Published in final edited form as:

Semin Perinatol. 2016 October ; 40(6): 391–397. doi:10.1053/j.semperi.2016.05.006.

Perinatal Management: What's Been Learned Through the Network?

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Abstract

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network (NRN) has examined the effects of various obstetrical perinatal interventions and neonatal delivery room practices on the newborn with particular focus on those born preterm. Studies exploring the effects and safety of various antepartum maternal medications and the effects of the route and timing of delivery are examined. The NRN has contributed key studies to the evidence base for the International Liaison Committee on Resuscitation neonatal resuscitation guidelines. These studies are reviewed including research on timing of cord clamping, the importance of maintaining euthermia immediately after birth, delivery room ventilation strategies, outcomes following delivery room cardiopulmonary resuscitation and the effects of prolonged resuscitation efforts. In addition, the NRN's detailed outcome data at the lowest gestational ages has greatly influenced how providers counsel families regarding the appropriateness of resuscitation efforts at the lowest gestational ages.

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DISCLOSURES

The authors have no conflicts to disclose.

INTRODUCTION

The transition from intrauterine to extrauterine life requires timely and precise anatomic and physiologic adjustments.[1] Both obstetrical and pediatric practices during the perinatal period can affect successful transition with possible positive and negative downstream consequences. For over two decades, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) has furthered our understanding of the neonatal effects of various antepartum obstetrical interventions particularly for preterm infants. In addition, the NRN has contributed key studies to the evidence base for the International Liaison Committee on Resuscitation (ILCOR) neonatal resuscitation guidelines which serve as the backbone for neonatal resuscitation practices across the world.

NRN EVALUATION OF THE EFFECTS OF OBSTETRICAL PERINATAL MANAGEMENT ON THE NEONATE

Antenatal Steroids Improve Neonatal Outcomes

Early NRN papers[2–4] concluded that antenatal steroid (ANS) exposure reduces neonatal mortality and various morbidities, including respiratory distress syndrome (RDS), necrotizing enterocolitis (NEC) and intracranial hemorrhage (ICH) supporting the conclusions of investigators outside the NRN.[5–7] Data from the NRN Generic Data Base (GDB) suggested that antenatal corticosteroids improved blood pressure stability in the first 24 hours of life.[8] The benefits of reduced ICH were not outweighed by increased rates of sepsis even in pregnancies with preterm premature rupture of membranes.[9] Several large NRN observational studies suggested benefits on short and long term neonatal outcomes when mothers received betamethasone compared to dexamethasone.[10,11]

Many premature neonates, however, are born prior to the administration of a complete course of ANS due to insufficient time in cases of progressive preterm labor or the need for expedited delivery for either maternal or fetal indications.[12] Previous non-NRN studies that evaluated the role of ANS on neonatal and childhood neurodevelopmental outcomes compared patients who received a *partial* course of ANS to those who received no ANS and to those who received a complete course of ANS.[13,14] Studies evaluating the long term neurodevelopmental effects of ANS in premature infants have reported conflicting results; such differences could be due to variability in the combination of a *partial* ANS course with either a complete ANS course or no ANS course. Data were limited on the comparative effects of no ANS, partial or a complete course of ANS on neonatal and early childhood neurodevelopmental outcomes of extremely premature infants. Studies from the NICHD NRN participating centers reduced the knowledge gap in this area. Carlo *et al* evaluated neurodevelopmental outcomes at 18–22 months corrected age, in relation to completeness of ANS exposure among 10,541 extremely premature infants (gestational age 22–25 weeks).[15] Sub-group analysis demonstrated that a partial course reduces death or neurodevelopmental impairment (NDI), compared with no ANS.[15] Such studies provide support for prompt administration of ANS even in situations where lack of time prevents the possibility of a complete course of ANS prior to an extremely preterm birth. The differential dose-

dependent beneficial effect of ANS on neonatal and early childhood neurodevelopmental outcomes may have implications for the design of future trials where the primary outcome of trials is ICH or neurodevelopmental outcome. These data may also help to improve the outcome estimators currently in use, by using ANS exposure trichotomized as no, partial or complete steroid administration.

Antenatal Tocolysis With Indomethacin is Not Associated With Improved Neonatal Outcomes

Prematurity contributes significantly to neonatal morbidities and mortality.[16] Although infants may be born preterm for a variety of reasons, preterm labor remains a major cause of preterm birth. Many different etiologies contribute to the occurrence of preterm labor. Various targeted therapies including β-adrenergic agents, magnesium sulfate, oxytocin antagonists and prostaglandin inhibitors have been investigated in hopes of stopping the progression of preterm labor. Indomethacin had long been used as a tocolytic and in randomized trials it prolongs the pregnancy compared to placebo. However, concerns were raised about possible deleterious effects on the fetus and newborn including increased risk for necrotizing enterocolitis and intraventricular hemorrhage (IVH). Doyle et al used the NRN GDB to compare outcomes of very low birth weight (VLBW) who were exposed to antenatal indomethacin versus those that were not.[17] After controlling for antenatal corticosteroids, maternal preeclampsia, gestational age and birth weight, antenatal indomethacin was significantly associated with increased rates of IVH, but not neonatal death. The authors suggested that caution was warranted and more rigorous investigation needed before such therapy to prevent preterm labor was widely adopted.

Antenatal Phenobarbital Does Not Prevent Intracranial Hemorrhage (ICH)

ICH is a major neurologic morbidity among extremely premature infants. Severe ICH is associated with significant neonatal morbidities, including post-hemorrhagic hydrocephalus and need for ventriculo-peritoneal shunt, as well as subsequent adverse neurologic outcomes such as cerebral palsy and mental retardation.[18,19] Several non-NRN studies suggested that antenatal phenobarbital might reduce the frequency of intracranial hemorrhage and death in premature neonates.[20–22] A multi-center, randomized, placebo-controlled trial was conducted by the NRN to determine the effect of antenatal phenobarbital on the frequency of ICH and early death. A total of 610 women, who were 24 to 33 weeks' pregnant and who were expected to deliver their infants within the next 24 hours were enrolled. Disappointingly, the incidence of ICH or death within 72 hours after birth was comparable between the phenobarbital and placebo groups (24 versus 23% p=NS, relative risk ratio of 1.1; 95% C.I., 0.8 to 1.4).[23] In a small subset of the study population, exposure to antenatal phenobarbital did not cause significant sedation in the newborns as judged by behavioral state and heart rate responses.[24] A follow-up study of the main trial evaluated 18–22 month neurodevelopmental outcomes of the available enrolled infants (n=436). No difference in growth parameters, rates of cerebral palsy, median Bayley II Mental Developmental Index (85 vs 86) or median Psychomotor Developmental Index (91 vs 91) was found for the phenobarbital versus placebo group.[25] The findings from the NRN antenatal phenobarbital studies are consistent with the conclusion of a recent meta-analysis by Crowther and

colleagues, which does not support the administration of maternal phenobarbital to prevent neonatal ICH or to protect the infant from neurologic disability in childhood.[26]

Neonatal Effects of Antenatal Magnesium Sulfate Administration

Antenatal magnesium sulfate is commonly administered to women at risk of preterm delivery for multiple indications including tocolysis, pre-eclampsia and more recently neuroprotection of the newborn.[27,28] Whether antenatal magnesium sulfate is associated with cardiorespiratory instability and neonatal morbidities is unclear. There have been conflicting and inconsistent reports of the effects of antenatal magnesium sulfate on immediate neonatal outcomes. In the Magnesium and Neurological Endpoints Trial (MagNET) among preterm infants (24–33 weeks gestational age (GA)), antenatal magnesium sulfate was associated with higher risk of death, ICH, periventricular leukomalacia (PVL) and cerebral palsy, compared to placebo.[29,30] The Beneficial Effects of Antenatal Magnesium Sulfate (BEAM) NICHD Maternal Fetal Network Trial did not show any association between cord blood magnesium level and need for resuscitation in the delivery room.[31] Two other large randomized controlled trials of antenatal magnesium sulfate versus placebo for fetal neuroprotection also did not demonstrate any significant difference in neonatal mortality and morbidity, including need for resuscitation in the delivery room and hypotension.[27,28]

A recent NICHD NRN study by De Jesus and colleagues evaluated the association of antenatal magnesium sulfate with neonatal cardiorespiratory stability and morbidities in diverse groups of high risk infants outside of the randomized controlled trial setting.[32] This study was a retrospective analysis of a recent cohort from the NRN GDB for premature infants (GA < 29 weeks). The study included 1,544 infants (n=1,091 exposed to antenatal magnesium versus n=453 who were not). Antenatal magnesium sulfate was associated with lower risk of hypotension in the first 24 hours of life and reduced need for endotracheal intubation on day 3 after adjusting for GA, ANS exposure and pregnancy induced hypertension.[32] In view of a recent American College of Obstetrics and Gynecology opinion statement supporting the use of magnesium sulfate in women at risk of preterm birth for neuroprotection in surviving infants[33], it is likely that the use of antenatal magnesium sulfate will continue to increase. This recent NICHD NRN study provides additional support regarding the safety of antenatal magnesium sulfate for preterm infants.

Cesarean Delivery and Avoidance of Labor Do Not Prevent ICH or Neurodevelopmental Impairment (NDI) in Preterm Infants

The causes of ICH and PVL are diverse and likely multifactorial with the most immature infants at highest risk. Both ICH and PVL correlate with adverse neurologic outcome.[34] Initially it was thought that the stress of labor and vaginal birth might contribute to the burden of ICH and PVL in preterm infants.[35] However a study from the NRN which included 1765 very low birth weight infants and controlled for important risk factors such as gestational age, maternal risk factors, and presentation, found that cesarean delivery did not reduce ICH or mortality.[36] The odds ratio for neonatal death was 1.00 (95% confidence interval 0.71–1.41); for IVH, the odds ratio was 0.85 (95% confidence interval 0.61–1.19). These data suggest that after accounting for certain maternal and fetal factors, cesarean

delivery is not associated with a lower risk of either mortality or IVH.[36] Similarly, for extremely low birth weight (ELBW) infants born by cesarean, labor itself does not appear to play a significant role in adverse neonatal outcomes or neurodevelopmental impairment at 18 to 22 months.[37]

Effects of Time and Place of Delivery on Outcomes of VLBW infants

The NRN has examined the impact of birth at night, on the weekend and during the first month of the academic year when trainees are less experienced.[38] Outcomes were assessed from 11,1137 infants from 2001–2005 from the NRN GDB. The timing of birth did not affect mortality rates, short term morbidities (except retinopathy of prematurity) nor neurodevelopmental outcomes.[38] Since the timing of birth had little effect on the risks of death and morbidity for VLBW infants, it was suggested that staffing patterns were adequate to provide consistent care.

VLBW infants born at non-subspecialty perinatal centers have excess morbidity and mortality.[39] The NRN GDB provided data to demonstrate that the promotion of national guidelines recommending the transfer of high-risk mothers to subspecialty perinatal centers reduces mortality and morbidity through the reduction of preterm infants delivered at nontertiary maternity hospitals. The odds of death or major morbidity for VLBW infants born at nontertiary perinatal centers was 3 times that of infants born at subspecialty perinatal centers after controlling for demographic variations (odds ratio: 3.05 [95% confidence interval:2.1–4.4]).[40]

NRN EVALUATION OF THE EFFECTS OF NEONATAL DELIVERY ROOM MANAGEMENT

The Influence of Umbilical Cord Management

In the past decade there has been increasing interest in the potential risks and benefits of delayed cord clamping. Oh and colleagues from 3 NRN centers conducted a randomized unmasked controlled trial of immediate (<10s) versus delayed cord clamping (30–45s) and examined the effect on venous hematocrit at 4 hours of age in 33 infants who were 24–28 weeks gestational age at birth. Hematocrit was higher in the delayed cord clamping group. The need for delivery room resuscitation was identical between groups. This study is one of several that ILCOR included in their most recent systematic review[1] which found that delayed cord clamping is associated with less IVH of any grade, higher blood pressure, less need for transfusion after birth and less NEC. Based on the ILCOR review, the 2015 American Heart Association (AHA) neonatal resuscitation guidelines states that delayed cord clamping for longer than 30 seconds is reasonable for infants who do not require resuscitation at birth.[41]

Importance of Maintaining Normal Temperature of Low Birth Weight Infants in the Delivery Room

For years it has been understood that the admission temperature of a newborn is strongly associated with mortality. Much of the data to support this came from older studies in the 20th century.[1] Laptook et al used the NRN GDB to demonstrate that in a more recent cohort

of 5277 VLBW infants with access to high levels of neonatal intensive care, hypothermia upon admission to the NICU remains a common problem especially for the most preterm.[42] On adjusted analyses, admission temperature was still inversely related to mortality (28% increase per 1°C decrease). This work was included in the most recent ILCOR systematic review regarding the profound importance of maintaining temperature in the delivery room.[1] The most recent AHA neonatal resuscitation algorithm includes increased emphasis on maintaining a normal temperature immediately after birth.[43]

Must Every Extremely Preterm Neonate Be Intubated in the Delivery Room?

Early observational studies demonstrated an association between early use of continuous positive airway pressure (CPAP) after birth and lower rates of chronic lung disease. Based on these studies, Finer et al. performed a feasibility trial of CPAP in the delivery room setting at 5 NRN sites.[44] The investigators established that providing CPAP and positive end expiratory pressure (PEEP) to preterm infants in the delivery room is feasible. They also demonstrated that it was possible to randomize infants to different respiratory support strategies in the delivery room.

Subsequently, the NRN undertook the SUPPORT Trial (Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial), a 2 × 2 factorial randomized trial of preterm infants 24–27 $^{6/7}$ weeks gestation.[45] In the delivery room component of the trial, infants were randomly assigned to either immediate CPAP treatment with a limited ventilation strategy, or to intubation and surfactant treatment after birth. The primary outcome, bronchopulmonary dysplasia (BPD) or death at 36 weeks post-menstrual age, did not significantly differ between arms. However, infants in the CPAP arm experienced significantly lower rates of intubation and post-natal corticosteroids for BPD and significantly fewer days of mechanical ventilation.

At 18 to 22 months corrected age, there was no significant difference between treatment groups regarding death or neurodevelopmental impairment.[46] However, infants in the CPAP arm experienced less respiratory morbidity, such as wheezing, respiratory illness, and emergency room visits for breathing problems by 18–22 months corrected age.[47]

In pooled analysis of SUPPORT and other contemporaneous large CPAP trials, early CPAP use is associated with a reduction of BPD or death in extremely preterm infants, compared with intubation and prophylactic surfactant administration.[48] Based on these findings, the American Academy of Pediatrics Committee on Fetus and Newborn endorsed early CPAP with selective surfactant administration as an alternative to prophylactic surfactant administration in preterm infants.[49] Similarly, the 2015 ILCOR[1] and 2015 AHA[43] neonatal resuscitation guidelines assert that spontaneously breathing preterm newborns with respiratory distress may be supported with CPAP initially rather than with routine intubation for administering positive pressure ventilation.

Outcomes After Delivery Room Cardiopulmonary Resuscitation (DR-CPR) for ELBW Infants

ELBW infants frequently receive DR-CPR but few studies have provided information about neurodevelopmental outcomes.[50] Using an NRN GDB cohort of 8685 ELBW infants, rates

of DR-CPR per week of gestation and variability in use of DR-CPR among NRN centers were examined.[41] For the entire cohort, 15% received DR-CPR but rates varied between centers from 7–28%. Mortality as well as short and long term morbidities including neurodevelopmental impairment were compared between infants who were or were not exposed to DR-CPR. Over 84% of the available cohort was seen at 18–22 month follow-up which is by far the most comprehensive follow-up data available regarding newborns who received DR-CPR. Infants who received DR-CPR had more morbidity including grade 3 to 4 IVH (OR, 1.47; 95% CI, 1.23–1.74), BPD (OR, 1.34; 95% CI, 1.13–1.59), death by 12 hours (OR, 3.69; 95% CI, 2.98–4.57), and death by 120 days after birth (OR, 2.22; 95% CI, 1.93–2.57). Rates of neurodevelopmental impairment in survivors (OR, 1.23; 95% CI, 1.02–1.49) and death or neurodevelopmental impairment (OR, 1.70; 95% CI, 1.46–1.99) were higher for DR-CPR infants. Only 14% of DR-CPR recipients with 5-minute Apgar score <2 survived without neurodevelopmental impairment.[41] This data draws attention to the fact that DR-CPR is a prognostic marker for higher rates of mortality and neurodevelopmental impairment for ELBW infants and raises questions as to whether new DR-CPR strategies and training are needed for this unique population. Since this publication, the American Academy of Pediatrics/AHA Neonatal Resuscitation Program has diligently worked to develop better tools and methods for teaching about DR-CPR for ELBW infants.

When Is It Appropriate to Discontinue Resuscitative Efforts?

Before the era of therapeutic hypothermia, a majority of observational studies showed consistently poor outcomes in newborns with Apgar scores of 0 at 10 minutes of life.[51] Although these studies had considerable limitations (retrospective studies with small numbers, possible selection bias, lack of information about adequacy of resuscitation and variable duration for outcome assessment), available evidence at that time showed that more than 95% of these neonates either die or have severe disability.[51] ILCOR guidelines in 2010 recommended that it is appropriate to consider stopping resuscitation efforts if the newborn heart rate remains undetectable for 10 minutes despite resuscitative efforts.[52] Laptook et al conducted a secondary analysis of infants enrolled in the NICHD NRN whole body hypothermia trial to determine whether Apgar scores at 10 minutes are associated with death or disability after perinatal hypoxic ischemic encephalopathy.[53] In this study, an Apgar score of 0 at 10 minutes occurred for 25 newborns. Although rates of death/disability at 18–24 month follow up remained very high (76%), in contrast to previous studies, 6 of the 13 survivors had either mild or no disability at 18–24 months. Natarajan *et al* studied outcomes of the same cohort at 6–7 years of age.[54] From the original cohort of 25 newborns with an Apgar score of 0 at 10 minutes, 11 newborn survived to this age. Five of those infants were free of any moderate or severe disability. These two studies have started a rigorous debate on when to discontinue resuscitation in the delivery room and raised concern about uniformly discontinuing the resuscitative efforts if the Apgar score remains 0 at 10 minutes. Strengths of these studies such as containing a contemporary cohort, prospective data collection, uniform gestational age and rigorous standardized follow up data with low attrition make the data compelling. As both studies are secondary analysis of infants who survived and were deemed not too sick to approach for enrollment in a randomized controlled trial, there is a risk of selection bias and overestimation of effect size. Also, the small number of patients, availability of hypothermia and lack of information about quality of resuscitative efforts may

make these results not uniformly applicable. None the less, these studies have reinvigorated the debate on when to discontinue resuscitation. As a result, the recent 2015 ILCOR guidelines emphasized that such a decision should be individualized and variables such as availability of therapeutic hypothermia, timing of insult and quality of resuscitation should be considered.[1]

How Aggressive Should We Be With Resuscitative Efforts at Extremely Low Gestational Ages?

The many NRN papers reporting detailed and thorough short and long term outcomes for extremely low gestational age infants have significant potential to influence providers' willingness or reluctance to offer intensive resuscitation efforts in the delivery room. The prospective data collection, exceptionally high rates of follow up for the NRN delivery cohorts and the rigorous standardized developmental exams add essential information as medical providers interact and counsel prospective parents facing an extremely preterm birth. Reports including some of the most recent NRN cohorts describe survival and outcomes for infants born as early as 22 weeks GA.[16,55] Survival has increased most markedly for infants born at 23 and 24 weeks'gestation and survival without major morbidity has increased for infants 25–28 weeks.[16] An exceptionally important paper from the NRN details the importance of not just considering GA when considering the risks and benefits of offering intensive care to an extremely preterm infant. The work of Tyson *et al* highlights that the likelihood of a favorable outcome with intensive care can be better estimated by consideration of additional factors such as gender, exposure or not to ANS, whether a single or multiple birth, and birth weight.[56] The web-based tool (www.nichd.nih.gov/neonatalestimates) allows clinicians to use the findings in estimating the likelihood that intensive care will benefit individual infants, after considering the extent to which outcomes in their center might differ. The American Academy of Pediatrics Neonatal Resuscitation Program highlights the web-based tool in their neonatal resuscitation education materials and website.[57] An updated study with data from the most recent cohorts of extremely premature infants is warranted.

The Informed Consent Process Limits Generalizability of Randomized Delivery Room Intervention Studies

In order to obtain prospective informed consent for delivery room studies, investigators must obtain consent from parents before the birth of potentially eligible infants. As shown from the SUPPORT trial experience, the antenatal consent process results in selection bias.[58] Compared with SUPPORT study participants, eligible but non-enrolled infants were significantly less likely to be exposed to maternal ANS and antibiotics, had significantly lower 1 and 5 minute Apgar scores, and required significantly higher levels of delivery room interventions such as intubation and chest compressions.[59] The antenatal consent practice used in the SUPPORT trial likely contributed to this selection bias. Combined, maternal conditions (such as active labor or health issues) and inadequate time accounted for 47% of cases when mothers of potentially eligible infants were not approached for informed consent.[58] This ancillary study was uniquely possible because characteristics of eligible but non-enrolled infants were included in the NRN GDB. Study results inform the ongoing

debate about the ethical and scientific implications of antenatal consent practices for delivery room research.[60]

CONCLUSION

The NRN has contributed significantly to our understanding of how perinatal management of mothers and newborns in the delivery room effects neonatal outcomes. Much more needs to be investigated about perinatal practices and the NRN is poised to address key perinatal questions in the coming years.

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