neonatal outcomes according to mode of delivery

The incidence and crude and adjusted RRs of maternal and neonatal outcomes according to mode of delivery are listed in Tables 1 and 2. Outcomes varied substantially by mode of delivery and some of them were obviously associated with only one mode of delivery (e.g. III-IV degree perineal tears). If a condition was inherent of a mode of delivery, then no comparative analysis was performed.

We assessed the outcomes by mode of delivery with bivariate and multivariate analyses in order to control for all possible confounders that can be both related to the need of an operative delivery and to the increased risk of adverse outcomes.

Considering either SVD or VD (SVD plus AVD) as the reference, CD was associated with a significantly higher risk of

Table 4 Adjusted outcomes (individual and composite) by assisted vaginal delivery rates outlier status

	Assisted vaginal delivery outlier		
	Within expected	Above expected	Below expected
Maternal complications	***% (95% CI)***	***% (95% CI)***	***% (95% CI)***
Major PPH	0.43 (0.41-0.45)	0.49 (0.47-0.51)	0.20 (0.19-0.22)
Hysterectomy	0.06 (0.05-0.07)	0.04 (0.03-0.04)	0.04 (0.03-0.05)
Wound hematoma	0.31 (0.31-0.33)	0.34 (0.33-0.36)	0.32 (0.31-0.34)
TED	0.04 (0.03-0.04)	0.03 (0.02-0.03)	0.06 (0.05-0.07)
Uterine rupture	0.01 (0.01-0.01)	0.02 (0.02-0.02)	0.01 (0.01-0.01)
Life threatening composite	0.76 (0.74-0.78)	0.80 (0.78-0.83)	0.53 (0.51-0.55)
Minor PPH	2.38 (2.34-2.42)	2.97 (2.91-3.04)	1.91 (1.86-1.95)
III-IV degree tears	0.32 (0.31-0.33)	0.39 (0.37-0.40)	0.29 (0.28-0.30)
Wound Dehiscence	0.17 (0.16-0.17)	0.15 (0.14-0.15)	0.17 (0.16-0.18)
Endometritis-Infection	0.46 (0.45-0.47)	0.46 (0.44-0.48)	0.43 (0.41-0.44)
Bowel or bladder injury	0.03 (0.03-0.03)	0.03 (0.02-0.03)	0.03 (0.02-0.03)
Anaesthesiological	0.04 (0.04-0.04)	0.05 (0.05-0.06)	0.05 (0.05-0.05)
Other*	0.13 (0.12-0.14)	0.14 (0.12-0.16)	0.10 (0.09-0.12)
Non-life threatening composite	3.22 (3.17-3.26)	3.83 (3.76-3.91)	2.45 (2.41-2.50)
Overall composite	3.96 (3.91-4.01)	4.61 (4.52-4.70)	2.97 (2.91-3.03)
Neonatal complications	***% (95% CI)***	***% (95% CI)***	***% (95% CI)***
Mortality <7 days	0.10 (0.08-0.11)	0.20 (0.17-0.23)	0.04 (0.03-0.03)
Mortality <28 days	0.07 (0.05-0.09)	0.16 (0.13-0.20)	0.06 (0.05-0.07)
Neurologic symptoms	0.19 (0.17-0.22)	0.47 (0.39-0.53)	0.05 (0.05-0.06)
Life threatening composite	0.22 (0.19-0.24)	0.65 (0.54-0.76)	0.10 (0.08-0.11)
Pulmonary disorders	1.46 (1.37-1.54)	2.65 (2.45-2.84)	0.66 (0.61-0.70)
Bacterial infections	0.55 (0.52-0.58)	1.10 (0.98-1.22)	0.43 (0.40-0.46)
pH < 7.00	0.48 (0.46-0.49)	0.36 (0.33-0.38)	0.65 (0.61-0.69)
BD > 12 mmol/L	1.31 (1.28-1.34)	1.50 (1.46-1.54)	1.26 (1.22-1.30)
Apgar < 7	0.70 (0.67-0.72)	1.03 (0.91-1.15)	0.61 (0.57-0.64)
Other**	5.04 (4.81-5.27)	7.83 (7.33-8.33)	1.65 (1.49-1.82)
Non-life threatening composite	6.34 (6.11-6.58)	9.02 (8.52-9.52)	3.37 (3.15-3.58)
Overall composite	6.52 (6.34-6.71)	9.77 (9.38-10.16)	3.52 (3.35-3.68)

Footnotes. Outcomes were adjusted by maternal age, maternal body mass index, gestational age at delivery, pregnancy at risk, parity, fetal presentation, number of fetuses, presence of previous CD, neonatal birth weight, grade of urgency (e.g. maternal or fetal compromise requiring immediate delivery) and cluster variables: centers with NICU and obstetric volume per center (number of deliveries/year).
PPH, post-partum hemorrhage; TED, thromboembolic disease; BD, base deficit.
*Any other condition requiring admission to Intensive Care Unit.
**Any other condition requiring admission to Neonatal Intensive Care Unit in term neonates (37–42 weeks).

endometritis-infection (adjusted RRs 4.74 and 4.33 respectively) and selective neonatal complications such as pulmonary disorders (adjusted RRs 2.07 and 2.12, respectively). The risk of Apgar score less than 7 at five minutes was higher in CDs than SVDs (adjusted RR 2.06), and any other condition requiring NICU admission in neonates at term occurred more frequently in CDs than VDs (adjusted 1.99). In regard to the "protective effect", CD was associated with a better composite maternal outcome for life threatening complications than VD. However the difference was not significant if the comparison considered only SVD.

When compared with SVD, AVD had a significantly higher risk of major and minor PPH (adjusted RRs 2.41 and 1.41, respectively), III-IV degree tears (adjusted RRs 2.26) and life threatening, non-life threatening and overall composite adverse maternal outcomes (adjusted RRs 2.24, 1.57 and 1.67, respectively).

As for the neonate, AVD was associated with a higher risk of mortality within 28 days (adjusted RRs 7.12), arterial cord pH less than 7.00 and base deficit greater than 12 mmol/l (adjusted RRs 7.02 and 3.28, respectively), Apgar score less than 7 at five minutes (adjusted RR 5.00), and life threatening, non-life threatening and overall composite neonatal morbidities (adjusted RRs 3.31, 1.78 and 1.92 respectively).

Multivariate Analysis of Maternal and Neonatal Outcomes According to Outlier Status

Adjusted maternal and neonatal outcomes according to the outlier status for CD and AVD are described in Tables 3 and 4, respectively.

With regard to caesarean deliveries, the "above" group had worse maternal outcomes if compared to the "within" reference group. The incidence of major and minor PPH, hysterectomy,

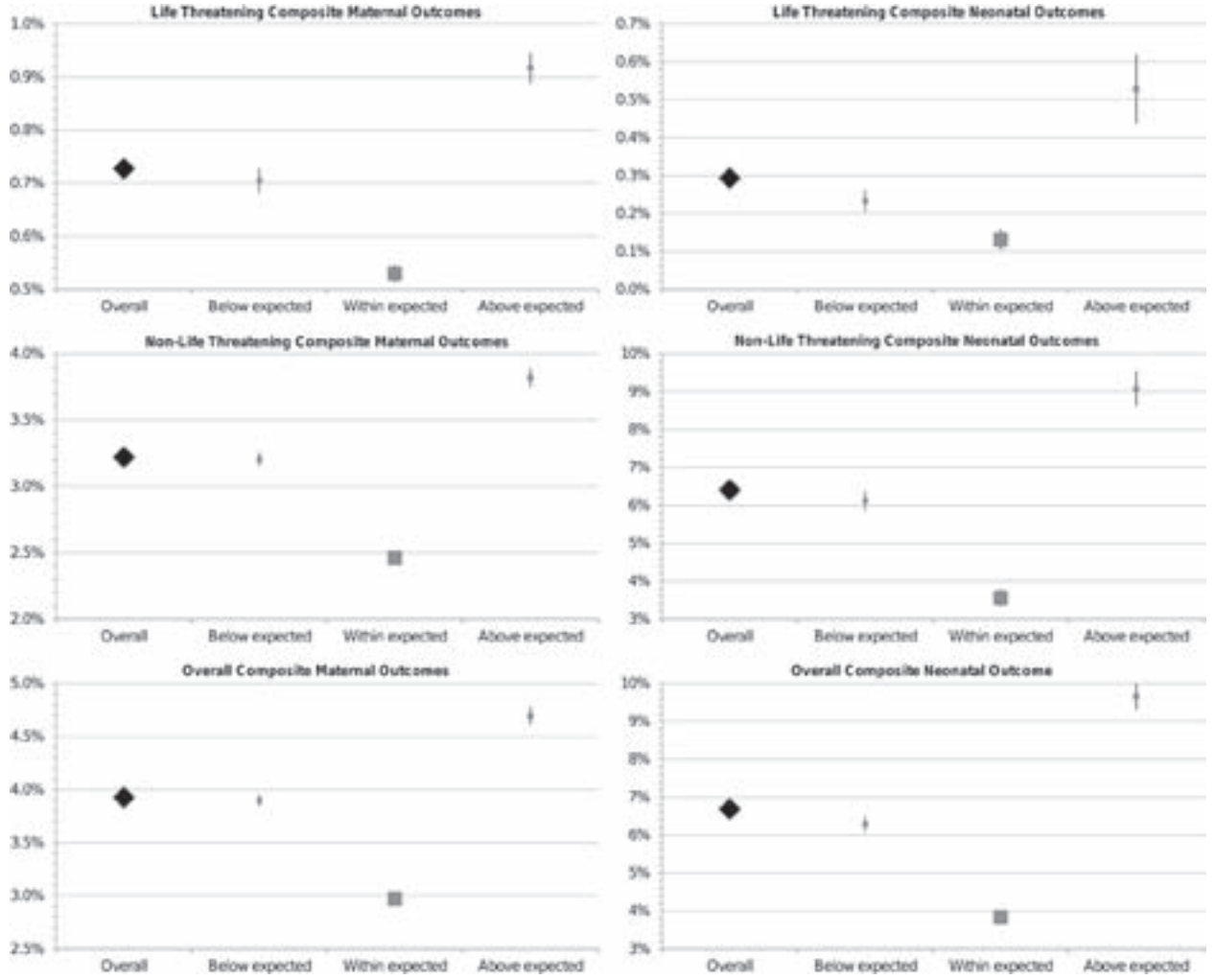

Figure 2 Forest plots of life threatening, non-life threatening and overall composite maternal and neonatal complications, by caesarean delivery rates outlier status.

III-IV degree tears, endometritis-infection, any other condition requiring admission to intensive care anaesthesiological complications, and non-life threatening unit, as well as life threatening, non-life threatening and and overall composite maternal adverse outcomes) were overall composite maternal adverse outcomes, was significantly higher in centers with above the expected CD rates. This group showed also significantly higher frequencies of almost all the neonatal complications (except for cord pH <7).

It is of interest to note that similar results were also observed in centers with CD rates below the expected (Table 3).

Higher rates of selected maternal complications (PPH, wound hematoma, uterine rupture, III-IV degree tears, anaesthesiological complications, and non-life threatening and overall composite maternal adverse outcomes) were also observed in centers with AVD rates above the expected. This group had also significantly higher rates of unfavorable neonatal outcomes for almost all the considered conditions. Inversely, institutions with an AVD rate below the expected had significantly better maternal and neonatal outcomes than the "within" AVD rates institutions (Table 4).

Discussion

There is a worldwide growing debate on quality assessment in obstetric care and this issue represents an important part of the National Health Systems (NHS) agenda [21-24].

Whether processes or outcome measures are used as markers of quality, an ideal assessment should encompass variables that are clinically relevant, easy to define and observe. Although the evaluation of CD rates – according to their adjusted rates – has been suggested as one of the most important indicators of quality, it has been criticized because of its controversial ability to capture both maternal and neonatal outcomes [8].

Our multicenter study is the first to determine the adjusted incidence of adverse maternal and neonatal outcomes according to institutional outlier status for both adjusted AVD and CD rates. We observed that both centers with CD rates above or below the expected had a higher incidence of almost all the maternal and neonatal clinically significant adverse outcomes. Moreover, centers with higher-thanexpected AVD rates showed higher incidence of complications, whereas those with a rate of AVD below the expected had a significantly lower rate of selected and composite maternal and neonatal outcomes (Figures 2 and 3).

These results are of clinical relevance. As first, both CD rates and AVD rates must be considered for a correct evaluation of the performance of every maternity unit. If assisted vaginal deliveries are not considered as part of the quality care

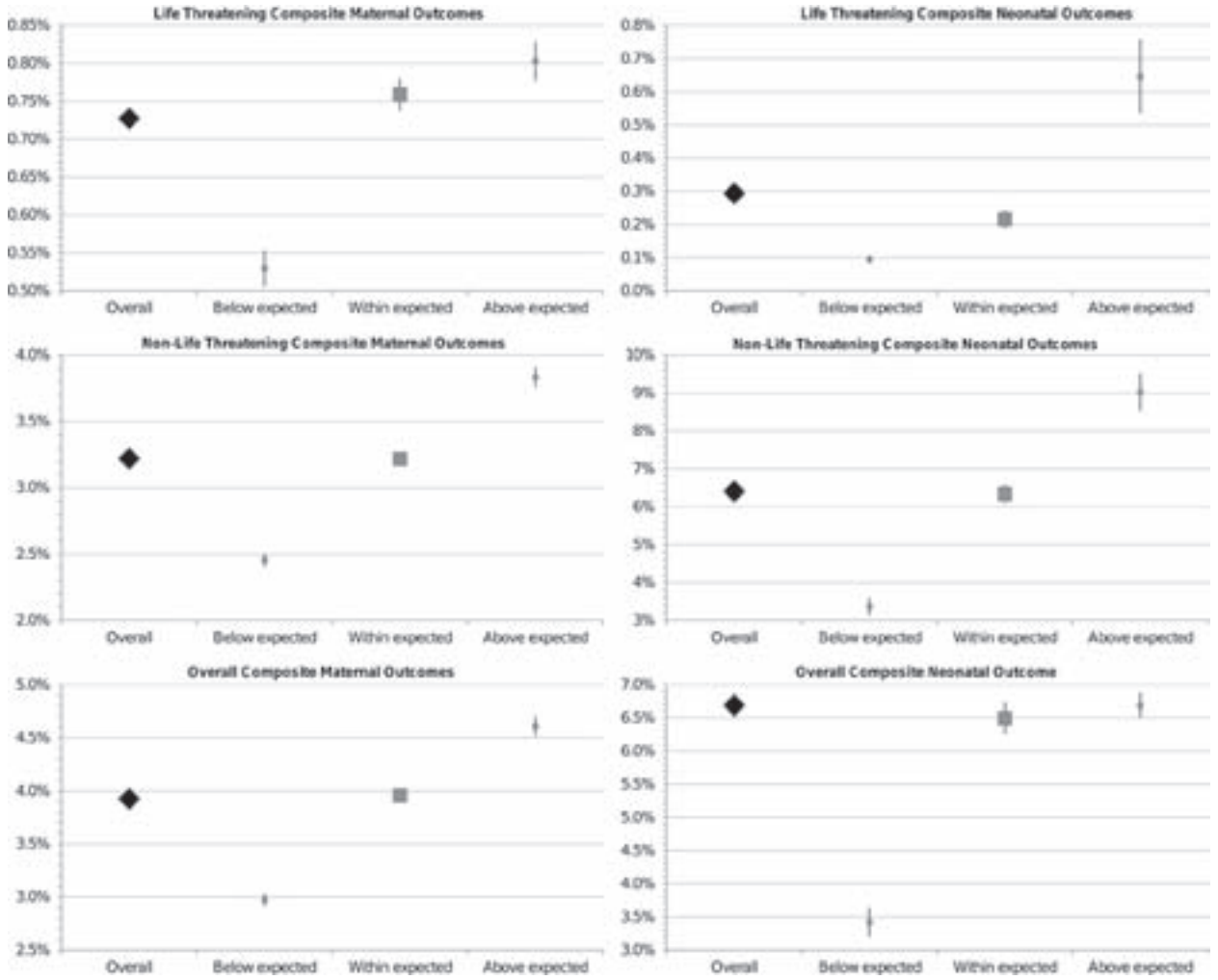

Figure 3 Forest plots of life threatening, non-life threatening and overall composite maternal and neonatal complications, by assisted vaginal delivery rates outlier status.

assessment, the evaluation can be misleading. Centers with CD rates within the expected can in fact be thought to provide a good care, while they may actually dispense less optimal levels of care if their AVD rates are found to be higher-than-expected. The status of center G represents an example: the adjusted CD rate was within the expected and thus associated with "good outcomes", but its "above" AVD rate was associated with an increased risk of complications. Second, both CD rates above and below the expected can be considered as an indicator of increased risk of maternal or neonatal morbidities. In this regard, it is clear that the best maternal and neonatal outcomes are offered by those institutions, as center E, that maintain a CD rate within the expected range and have a simultaneous low rate of AVD.

From our data, it seems that mode of delivery by itself cannot completely explain the differences in the most severe adverse maternal and neonatal outcomes as observed in different outlier status of operative deliveries.

In fact, if compared with SVD, as demonstrated in other studies [25], AVDs were associated with an increased risk of selected maternal and neonatal composite adverse outcomes. Caesarean deliveries, instead, increased only the risk of endometritis, newborn pulmonary disorders and Apgar less than 7 at five minutes.

The causal link between above and below the expected risk-adjusted CD rates and poorer maternal and especially neonatal outcomes is unclear. This relationship does not imply causality, but suggests that an association is present.

Despite the differences in study design, our results support the conclusions of Gould, Bailit, Srinivas: institutional CD rates both "above" or "below" the expected may be considered as indicators of increased risk of maternal or neonatal morbidities. Gould et al. focused their analysis only on outcomes of low risk pregnancies [5]. Bailit et al. evaluated the risk of adverse maternal and neonatal outcomes by considering only the outlier status for primary and not overall adjusted CD rates [6,7]. Srinivas et al. considered only selected measures of complications, such as maternal wound infection, postpartum hemorrhage, blood transfusion and neonatal mortality, asphyxia or seizures [8]. The main limitation of these studies was the model of risk adjusting outcomes. All of them based their analyses on retrospective collection of pregnancy data derived from birth certificates and hospital discharge records containing ICD-9 diagnoses codes. Moreover they did not consider relevant variables for risk adjustment such as, for example, maternal BMI, obstetric volume and conditions of impeding maternal or neonatal compromise. Medical records, birth certificates, diagnosis related group codes (DRG) and International Classification of Diseases - 9th Revision (ICD-9) codes are commonly used as resources for research and

quality surveillance in obstetric practice. However, these large datasets, which are usually used for other purposes such as for insurances or health statistics, often lack the information needed to homogenously risk-adjust the outcomes of interest for patient characteristics. [21,22,26,27]. Even though our study was not based on a large number of deliveries, it should be considered as one of the few in which the operative delivery rates and the incidence of maternal and neonatal complications were adjusted for unambiguous data. Information on maternal characteristics, antenatal obstetric conditions/risk factors and maternal/ neonatal outcome variables was prospectively gathered in a dedicated database that allowed us to collect standardized and homogeneous data, excluding only 3.6% of the records from the final analysis because of missing data. Nevertheless our study, by prospectively collecting information on twelve maternal and ten neonatal adverse outcome variables, provided the information that overall CD rates – not only primary – may be considered as a measure of quality of care.

In regard to the association of outlier status for CD rates and neonatal morbidity, it might be hypothesized that increased morbidity observed in the "below" CD rate group might suggest that certain infants delivered vaginally could potentially have benefited from caesarean delivery. Alternatively, in these centers, an inappropriate delayed timing in the conduction of the delivery might have resulted in a higher rate of neonatal morbidity.

The increased rate of neonatal complications observed in the "above" CD rate group might be explained considering that the selection process in this group, though leading to more caesarean deliveries, failed to consider many cases that might have benefited from the caesarean delivery [5].

Moreover, strategies for managing labor and organizational models may vary between institutions and these might account for both different incidences of adverse outcomes and operative delivery rates [23,24,28].

Walsh et al. observed that both AVDs and CDs in the second stage of labor are associated with a similar increased risk of serious neonatal complications [29]. In our context, we may suppose that any inappropriate anticipation of an obstetric intervention in the second stage of labor, without respecting its "physiological" duration or without managing second stage according to the recommended guidelines, might increase the rate of both caesarean and operative deliveries and worsen the obstetric outcomes [22,24,28].

The literature does not clarify whether the hospital delivery volume might influence both the rate of operative deliveries and of maternal and neonatal complications [18-20,30]. In this regard, it is possible that smaller units might have a lower threshold for operative deliveries due to organizational reasons and lack of resources required to respond to medical emergencies. For the same reasons, these institutions could also present worse outcomes. This might not be the case of our study, because inter institutional variations in operative delivery rates and frequencies of adverse outcomes remained either between centers with less than 1000 deliveries/year and institutions with more than 1000 deliveries/year, despite the inclusion of obstetric volume, of type of neonatal organization (NICU availability) and delivery grade of urgency (emergency – no emergency) into the adjusted model. As suggested by Janakiraman et al., it might be that the increased risk of maternal and neonatal complications could be related to hospital performance, independently from delivery volumes [20].

Despite the clinically relevant conclusions, we are aware that our study has its limitations. First, we did not consider separately every antenatal risk factor, labeling the pregnancy as "at risk" according to selected groups of risk conditions. However, other studies adopted this classification considering that a successful model for adjusting assisted delivery rates should consider the most relevant risk factors that must be acceptable to practicing obstetricians [21-23,31]. Second, we did not include other variables, such as race/ethnicity or socioeconomic status or habits (e.g. smoking), in the risk adjustment. However, the former was not assessed because of the very low prevalence of non-Caucasians in our region and considering this variable should not have a relevant role in the prediction of operative delivery [32]; the latter was not considered because the collected data included all the clinical adverse conditions that are associated with "bad" habits (e.g. intrauterine growth restriction, preterm delivery). Third, there is no wide agreement on which indicators of outcome need to be evaluated to assess obstetric quality. In this regard, we considered the short term clinically meaningful indicators that are included in the Agency for Health Care Research and Quality report, in the Adverse Outcome Index and in the recent model proposed by Sibanda et al. on behalf of the Royal College of Obstetricians and Gynaecologists [33-36]. Finally, a further limitation of our study was the inability to assess what factors contributed to adverse outcomes in the outlier settings. In this context caesarean and assisted vaginal deliveries might reflect the differences to a selected processes of care (e.g. training, adherence to guidelines) that might explain inter-institutional variation of outcomes [30]. Nonetheless the aim of our study was not to measure the process of care, but to evaluate whether variations of both CD and AVD rates among institutions could explain differences in outcomes.

Conclusions

Our results support the belief that evaluating the CD rates without taking into account the AVD rates might not provide a reliable view of obstetric performance. In this context, the case-mix adjustment for a complete and standardized set of variables and the knowledge of the outlier status for both assisted vaginal and caesarean deliveries are crucial to properly assess the level of care among institutions, giving the opportunity to modify the management and improve the outcomes [4,37].

However we are aware that more research is required to develop a consensus about accepted, reproducible and clinically relevant indicators of maternal and neonatal outcomes that need to be evaluated in the process of labor audit [38].

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Contribution of Prepregnancy Body Mass Index and Gestational Weight Gain to Caesarean Birth in Canada

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Abstract

Background: Overweight and obese women are known to be at increased risk of caesarean birth. This study estimates the contribution of prepregnancy body mass index (BMI) and gestational weight gain (GWG) to caesarean births in Canada.

Methods: We analyzed data from women in the Canadian Maternity Experiences Survey who had a singleton term live birth in 2005-2006. Adjusted odds ratios for caesarean birth across BMI and GWG groups were derived, separately for nulliparous women and parous women with and without a prior caesarean. Population attributable fractions of caesarean births associated with above normal BMI and excess GWG were calculated.

Results: The overall caesarean birth rate was 25.7%. Among nulliparous and parous women without a previous caesarean birth, rates in obese women were 45.1% and 9.7% respectively, and rates in women who gained above their recommended GWG were 33.5% and 8.0% respectively. Caesarean birth was more strongly associated with BMI than with GWG. However, due to the high prevalence of excess GWG (48.8%), the proportion of caesareans associated with above normal BMI and excess GWG was similar [10.1% (95% CI: 9.9-10.2) and 10.9% (95% CI: 10.7-11.1) respectively]. Overall, one in five (20.2%, 95% CI: 20.0-20.4) caesarean births was associated with above normal BMI or excess GWG.

Conclusions: Overweight and obese BMI and above recommended GWG are significantly associated with caesarean birth in singleton term pregnancies in Canada. Strategies to reduce caesarean births must include measures to prevent overweight and obese BMI prior to conception and promote recommended weight gain throughout pregnancy.

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Background

The prevalence of overweight and obesity, defined as a body mass index (BMI) of 25-29.9 kg/m2 and ≥ 30 kg/m2 respectively, has been increasing globally [1]. In Canada, based on measured height and weight, the prevalence of obesity among adult women rose from 16% in 1978 to 23% in 2004 [2]. Correspondingly, rates of obesity are also increasing among pregnant women. Overweight and obese women are known to be at increased risk of serious pregnancy complications including caesarean birth [3-6]. These caesarean births in turn increase women's risk of infection, haemorrhage, damage to the intestines or bladder, and negatively affect early parenting outcomes [7-9]. Caesarean births also increase the risk of long-term complications such as abnormal placentation during subsequent pregnancies and place excess strain on the healthcare system [7,10,11]. Canadian caesarean birth rates rose from 18% in 1995-1996 to 28% in 2010-2011 [12,13].

The concomitant increase in overweight and obesity and caesarean births make it important to study to what degree maternal weight is contributing to these births. During pregnancy, maternal weight is a product of both prepregnancy body mass index (BMI), hereafter referred to as BMI, and gestational weight gain (GWG). Estimating the magnitude of the independent as well as joint association between these determinants and caesarean births is essential for designing interventions that promote healthy pregnancy outcomes. However, to date, few studies have quantified the proportion of caesarean births at the population level that are associated with above normal BMI [14-16] and no studies have quantified the proportion associated with excess GWG. Data from the Canadian Maternity Experiences Survey provided a unique opportunity to address this issue for Canada.

Methods

Study population

This study used data from the Public Health Agency of Canada's Canadian Maternity Experiences Survey (MES). The MES was a cross-sectional survey of a stratified random sample of women who had a singleton live birth in Canada between November 2005

and May 2006. Women were identified using recent births drawn from a Census-based sampling frame. Women were eligible for the study if they were at least 15 years of age and were living with their infant at the time of data collection. Women living on First Nations reserves or in institutions were excluded. Data were collected by female interviewers between October 2006 and January 2007 using a computer-assisted telephone interview application. The majority (97%) of interviews were conducted between five and nine months postpartum. Out of 8,244 eligible women, 6,421 (78%) agreed to participate. In consideration of the sample design and non-participation, each MES record was assigned a sampling weight. The 6,421 respondents were thus weighted to represent 76,508 women nationally who had a singleton live birth between November 2005 and May 2006. Survey questions covered a broad range of pregnancy, birth and postpartum experiences. All data were based on women's reports. Detailed information on the survey's development, methodology and content has been reported elsewhere [17].

We excluded women with missing information on BMI or GWG (n = 79), as these were the principal determinants of interest. Mode of birth information was complete. We also excluded preterm births (< 37 weeks gestation) (n = 568) and women who were less than 18 years old (n = 183), as the BMI classification used was derived for ages 18 and older. These exclusions resulted in a final sample of 5,591 women weighted to represent 67,058 women.

Outcomes

The primary outcome was caesarean birth (planned and unplanned). Caesarean births were classified as planned if the decision about the mode of birth was made before the woman went into labour.

Determinants

Prepregnancy BMI and GWG were the principal exposures of interest. They were derived from the following questions:

i) How tall are you without shoes on?
ii) Just before your pregnancy, how much did you weigh?
iii) How much weight did you gain during your pregnancy?

We categorized women according to the World Health Organization (WHO) standard as either being underweight (BMI < 18.5 kg/m2), normal weight (18.5 ≤ BMI < 25), overweight (25 ≤ BMI < 30) or obese (BMI ≥ 30). Women were also classified according to the Institute of Medicine's recommended GWG ranges (Table 1) [18], as having gained above, within or below the recommended weight for their BMI.

Covariates

We studied additional reproductive, health care, sociodemographic and psychosocial characteristics as potential confounders of the association between BMI, GWG and mode of birth. Birthweight-for-gestational-age was derived using a Canadian reference to categorize infants below the standard 10th percentile as small-forgestational age (SGA) and those above the standard 90th percentile as large-for-gestational age (LGA) [19]. Sociodemographic variables assessed included the household's low income cut-off level (LICO), which is a measure of the income threshold below which a family will likely spend 20 percentage points more than the average family on food, shelter and clothing [20]. Ethnicity was based on mother's country of birth, grouped according to world regions; mothers born in Canada were categorized as Aboriginal off-reserve and non-Aboriginal. The MES questions for variables whose definitions are not self-evident are indicated in Table 2. Categorizations (for non-dichotomized variables) used in analyses are indicated in Table3in theresults section.

Table 1 Gestational weight gain (GWG) recommendations

Prepregnancy BMI (kg/m^2)	Recommended GWG (kg)
Underweight: BMI < 18.5	12.5 - 18.0
Normal weight: 18.5 ≤ BMI < 25	11.5 - 16.0
Overweight : 25 ≤ BMI < 30	7.0 - 11.5
Obese: BMI ≥ 30	5.0 - 9.0

Statistical analysis

Percentages were used to report observed distributions of BMI and GWG across maternal characteristics. We calculated adjusted odds ratios (ORs) for having a caesarean birth using multivariable logistic regression. With the exception of maternal age, all variables were treated as categorical in regression models. Records with missing values for covariates other than LICO were excluded from models (< 4%). Due to a larger number of missing LICO values (8.0%), a missing category was included for this variable. We calculated ORs across BMI and GWG groups for caesarean births overall as well as for unplanned and planned caesarean births. Normal BMI and within recommended GWG were the reference groups.

BMI and GWG were included in all multivariable models in order to estimate their independent associations (ORs) with caesarean birth. Other covariates were selected into models purposefully using the following steps [21]. Based on the Wald test from univariable logistic regression models, we initially included any variable with a p-value below 0.25. Covariates were then removed from the model if they were statistically nonsignificant and not a confounder. Significance was evaluated at the 0.05 level and confounding as a change of 15% or higher in the effect of BMI or GWG on the mode of birth outcome being modeled. To address significant interaction between parity, prior caesarean, BMI, GWG and mode of birth, we stratified our analysis into three subgroups: nulliparous, parous without previous caesarean and parous with previous caesarean. As health problems before or during pregnancy and a health care provider trying to induce labour may be on the causal pathway between BMI, GWG and mode of birth, we assessed results from models with and without these variables.

The contribution to caesarean births of overweight or obese BMI and more than recommended GWG was estimated using population attributable fractions (PAFs). The calculation of PAFs has the advantage of incorporating the increased risk due to high BMI or GWG and the prevalence of these two determinants, in order to provide an estimate of the potential reduction in caesarean birth if high BMI and GWG were eliminated. We calculated PAFs directly from our multivariable logistic regression models using the sequential and average attributable fraction method which takes into account that ORs are adjusted for confounders [22].

All analyses were carried out using sampling weights. We calculated variances using bootstrap weights to capture the variability introduced by the sample design and weighting adjustments [23]. We used SAS EG software, Version 5.1, copyright SAS Institute Inc. [24]. Review by an ethics board was

Table 2 Definitions of selected covariates

Variable	MES question
Reproductive/health care factors	
Health care provider started labour	*Did your healthcare provider try to start or induce your labour by the use of medication or some other technique?*
Prepregnancy health problems	*Before your pregnancy, did you have any medical conditions or health problems that required you to take medication for more than 2 weeks, have special care or extra tests during your pregnancy?*
During pregnancy health problems	*During your pregnancy, did you develop any new medical conditions or health problems that required you to take medication for more than 2 weeks, have special care or extra tests?*
Antenatal care provider	*From which type of healthcare provider, such as an obstetrician, family doctor or midwife, did you receive most of [your prenatal] care?*
Psychosocial factors	
Support	*During your pregnancy, how often was support available to you when you needed it?* None/a little/some/most/all of the time.
Stressful life events	High stress was defined as experiencing 3 or more of the following 12 events in the year before the birth: *close family member hospitalized, move to a new address, homelessness, woman or partner lost job, woman or partner went to jail, more than usual arguments with partner, partner not wanting pregnancy, separation or divorce, bills that could not be paid, a physical fight, someone close having a problem with alcohol or drugs, someone close dying.*
History of depression	*Before your pregnancy, had you ever been prescribed anti-depressants or been diagnosed with depression?*

not required, as the MES data are anonymous and this study did not generate identifying information.

Results

The prevalence of overweight and obese BMI was 20.9% and 13.3% respectively. Almost one-half (48.8%) of women gained above the recommended weight for their BMI. The two determinants were strongly associated with each other; 60.3% of obese versus 30.2% of underweight women gained more than the recommended weight and 12.2% of obese versus 24.8% of underweight women gained less than the recommended weight. The distribution of covariates within BMI and GWG groups is shown in Table 3.

Association between caesarean birth and prepregnancy BMI and GWG

The overall caesarean birth rate was 25.7%, with substantial variation across parity and prior caesarean group strata. Among nulliparous women, parous women with no prior caesarean and parous women with a prior caesarean, caesarean birth rates were 29.6%, 5.8% and 80.2% respectively. Among nulliparous and parous women without a previous caesarean, rates in obese women were 45.1% and 9.7% respectively, and rates in women who gained above their recommended GWG were 33.5% and 8.0% respectively (Table 4). The incidence of caesarean births increased in all groups as BMI and GWG increased, except for GWG among parous women with a prior caesarean. In this group the trend was reversed; but adjusted ORs were not significantly different (Table 4). The high caesarean birth rates (above 75%) in parous women with a prior caesarean and low rates (below 10%) in parous women with no prior caesarean limited the scope for detecting significant decreases or increases in risk in these groups.

The adjusted risk of caesarean birth did not differ significantly between underweight and normal-weight women; it also did not differ significantly between women who gained less than the recommended amount and those who gained within the recommended amount (Table 4). The risk was significantly elevated among women who were overweight (OR = 1.23 [1.04-1.47]), obese (OR = 1.95 [1.61-2.36]), or had gained more than the recommended amount (OR = 1.36 [1.17-1.59]). Among nulliparous women who were overweight, obese or above their recommended GWG, the overall risk of caesarean birth was increased, with most of the increase attributable to unplanned caesareans. Among parous women with no prior caesarean, the risk of caesarean birth was low, but significantly elevated among those who were obese (OR = 2.03 [1.17-3.53]) or above their recommended GWG (OR = 1.75 [1.13-2.71]). There was no significant relationship between caesarean births and BMI or GWG among women with a previous caesarean (Table 4). Adjusting for women's reports that their health care provider tried to induce labour, or that they experienced health problems before or during pregnancy, did not significantly change these risk patterns (data not shown).

Population attributable fractions of caesarean births associated with BMI and GWG

The fractions of caesarean births associated with overweight or obese BMI and more than recommended GWG are presented in Table 5. Among all women, 10.1% (9.9-10.2) of caesareans were associated with overweight or obese BMI and 10.9% (10.7-11.1) were associated with above recommended GWG. One in five caesareans (20.2% [20.0-20.4]) was associated with either above normal BMI or excess GWG. Results were similar for nulliparous women. In parous women with no previous caesarean, the proportion of caesareans associated with above recommended GWG was twice that of overweight or obese BMI (23.6% [23.0-24.2] versus 10.9% [10.4-11.4]). Almost one third (31.8% [31.3-32.4]) of caesarean births in this group were associated with either above normal BMI or excess GWG.

Discussion

The nationally representative nature of the MES allowed us to estimate PAFs of caesarean births associated with overweight and obese BMI and above recommended GWG. We found that

Table 3 Distribution (%) of covariates across prepregnancy body mass index (BMI) and gestational weight gain (GWG) categories*

	Prepregnancy BMI				Recommended GWG		
	Under-weight	Normal weight	Over-weight	Obese	Below	Within	Above
Percent of study sample	5.9	60.0	20.9	13.3	18.1	33.1	48.8
Reproductive/health care factors							
Maternal age at birth**							
≤24	27.3	14.7	13.5	14.3	14.5	11.9	17.5
25-29	29.4	33.8	34.8	38.0	32.0	33.8	35.5
30-34	30.2	33.3	34.3	32.8	32.3	35.9	31.8
≥35	13.2	18.2	17.4	15.0	21.2	18.3	15.2
Nulliparous	50.3	47.5	37.8	40.6	39.6	41.2	49.0
Birthweight-for-gestational age†							
SGA	17.0	8.2	7.4	6.2	13.6	8.6	6.1
AGA	78.2	85.2	78.4	77.0	81.0	81.6	79.5
LGA	4.7	9.6	14.2	16.8	5.4	9.8	14.4
Health care provider started labour‡	36.6	42.5	47.6	58.9	41.1	41.6	49.3
Prepregnancy health problems	14.1	12.7	16.7	19.3	15.2	14.3	14.3
During pregnancy health problems	17.3	22.3	23.2	32.7	27.1	22.2	23.0
Antenatal care provider							
Obstetrician/ gynaecologist	59.0	58.6	56.6	60.2	61.1	58.9	57.1
General practitioner	36.0	34.2	36.5	35.7	33.1	34.4	36.0
Midwife/nurse	5.0	7.3	6.9	4.2	5.8	6.7	6.9
Sociodemographic factors							
Low-income-cut-off							
≤LICO	29.7	15.8	18.5	21.0	19.8	16.3	18.2
>LICO	57.6	76.3	73.6	72.3	72.5	75.5	73.8
Missing	12.7	7.9	7.9	6.7	7.7	8.2	8.0
Education							
Less than high school	14.4	5.5	6.6	8.2	6.5	4.5	8.1
High school graduate	21.7	17.5	20.6	24.6	18.3	19.0	20.0
Post-secondary diploma	31.8	36.2	39.3	43.2	37.6	35.7	38.8
University graduate	32.1	40.8	33.4	24.0	37.6	40.9	33.2
Region/province							
Atlantic	3.4	4.8	7.2	9.2	3.9	5.4	6.7
Quebec	25.6	24.8	25.3	20.5	24.4	26.2	23.1
Ontario	40.7	38.7	34.5	40.3	39.1	37.8	38.0
Prairies	17.6	18.0	22.0	20.3	18.6	18.0	20.0
British Columbia	12.6	13.4	10.5	9.12	13.5	12.1	11.7
Territories	0.1	0.4	0.5	0.6	0.6	0.4	0.4
Urban residence	87.2	82.5	80.4	79.6	84.9	82.3	80.7
Ethnicity (country of birth)							
Canada/Aboriginal off-reserve	2.4	3.4	4.4	6.1	2.5	2.7	5.3
Canada/non-Aboriginal	57.2	71.0	77.7	78.8	65.5	72.5	75.4
Europe/Western	4.7	7.1	4.0	4.8	6.3	5.9	5.9
Africa/Mid East/Latin	10.6	7.3	7.7	5.1	10.2	7.9	5.8
East/South Asia/Pacific	25.2	11.2	6.2	5.4	15.5	11.1	7.6
Married††	84.2	93.1	93.0	89.2	92.3	93.9	90.6
Psychosocial factors							
No/some social support	12.6	12.3	12.8	14.5	14.0	12.6	12.3
3+ stressful events	22.3	15.2	16.3	21.4	15.0	15.3	18.2
History of depression	14.6	13.4	16.4	22.5	15.0	13.7	16.5
Smoked 3rd trimester	15.0	9.1	10.2	12.2	10.4	8.2	11.2
Drank alcohol in pregnancy	8.2	12.4	10.1	8.0	10.4	12.4	10.5

*Some columns do not sum to 100% due to rounding. **Regression models used continuous age variable. †SGA: small-for-gestational-age, AGA: average-for-gestational-age, LGA: large-for-gestational-age. ‡Among women who attempted vaginal birth. ††Married or common law.

Table 4 Crude risks (%) and adjusted* odds ratios (ORs) for caesarean birth, by parity and previous caesarean status

	Caesarean birth		Unplanned caesarean		Planned caesarean	
	%	OR (95% CI)	%	OR (95% CI)	%	OR (95% CI)
All women						
Underweight	20.9	1.01 (0.74,1.38)	8.3	0.82 (0.52,1.29)	12.6	1.25 (0.82,1.91)
Normal weight	22.9	1	11.0	1	11.9	1
Overweight	28.3	**1.23 (1.04,1.47)**	13.5	**1.38 (1.08,1.76)**	14.8	1.10 (0.88,1.37)
Obese	36.8	**1.95 (1.61,2.36)**	19.1	**2.29 (1.77,2.96)**	17.6	**1.45 (1.13,1.85)**
GWG < recommended	20.1	0.89 (0.71,1.10)	7.6	0.77 (0.56,1.06)	12.4	0.99 (0.75,1.30)
GWG = recommended	22.8	1	10.3	1	12.6	1
GWG > recommended	29.8	**1.36 (1.17,1.59)**	15.7	**1.40 (1.12,1.74)**	14.1	**1.23 (1.01,1.51)**
Nulliparous						
Underweight	22.3	0.96 (0.62,1.50)	12.9	0.76 (0.45,1.27)	9.4	1.53 (0.70,3.34)
Normal weight	25.9	1	19.7	1	6.2	1
Overweight	34.9	**1.37 (1.05,1.78)**	27.4	**1.36 (1.02,1.81)**	7.5	1.18 (0.75,1.85)
Obese	45.1	**2.29 (1.72,3.06)**	37.7	**2.41 (1.78,3.25)**	7.3	1.13 (0.63,2.03)
GWG < recommended	23.6	0.87 (0.64,1.19)	15.4	0.79 (0.54,1.15)	7.9	1.08 (0.63,1.84)
GWG = recommended	25.9	1	19.5	1	6.4	1
GWG > recommended	33.5	**1.35 (1.08,1.70)**	26.9	**1.43 (1.12,1.84)**	6.6	0.98 (0.66,1.48)
Parous, no prior caesarean						
Underweight	3.5	0.84 (0.22,3.17)	2.6	1.41 (0.29,6.89)	0.9	0.37 (0.01,13.96)
Normal weight	4.8	1	2.1	1	2.7	1
Overweight	6.6	1.01 (0.61,1.69)	4.2	1.38 (0.71,2.71)	2.4	0.66 (0.27,1.61)
Obese	9.7	**2.03 (1.17,3.53)**	5.3	**2.26 (1.04,4.87)**	4.4	1.73 (0.78,3.83)
GWG < recommended	3.4	0.79 (0.40,1.57)	1.0	0.45 (0.13,1.56)	2.4	1.20 (0.48,3.02)
GWG = recommended	4.5	1	2.5	1	2.0	1
GWG > recommended	8.0	**1.75 (1.13,2.71)**	4.4	1.75 (0.96,3.20)	3.5	1.68 (0.85,3.32)
Parous, prior caesarean						
Underweight	77.3	1.37 (0.43,4.36)	6.9	1.13 (0.06,20.79)	70.4	1.26 (0.43,3.65)
Normal weight	77.9	1	5.9	1	72.1	1
Overweight	84.3	1.53 (0.85,2.77)	8.0	1.67 (0.61,4.62)	76.3	1.18 (0.69,2.01)
Obese	82.3	1.50 (0.77,2.91)	9.7	2.01 (0.71,5.66)	72.7	1.08 (0.62,1.91)
GWG < recommended	82.2	1.14 (0.57,2.29)	8.5	1.22 (0.39,3.79)	73.7	1.05 (0.55,2.00)
GWG = recommended	80.0	1	7.6	1	72.4	1
GWG > recommended	79.8	1.03 (0.62,1.71)	6.4	0.76 (0.29,1.96)	73.4	1.14 (0.71,1.81)

[Statistically significant values are bolded.]
*All women: BMI models adjusted for GWG and GWG models adjusted for BMI; also adjusted for maternal age, parity, weight-for-gestational age, prepregnancy health problems, antenatal care provider, low-income-cut-off, educational attainment, province of residence, ethnicity, support, stress and history of depression. Parity/previous caesarean subgroups: adjusted for same covariates, except parity.

one in five (20.2%) caesarean births was associated with above normal BMI or excess GWG. Overall, a similar proportion of caesareans births was associated with above normal BMI and excess GWG (10.1% and 10.9%, respectively), but these proportions varied substantially with parity and previous caesarean e.g. from 25.7% to 20.6%. There is no consensus on an status. As expected, the incidence of caesarean births in- optimal caesarean rate. However, a rate of 20.6% in creased with increasing BMI and GWG, with a stronger singleton term pregnancies would bring the overall caeassociation with unplanned caesarean births. Although sarean rate closer to the 5%-15% range suggested by causality cannot be inferred due to the observational WHO [25]. nature of our data, it is noteworthy that in principle, Few previous studies have calculated the PAF of caeif the caesarean births associated with BMI and GWG sareans due to maternal weight. Lu et al. attributed were eliminated, Canada's caesarean rate among single-11.6% of caesareans in Alabama in 1995-1999 to obesity ton term pregnancies could be reduced by up to a fifth, (> 29.0 kg/m2) at the first prenatal visit, an increase from 3.9% in 1980-1984 [14]. A Utah study attributed 38.8% of caesareans in 2001 to overweight or obesity at the time of birth thus also taking into account GWG [15]. Our PAF for overweight and obesity combined (10.1%) was similar to Lu et al.'s value for obesity alone, suggesting that a lower fraction of caesareans was attributable to high maternal weight in Canada in 2005-2006 compared to Alabama in 1995-1999. This is likely in part due to a lower Canadian prevalence of obesity (13.3%) than in Alabama (36.4%). Comparing our results to those in Utah is complicated by their use of maternal weight at birth as the determinant rather than BMI and recommended

Table 5 Adjusted* population attributable fractions (PAFs) of caesarean births associated with overweight or obese prepregnancy body mass index (BMI) or above recommended gestational weight gain (GWG)

	PAF (%, 95% confidence interval)			
	All women	**Nulliparous**	**Parous, no prior caesarean**	**Parous, prior caesarean**
Overweight or obese (BMI ≥ 25)	10.1 (9.9, 10.2)	11.1 (10.9, 11.2)	10.9 (10.4, 11.4)	3.3 (3.2, 3.5)
GWG > recommended	10.9 (10.7, 11.1)	10.7 (10.5, 10.9)	23.6 (23.0, 24.2)	0.3 (0.1, 0.4)
Overweight or obese (BMI ≥ 25) or GWG > recommended	20.2 (20.0, 20.4)	21.1 (20.9, 21.3)	31.8 (31.3, 32.4)	3.6 (2.4, 3.8)

*All women: BMI models adjusted for GWG and GWG models adjusted for BMI; also adjusted for maternal age, parity, weight-for-gestational age, prepregnancy health problems, antenatal care provider, low-income-cut-off, educational attainment, province of residence, ethnicity, support, stress and history of depression. Parity/previous caesarean subgroups: adjusted for all previous covariates except parity.

GWG. This methodological difference along with possible differences in the maternal weight distribution and obstetric practice in Utah and Canada may explain the much higher PAF observed in that study.

It is also noteworthy that compared to overweight and obese BMI, a similar proportion of caesarean births was associated with excess GWG due to the high prevalence of above recommended GWG. The additional risk posed by GWG was attenuated among parous women with previous caesarean births at high risk of repeat caesarean births, while it was magnified among parous women without a previous caesarean birth at low risk of caesareans. Among parous women without a prior caesarean birth the overall rate of caesarean birth was less than half the population rate; however, twice as many caesarean births were associated with above recommended GWG compared to overweight or obese BMI (23.6% versus 10.9%). Unfortunately, few women report being counselled about GWG [26]. This represents a missed opportunity for prevention, since health care providers are likely more able to impact GWG than BMI, as few women seek preconceptional care but most receive prenatal care within the first trimester [27].

Our study has some limitations. Although self-reported data on BMI and GWG are highly correlated with measured values, they tend to underestimate these values [28,29]. This could have resulted in overestimated associations between BMI, GWG and caesarean births [28]. Additionally, some residual confounding likely remains as we were unable to consider unmeasured factors. Data on indications for caesarean births would have increased our understanding of studied associations [30]. We were also not able to adjust for weight-related clinical conditions such as pre-eclampsia and diabetes, though there is some uncertainty about the degree to which such conditions are on the causal pathway, and should therefore not be adjusted for [4]. In addition, we made multiple comparisons which increases the chance of significant findings [31]; however, the associations noted in the results are plausible and we reported precise confidence intervals to support interpretation.

Conclusions

In summary, our study found that one in five caesarean births in singleton term pregnancies in women 18 years and older was associated with above normal BMI or excess GWG, and this proportion is likely to increase as the prevalence of overweight and obesity rises. Nulliparous women with above normal BMI and excess GWG are at particular risk for unplanned caesareans. Strategies to reduce caesarean births in Canada must include measures topreventoverweightandobeseBMI priortoconception and promote recommended weight gain throughout pregnancy.

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blood tests to determine whether a newborn has jaundice. Not only were these processes far from accurate, but they would cause a lot of anxiety for parents and discomfort to newborns. The rise of non-invasive transcutaneous bilirubin testing (TcB) changed the way hospitals identified at-risk infants. Dräger's new JM-105 is one of the most advanced transcutaneous monitoring products available, measuring the yellowness of subcutaneous tissue in newborns as young as 35-weeks' gestational age. Providing instantaneous screening of bilirubin results, JM-105 also reduces the risk of infections: JM-105 is non-invasive; its sensor is gently pressed to a newborn infant's forehead while in a hospital; alternatively for babies 14 days of age at physician offices, measurements can be taken from the breastbone to obtain a bilirubin reading. Without the need to draw blood, the JM-105 can help to reduce the risk of infection. It also lessens readmission and length of stays: Bilirubin levels typically peak two-to-four days after birth – after most newborns have gone home. Due to this, jaundiced children are often readmitted for treatment. JM-105 detects at-risk newborns well before they leave the hospital, ensuring immediate treatment and, ultimately, reducing readmission and length-of-stay rates. Eliminates human error: Nurses or physicians can scan, measure, save and transfer patient data right from the device – eliminating time-consuming, manual transcription that often leads to human error. Enables faster decision-making: With quick access to patient data in one place, physicians and nurses can make faster treatment decisions based on accurate, timely information. Creates cost-effective testing practices: JM-105 reduces the frequency of costly lab tests and because it has a reusable probe, it eliminates the need for expensive disposables.

Treat Very Premature Babies More Aggressively

A new study out of the University of Iowa is encouraging more aggressive treatment of very premature babies. The study, of thousands of premature births, found that a tiny minority of babies born at 22 weeks who were medically treated survived with few health problems, although the vast majority died or suffered serious health issues. Leading medical groups had already been discussing whether to lower the consensus on the age of viability, now cited by most medical experts as 24 weeks. The study, one of the largest and most systematic examinations of care for very premature infants, found that hospitals with sophisticated neonatal units varied widely in their approach to 22-week-olds, ranging from a few that offer no active medical treatment to a handful that assertively treat most cases with measures like ventilation, intubation and surfactant to improve the functioning of babies' lungs. The study, involving nearly 5,000 babies born between 22 and 27 weeks gestation, found that 22-week-old babies did not survive without medical intervention. In the 78 cases where active treatment was given, 18 survived, and by the time they were young toddlers, seven of those did not have moderate or severe impairments. Of the 755 born at 23 weeks, treatment was given to 542. About a third of those survived, and about half of the survivors had no significant problems.

Differences in Immunoreactive Trypsin Values Between Type of Feeding and Ethnicity in Neonatal Cystic Fibrosis Screening: A Cross-Sectional Study

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Abstract

Background: We studied the differences in immunoreactive trypsin (IRT) in neonatal screening for cystic fibrosis (CF) associated individually with the age of the newborn, ethnicity and environmental temperature. In this study, we determine the overall influence of environmental temperature at birth, gender, feeding, gestational age, maternal age and ethnic origin on an abnormal IRT result.

Methods: Cross-sectional observational study. A sample was selected of newborns from Alicante (Spain) who underwent neonatal CF screening in 2012–2013. Primary variable: abnormal IRT levels (≥65 ng/ml). Secondary variables: gender, maternal origin, maternal age (years) (<20, 20–40, >40), gestational age (weeks) (<32, 32–37, >37), type of feeding (natural, formula, mixed and special nutrition), >20 days from birth to blood collection, and average temperature during the month of birth (in¡C). Using a multivariate logistic regression model the adjusted odds ratios (ORs) were estimated to analyze the association between atypical IRT levels and the study variables. The α error was 5% and confidence intervals (CI) were calculated for the most relevant parameters.

Results: Of a total of 13,310 samples, 199 were abnormal (1.34%). Significant associated factors: feeding method (natural → OR = 1; mixed → OR = 0.53, 95% CI: 0.31-0.89; formula → OR = 0.72, 95% CI: 0.48-1.07; special → OR = 21.88, 95% CI: 6.92-69.14; p < 0.001).

Conclusions: Newborns receiving special nutrition have a 20-fold higher risk for abnormal IRT levels, and screening is advisable once normalized feeding is initiated. It is advisable to consider ethnic variability. Seasonality was not important.

Background

Cystic fibrosis (CF) is one of the rare diseases for which newborn screening is recommended [1] based on the determination, in the first week of life, of immunoreactive trypsin (IRT) in dried blood spots collected on filter paper, because of its increased level in CF patients, likely related to obstruction of the pancreatic ducts [2].

Studies have shown that children diagnosed through screening have better nutritional and respiratory parameters [3,4], better intellectual development [5,6], and increased survival [7] than those diagnosed after presenting clinical manifestations [8-11].

These benefits, coupled with successful experiences in other countries and communities, have allowed implementation of newborn screening since that time. Newborn screening in the Valencian Community began in 2012 by quantification of IRT, which is elevated in the blood samples of newborns with cystic fibrosis due to pancreatic duct obstruction with trypsin reflux into the blood. The critical point is the establishment of the cutoff in the first sample. Each laboratory should establish its own cutoffs, considering that the IRT concentration is dependent on the age of the newborn and decreases notably from 20–21 days of age. A protocol that has proved effective is the three-stage strategy (IRT/DNA/ IRT) being used by several screening programs [12]. The main problem in the determination of IRT is a higher than expected percentage of false positive tests in some communities. The hypothesis is that the reference range for IRT may vary depending upon the ethnicity of the newborn.

The newborns of families from the north of Africa have higher IRT values and most positive newborn screenings in this population could be considered "false positives" [13]. Higher IRT values have also been found to be associated with sick infants [14]. Despite these considerations, no special strategy for premature infants and sick newborns is recommended. However, it may be useful to record the ethnicity of the newborn to enable its association with possible deviations in the analytical results. Cutoff values at 48 hours of life can be set in different ways: an absolute value, typically 60–65 ng/ml, although values up to 90–105 ng/ml are acceptable, or a changing value based on the results obtained over a period of time, which may be a day or a month, accepting values higher than the 90th, 95th or 98th percentiles for that period as pathological. All these findings have been summarized in an excellent review by Therrell Jr et al. [15].

Moreover, these factors have been individually analyzed for their impact on IRT values. As a new feature of the findings of these authors, in this study we assessed the conditions (room temperature, gender, gestational age, age of the child at

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extraction, maternal age and ethnicity) that can alter the normal levels of IRT, after one year of experience using a three-stage strategy protocol (IRT/DNA/IRT) through multivariate analysis. Furthermore, we used an innovative approach to assess the influence of nutrition type on altered IRT values.

Methods

Study population

Newborns in the province of Alicante.

Design and participants

Cross-sectional observational study. A sample of all newborns in the province of Alicante was selected to undergo neonatal screening (IRT/DNA/IRT) for metabolic diseases after informed consent was given by the parents or guardians (over 99% of the newborns) from March 2012 to February 2013. The dried blood sample on filter paper was required to meet the defined quality criteria [16]. Any child not meeting these requirements was excluded from the study. Additionally, all children with CF were excluded since IRT distribution data could be incorrect.

Variables and measures

The primary variable was defined as altered levels of IRT. This alteration was considered to be an IRT value at or above 65 ng/ml. Quantification of IRT was performed using the AutoDELFIA Neonatal IRT kit from Perkin Elmer, initially establishing the cutoff value of IRT at 65 ng/ml, as per the experiences of the majority of Spanish laboratories performing this test according to the Spanish Neonatal Screening Association (AECNE) [17]. Secondary variables were: child's gender, country of origin of the mother, maternal age (in years), gestational age (in weeks), type of feeding (natural, formula, mixed and special (nasogastric or intravenous), time from birth to blood collection and average temperature of the month of birth (in ¡C). The variables were grouped as follows: 1) Origin of the mother: Spain, Africa, America, Rest of Europe and Asia. This grouping was made based on the distribution of the origin of mothers in recent years carried out by the Department of Health of the Valencian Community [18]; 2) Maternal age: <20, 20–40 and >40 years of age. 3) Gestational age (in weeks): very preterm newborn <32, pre-term from 32 to 37, and term ≥37. These intervals were chosen based on the recommendations of the Standards Committee of the Spanish Society of Neonatology [19]; and 4) day of extraction: <20 and ≥20. The cutoff was chosen according to the screening protocol based on quantification of IRT in a second sample after 20 days of life [17].

Quantification of IRT was performed using AutoDELFIA Neonatal IRT kit from Perkin Elmer and the average temperature of the month of birth was obtained from the Spanish Meteorological Agency (AEMET) [20]. The remaining variables were obtained from the neonatal screening report.

Sample size

The final sample consisted of 13,310 children. With a 95% confidence level and a maximum expected proportion (p = q =0.5), the estimated error of the proportion of abnormal IRT was 0.85%.

Statistical analysis

A descriptive analysis of the variables was performed. Absolute and relative frequencies were used for qualitative variables, while means, standard deviations and 95th and 99th percentiles were used for quantitative variables. Differences were analyzed using nonparametric tests between subgroups of gender, ethnicity, maternal age, gestational age, type of feeding and days from birth to extraction of the blood sample. A multivariate logistic regression model was implemented to estimate the adjusted odds ratios (ORs) with the aim of analyzing the relationship between atypical IRT and the study variables. The ORs were adjusted by gender, origin of the mother, maternal age, gestational age group, feeding group, day of extraction group and temperature. The goodness of fit of the model was performed using the likelihood ratio test. In addition, we worked with the predicted probabilities of atypical IRT from the multivariate model to create graphs to help interpret the results. All analyses were performed at the 5% significance level and for each relevant parameter its associated confidence interval (CI) was calculated. All analyses were performed using IBM SPSS Statistics 19.

Missing data

The initial sample consisted of 14,877 newborns. However, those who did not have data for all the variables were excluded from this sample, leaving the sample size stated above.

Ethical issues

Neonatal screening studies were approved by the Ethics Committee of the Valencian Community, requiring the informed consent of the newborn's parent or guardian, in compliance with the current legislation in medical ethics. Moreover, the data, which are data from routine clinical practice in neonatal screening, were anonymized and encrypted, satisfying the data protection law.

Results

The gestational age of the total sample was 39.0 (SD 1.9) weeks, age at extraction was 5.4 (SD 3.3) days and maternal age was 31.6 (SD 6.7) years. Average monthly temperatures in Alicante during the period studied ranged from a low in February of 12.1¡C to a high of 27.7¡C in August. IRT values were not distributed normally according to the Kolmogorov-Smirnov normality test (p <0.0001) with a mean of 22.2 (SD 13.7) ng/ml, 95th percentile of 45.8 ng/ml and 99th percentile of 69.4 ng/ml. Table 1 summarizes the IRT data according to the groups established for the different covariates in the total sample.

Table 2 summarizes the descriptive and analytical information from the study sample (n = 13,310) according to IRT cutoff

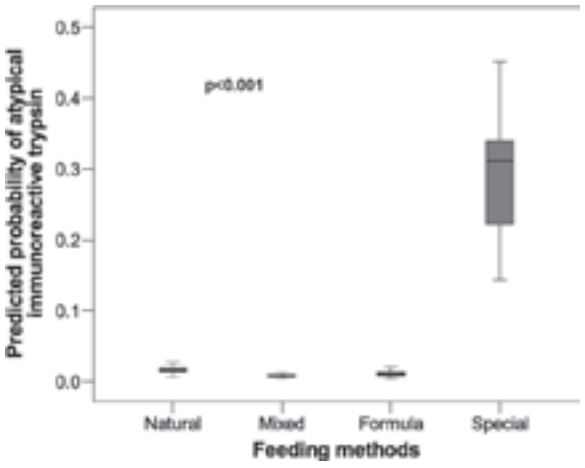

Figure 1 Predicted probability of atypical immunoreactive trypsin between feeding methods in newborns in a Spanish region. 2012–2013 data.

Table 1 Immunoreactive trypsin values (in ng/ml) in newborn screening

Variable	Mean (SD)	95% CI	Percentile 95	Percentile 99
*Gender:				
Male	21.5(13.7)	21.2-21.8	44.2	68.7
Female	22.8(13.5)	22.5-23.1	47.2	71.2
*Maternal origin:				
Spain	22.2(13.7)	21.9-22.4	45.6	69.3
Africa	24.0(17.2)	23.0-25.1	54.0	94.8
South America	20.8(11.3)	20.1-21.5	41.7	63.6
Rest of Europe	22.3(12.6)	21.5-23.0	45.6	71.6
Asia	20.1(12.1)	18.9-21.4	46.2	69.3
**Maternal age (y):				
<20	23.8(13.2)	22.5-25.1	52.0	73.3
20-40	22.1(13.7)	21.9-22.3	45.7	69.6
>40	22.9(14.2)	21.7-24.2	47.9	70.6
*Gestational age (w):				
<32	25.0(16.7)	23.2-26.8	53.9	83.0
32-37	23.2(11.7)	22.5-24.0	46.6	65.9
>37	22.0(13.8)	21.8-22.3	45.4	69.5
*Feeding methods:				
Natural	22.2(14.3)	21.9-22.4	46.1	71.5
Mixed	21.9(12.0)	21.4-22.4	44.0	62.8
Formula	22.2(12.4)	21.8-22.7	45.3	65.1
Special	53.3(52.9)	29.2-77.4	234.6	nd
*Extraction (d):				
<20	22.2(13.9)	22.0-22.5	46.1	70.3
≥20	15.4(19.8)	10.3-20.6	48.0	nd

*Kruskal-Wallis test ($p < 0.001$); **Kruskal-Wallis test ($p < 0.01$).
nd: not determined.
2012–2013 data for a Spanish region.

values (65 ng/ml). Most of the mothers were between 20 and 40 years of age (94.1%) and Spanish (75.3%). Most newborns were at term (>37 weeks) (86.8%) and were breastfeeding (65.0%).

The magnitude of atypical IRT was 1.5% (95% CI: 1.271.68%). Associated factors: male (OR = 0.88, 95% CI: 0.661.17, p = 0.385), maternal origin (Spain → OR = 1; Africa → OR = 1.5, 95% CI: 0.95-2.37; South America → 0.63, 95% CI: 0.32-1.25; rest of Europe → 0.88, 95% CI: 0.51-1.52; Asia → 1.21, 95% CI: 0.52-2.82; p = 0.219), maternal age (<20 → OR = 1.70, 95% CI: 0.83-3.49; 20-40 → OR = 1; >40 → OR = 1.06, 95% CI: 0.46-2.40; p = 0.353), gestational age (<32 → OR = 1.45, 95% CI: 0.49-4.25; 32-37 → OR = 0.59, 95% CI: 0.33-1.05; >37 → OR=1; p=0.137), feeding method (natural → OR = 1; mixed → OR = 0.53, 95% CI: 0.31-0.89; formula → OR = 0.72, 95% CI: 0.481.07; special → OR = 21.88, 95% CI: 6.92-69.14; p < 0.001), >20 days from extraction (OR = 1.51, 95% CI: 0.21-11.13, p = 0.684), and temperature (OR = 0.98, 95% CI: 0.95-1.00, p = 0.064).

On a Cartesian graph (Figure 1) feeding groups were plotted on the X-axis and predicted probabilities of atypical IRT on the Y-axis. This graph shows that the newborns who received special nutrition were more likely to have atypical IRT.

Discussion

When the differences in the IRT concentration in the total sample were studied according to type of feeding, IRT concentrations did not vary significantly between the three feeding groups (breastfeeding, formula and mixed). However, the elevated IRT levels in neonates receiving special feeding was striking, showing a significant difference. The mean IRT rose to more than double that of the other newborns, with many more of these newborns having IRT values above the cutoff. This was confirmed in the multivariate analysis, which showed that the probabilities of newborns receiving special nutrition being above the cutoff were about 20 times higher than those who were fed. This is undoubtedly associated with the fact that these children were subjected to special nutrition, due to their inherent disease, causing the increase in IRT. Although IRT is elevated in individuals with CF, an increase in IRT has also been seen in normal individuals with an immature ductal system, carriers of CF (66%), and in neonates with other diseases such as trisomy of chromosome 13, 18 and 21 [21], congenital infections (cytomegalovirus and other subclinical infections), renal failure, inadequate pancreatic perfusion and intestinal atresia. Higher IRT values are also associated with perinatal asphyxia [22] and sick infants [14]. On the other hand it has been reported that prenatal stress may be responsible for up to 25% of positive cases [22]. When IRT concentrations were examined by maternal ethnicity, clearly higher values were observed in newborns of African origin, with significant differences, a finding consistent with the literature [23]. In addition, slightly lower IRT

Table 2 Analysis of atypical immunoreactive trypsin (≥65 ng/ml) in newborns in a Spanish region

Variable	Total 13310 n(%)/x ± s	AIT 196 (1.5%) n(%)/x ± s	Not AIT 13114 (98.5%) n(%)/x ± s	Adj. OR	95% CI (Adj. OR)	p-value
Gender male	6861(51.5)	95(48.5)	6766(51.6)	0.88	0.66-1.17	0.385
Maternal origin:						
Spain	9994(75.1)	144(73.5)	9850(75.1)	1	1	0.219
Africa	953(7.2)	22(11.2)	931(7.1)	1.50	0.95-2.37	
South America	967(7.3)	9(4.6)	958(7.3)	0.63	0.32-1.25	
Rest of Europe	1061(8.0)	15(7.7)	1046(8.0)	0.88	0.51-1.52	
Asia	335(2.5)	6(3.1)	329(2.5)	1.21	0.52-2.82	
Maternal age (years):						
<20	358(2.7)	8(4.1)	350(2.7)	1.70	0.83-3.49	0.353
20-40	12531(94.1)	182(92.9)	12349(94.2)	1	1	
>40	421(3.2)	6(3.1)	415(3.2)	1.06	0.46-2.40	
Gestational age (weeks):						
<32	146(1.1)	6(3.1)	140(1.1)	1.45	0.49-4.25	0.137
32-37	1568(11.8)	13(6.6)	1555(11.9)	0.59	0.33-1.05	
>37	11596(87.1)	177(90.3)	11419(87.1)	1	1	
Feeding method:						
Natural	8698(65.3)	144(73.5)	8554(65.2)	1	1	<0.001
Mixed	1902(14.3)	16(8.2)	1886(14.4)	0.53	0.31-0.89	
Formula	2689(20.2)	30(15.3)	2659(20.3)	0.72	0.48-1.07	
Special	21(0.2)	6(3.1)	15(0.1)	21.88	6.92-69.14	
Days from extraction >20	47(0.4)	1(0.5)	46(0.4)	1.51	0.21-11.13	0.684
Temperature (°C)	18.7 ± 5.6	18.0 ± 5.2	18.8 ± 5.6	0.98	0.95-1.00	0.064

Abbreviations: *AIT* atypical immunoreactive trypsin, *Adj. OR* adjusted odds ratio, *CI* confidence interval.
Goodness-of-fit of the model: $X^2 = 53.19$, $p < 0.001$.
ORs were adjusted for: gender, maternal origin, maternal age, gestational age, feeding method, days from extraction and temperature.
2012–2013 data.

values were found in infants of Asian and American mothers. On comparing newborns of African ethnicity with the rest of the sample using multivariate analysis, there was an almost significant difference and a greater probability (OR 1.6) that the neonate of an African mother was more likely to have IRT levels above the reference value. Ethnic influence on IRT level has been studied previously [24], showing an overrepresentation of African Americans in screen-positive newborn infants (10% of the general population, rising to 28% in the positive population) despite the lower incidence of CF in this population. Note that in the present study maternal origin was divided into: Spain, rest of Europe, Africa, America and Asia; although Africa here corresponded primarily to countries in north Africa (mainly Morocco). Thus, newborns from north African families have higher IRT values and most of the positive newborn screens in this population could be considered "false positives" [13]. It should be noted that CF is the most common genetic disorder among Caucasian children. The incidence is variable: it is much less common in Asian and African populations than in European and North American populations, with variations within each country. The prevalence varies between a maximum of 1/2000 in Ireland and a minimum of 1/500,000 in Japan [23,24].

With respect to the other factors analyzed in this study, most behaved similarly to findings previously described by other authors [15,23,24], with the exception of temperature. This is possibly due to the variability between minimum and maximum temperatures throughout the year being much lower than in the regions in which this association has been observed [25]. Finally, there was no association with maternal age. This must be verified by future studies.

This work shows the need to establish cutoffs in IRT values adjusted to the ethnic and prematurity characteristics of the study population, as well as the need to postpone screening in those infants with conditions that require special feeding. This has the potential to reduce the number of inconclusive results, in which a second marker must be measured, either through DNA mutation analysis or taking a second sample for IRT retesting, thereby resulting in lower economic and emotional costs to the parents caused by unnecessary confirmations.

Strengths and limitations

The main strength of this study is its innovative approach to analyzing nutrition type when altered IRT values are present. Ethnicity is also evaluated in a manner different from that used by other authors. Furthermore, these factors were analyzed taking into account the ratio of all the altered IRT values, that is, through a mathematical multivariate model. Finally, the random error was less than 1%. As limitations, the IRT values analyzed are only useful for the population studied. Each neonatal cystic fibrosis screening center must define its own cutoff values and to do this the same methodology used in this work could be followed. Moreover, to minimize information bias, great care was taken in the collection of all variables. In addition, to avoid selection bias, all children who underwent neonatal screening

were included. Finally, although the statistical significance of the special type of nutrition was quite high, a wide confidence interval was obtained, therefore, in order to quantify OR more precisely, future studies using a larger sample size are needed.

Conclusions

In conclusion, newborns receiving special nutrition have much higher IRT values, with a 20-times greater likelihood of being above the set reference value, no doubt due to the underlying disease state. Thus, CF screening is advisable in sick infants with a special diet once breastfeeding, formula or mixed feeding is initiated. Newborns of African ethnicity, specifically children born to north African mothers, have higher IRT levels than those of other ethnic groups. An important factor to bear in mind is the increased ethnic variability resulting from increased migration.

The main learning point from this study is that we have to adopt new IRT cutoff points for children of certain ethnic backgrounds and for those who follow a special diet. However, we must be cautious, as these results must be verified by other authors in studies incorporating a large number of newborns.

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Adverse Effects of Small-Volume Red Blood Cell Transfusions in the Neonatal Population

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Abstract

Background: Adverse transfusion reactions in the neonatal population are poorly understood and defined. The incidence and pattern of adverse effects due to red blood cell (RBC) transfusion are not well known, and there has been no systematic review of published adverse events. RBC transfusions continue to be linked to the development of morbidities unique to neonates, including chronic lung disease, retinopathy of prematurity, intraventricular haemorrhage and necrotising enterocolitis. Uncertainties about the exact nature of risks alongside benefits of RBC transfusion may contribute to evidence of widespread variation in neonatal RBC transfusion practice. Our review aims to describe clinical adverse effects attributed to small-volume (10–20 mL/kg) RBC transfusions and, where possible, their incidence rates in the neonatal population through the systematic identification of all relevant studies.

Methods: A comprehensive search of the following bibliographic databases will be performed: MEDLINE (PubMed/OVID which includes the Cochrane Library) and EMBASE (OVID). The intervention of interest is small-volume (10–20 mL/kg) RBC transfusions in the neonatal population. We will undertake a narrative synthesis of the evidence. If clinical similarity and data quantity and quality permit, we will also carry out meta-analyses on the listed outcomes.

Discussion: This systematic review will identify and synthesise the reported adverse effects and associations of RBC transfusions in the neonatal population. We believe that this systematic review is timely and will make a valuable contribution to highlight an existing research gap.

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Background

Anaemia of prematurity (AOP) is a multifactorial condition with diminished plasma erythropoietin (EPO) levels in response to anaemia and hypoxia, reduced red cell life span, phlebotomy losses for laboratory testing, limited transplacental transfer of iron due to premature birth and dependence on hepatic EPO production [1]. Small-volume red blood cell (RBC) transfusions are often used to manage AOP with over 90% of preterm neonates with a birthweight at <1,000 g receiving at least one RBC transfusion [2,3]. RBC transfusions are given with the assumption that the transfusion will lead to an increase in oxygen delivery to tissues, thereby providing a rapid and effective intervention.

However, RBC transfusions are biological products, with recognised risks. Adverse effects may be classified broadly as those related to errors in the processing, storage and administration or as actual medical complications. Interpretation of the data from the UK Serious Hazards of Transfusion (SHOT) National Haemovigilance Scheme of a population-based epidemiological study of transfused patients has suggested that a disproportionate increased number of adverse events occur in children compared to adults, and more so in neonates [4]. A significant proportion of these reports were related to transfusion errors, including transfusion of an incorrect blood component. While SHOT has received numerous reports related to transfusion errors in the neonatal age group, there have been relatively fewer adverse reactions to transfusion reported. In the 2011 Annual SHOT report [5], there were no reports of transfusion-related lung injury (TRALI) in neonates. There were five paediatric reports classified as transfusion-associated circulatory overload (TACO) that included one neonate. It seems likely that there is under-recognition and/or under-reporting of transfusion-related adverse events in neonates [6,7] due to pre-existing critical illness, in particular around the recognition of TRALI [8] as many preterm neonates having intercurrent respiratory disease. This is compounded by the difficulties in defining adverse transfusion events in a neonatal setting.

There are several recognised potential adverse associations related to RBC transfusions unique to neonates [9]. Associations between receipt of RBC transfusions and development of necrotising enterocolitis [10], intraventricular haemorrhage [11,12] retinopathy of prematurity [13], chronic lung disease [14] as well as mortality [15,16] have all been described. The exact nature of these potential risks, alongside benefits of RBC transfusions, has likely contributed to widespread variation in

neonatal RBC transfusion practice [17]. To date, there has been no systematic collation of adverse effects due to, or associated with, RBC transfusion in neonates nor assessment of the degree to which biases operate to mitigate for or against the strengths of associations with risks.

Our review aims to describe clinical adverse effects attributed to small-volume (10–20 mL/kg) RBC transfusions and, where possible, their incidence rates in the neonatal population through the systematic identification of all relevant studies. It is likely that our review will find that reporting of adverse events related to neonatal transfusion is variably described in the literature and there is a need for standardisation of definitions in this area.

Methods/design

This review will be reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [18]. It has also been registered in the PROSPERO international prospective register of systematic reviews (registration number: CRD42013005107).

Study eligibility

We will include both randomised (including clusterrandomised and quasi-randomised) and non-randomised studies (including observational, cross-sectional, experimental and retrospective), with the proviso that any analysis will be carried out separately for randomised and non-randomised studies. Only studies examining the effects of RBC transfusion on neonates and have at least one outcome deemed relevant to our review will be included. Studies will not need to have a comparator group to be included; however, only those with a comparator group will be used in any meta-analysis. Our review will also focus its interpretation on those studies with a comparator group.

We will exclude reviews, case series with less than five neonatal participants, case reports, animal studies and laboratory (in vitro) studies. We will exclude studies that examine exchange transfusion, foetal (in utero) transfusion, large-volume transfusions and transfusions used in cardiac surgery and for extracorporeal membrane oxygenation (ECMO). These studies were excluded as we have chosen to focus on the potential adverse effects of small-volume RBC transfusions only.

Population

Neonates who received at least one RBC transfusion will be considered. Infants are defined for the purposes of this review as neonates less than 28 days of age and premature neonates (<37 weeks gestation) up to four weeks post-term corrected age.

Interventions

The intervention of interest is small-volume (10–20 mL/kg) RBC transfusions.

Comparators

For studies with a comparator group, we will include studies comparing

1. RBC transfusion with no RBC transfusion
2. Higher versus lower RBC transfusion threshold (or comparisons among RBC transfusion thresholds)
3. Higher versus lower RBC transfusion volumes
4. RBC transfusion products (e.g. leukodepletion, irradiation, age of RBC product, anticoagulant preparation versus non-modified)
5. RBC transfusion with an alternative therapy (e.g. erythropoietin-stimulating agents)

Outcomes

Depending on data availability, our outcomes will be considered separately for 'strong' (e.g. immune-mediated transfusion reactions) and 'less certain' (e.g. late-onset sepsis, NEC, BPD, severe ROP, etc.) causal pathways from transfusion to event.

Primary outcomes

1. Mortality associated with receipt of RBC transfusion
   i. Within 24–48 h of receipt of a RBC transfusion.
   ii. Before discharge from initial hospitalisation.
2. Complications during hospital stay Chronic lung disease (defined as requirement of supplemental oxygen at 36 weeks gestation), retinopathy of prematurity (grade 3 or above) [19], necrotising enterocolitis (stage 2 or greater using Bell's criteria) [20], intraventricular haemorrhage (grade 3 or 4) [21], adverse neurodevelopmental outcomes (at 18–24 months corrected age), cerebral palsy diagnosed following physician assessment or developmental delay (IQ or DQ > 2 standard deviations below the mean on a validated assessment tool of cognitive function), or blindness (visual acuity).

Secondary outcomes

1. Adverse transfusion events Immune-mediated transfusion reactions (acute haemolytic transfusion reactions, febrile non-haemolytic transfusion reactions and transfusion-related acute lung injury) within 48 h of receipt of RBC transfusion. Acute non-immune-mediated transfusion reactions (transfusion-related circulatory overload, metabolic complications including hypocalcaemia, hyperkalaemia, hyper/hypoglycaemia and hypothermia) within 48 h of receipt of RBC transfusion. Alloimmunisation, transfusion-associated graft versus host disease, post-transfusion purpura, infectious adverse effects (transfusion-transmitted infection, e.g. hepatitis B, hepatitis C, HIV, HTLV, parasites), bacterial contamination/sepsis, incorrect blood component transfused and/or adverse events or reactions associated with directed donation. If data availability allows, we will examine adverse transfusion events in the individual categories as outlined above.
2. Longer-term outcomes Long-term mortality, measured at 18–24 months, associated with previous transfusion complications/ events in the neonatal period.
3. Adverse neurodevelopmental outcomes at 18–24 months, associated with previous transfusion complications/events in the neonatal period. Composite outcomes of relevance or additional adverse events not previously identified will also be included.

Search strategy

There will be no language restrictions, and we will attempt to translate articles in languages other than English, depending on translational services available. Literature published from 1990 onwards will be searched and studies clearly completed prior to 1990 will be excluded. These studies will be excluded as since the 1990s, increasingly restrictive RBC transfusion practices have been introduced and changes in RBC products transfused (primarily leukoreduction) have occurred. Literature and studies from 1990 onwards are more likely to reflect current neonatal transfusion practices. We will include studies available as full-text publications only as it will be difficult to apply all

selection criteria and extract data for abstract-only publications. A comprehensive search of the following bibliographic databases will be performed, including MEDLINE (PubMed/OVID), EMBASE (OVID) and the CENTRAL database of the Cochrane Library. We will also undertake hand searching of reference lists and contact authors of relevant studies. We will not review other grey literature. The search strategy will include only terms relating to and describing the participants and the intervention. We will use both free-text terms and controlled vocabulary.

Selection of studies

Two reviewers will independently screen all electronically derived citations/abstracts of papers identified by the review search strategy for relevance. At this stage, screening will be based on title and abstract, and only clearly irrelevant studies will be excluded. Full text will be obtained for a selection of potentially relevant studies. The two reviewers will then formally assess the full texts for eligibility. If necessary, further information will be sought from the authors where articles contain insufficient data to make a decision about eligibility. Potential disagreements between the review authors will be resolved by consensus. If an agreement cannot be reached, a third reviewer will adjudicate. Details of excluded studies will be recorded as well as reasons for exclusion. The review authors will not be blinded to names of authors, institutions, journals or the outcomes of the trials. If any of the review group is an author on a paper identified in the search, they will be excluded from making a decision whether or not to include the study in the review, and another member of the group will make the decision.

Data extraction

Two authors will conduct data extraction independently using a data extraction form designed and piloted specifically for this systematic review. The pilot process for the data form will involve the two authors extracting data from at least one of each of the included study types for the review. The data extraction forms will then be reviewed by the two senior members of the authorship group and revised as required. Data extracted will include information regarding study design, participants, definitions of adverse effects and associations (outcomes), RBC transfusion regimen and the control/comparison if applicable, neonatal adverse effects reported and results relevant to the review, the risk of bias assessment, including an assessment on confounding, relevance and funding sources. Specific details regarding adverse effects and associations, including grade or severity, will also be collected including were they clearly defined a priori and what was the period of follow-up of study participants.

If an agreement cannot be reached over any aspects of data extraction, a third reviewer will adjudicate.

Methodological quality assessment and risk of bias assessment

Studies will not be excluded based on quality of research methods. A formal risk of bias assessment will be performed. For randomised controlled trials, the Cochrane Collaboration's tool for assessing risk of bias will be used. For non-randomised studies, a modified Newcastle-Ottawa Scale (NOS) will be used to assess the quality of non-randomised studies and it will also be used to assess those without a comparator group. We are aware that the Cochrane Collaboration is developing a new risk of bias tool for non-randomised studies. If a working draft is available in time, we will also consider relevant items from this tool for inclusion into our risk of bias assessment (modified NOS). We plan to undertake sensitivity analysis by grading studies at low or high risk of bias (qualitative assessment only). We will factor in all aspects of risk of bias, for both qualitative and quantitative syntheses, when interpreting the evidence, and this will include formal risk of bias assessments, study design and quantity of data. We will separately present findings in tables for comparative and non-comparative studies. Although conclusions will be drawn from both groups, the focus of interpretation will be on studies with comparator arms, and this will apply for any quantitative analysis.

Analysis plan

Qualitative synthesis

The main analysis will be descriptive. We will provide a qualitative synthesis from the eligible studies, categorised by the type of adverse effect for primary outcomes and causal pathway for secondary outcomes. This section aims to provide a summary of adverse effects attributed to the receipt of RBC transfusion in the neonatal population.

Quantitative synthesis

If data allows a quantitative analysis of outcome data, we will analyse separately randomised and non-randomised studies. We are expecting that there will be heterogeneity among included studies, and hence, random effects models will be used to calculate separate pooled estimates for each study type. If available and according to study design, odds ratios (ORs), risk ratios (RRs), hazard ratios (HRs) and incidence ratios (IRs) will be pooled separately. If the number of studies providing data is small, and if the number of events is rather small, then it is expected that these relative measures will yield similar results. In this case, and in order to reduce heterogeneity and provide more robust estimates, we will attempt to transform ORs, RRs and HRs into a single metric [22], and we will support this strategy with a sensitivity analysis by type of measure.

We will explore clinical heterogeneity concentrating on the different RBC transfusion strategies and settings. Statistical heterogeneity (where meta-analysis is feasible) will be assessed by the I2 test, with values above 80% classed as considerable heterogeneity. We will approach pooling cautiously, and if I2 > 80%, we will not provide pooled results, but instead we will provide information either on a table or an un-pooled forest plot. If the data permits, we will carry out subgroup analysis and sensitivity analysis based on the different types of effect measure (if they have been combined as mentioned earlier). We will also carry out sensitivity analysis based on the risk of bias assessment in terms of selection bias, and any identified confounding factors.

Discussion

This systematic review will identify and synthesise the reported adverse effects and associations of RBC transfusions in the neonatal population.

The limited reporting of adverse effects in neonatal transfusion trials, the quality of the studies identified as well as the risk of bias inherent in studies in this area are likely to be significant limitations to our review [9]. However, the identification and collation of all current known adverse effects due to, or associated with, RBC transfusion in neonates are key steps in improving the reporting of these important events. The need for standardised neonatal definitions for all relevant adverse effects

is also likely to be highlighted by this review, as well as the need for consistent reporting.

By drawing together the current known adverse effects and associations of RBC transfusion in neonates, we aim to provide a clear overview of this area and clarify future research areas. This protocol may also be used in the future to examine the potential adverse effects of other blood products and intravenous fluids used in the neonatal population. We believe that this systematic review is timely and will make a valuable contribution through highlighting existing research gaps.

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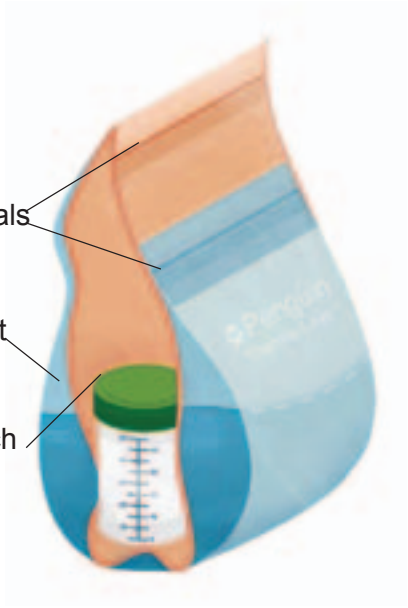

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