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Perinatal management: What has 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 have greatly influenced on how providers counsel families regarding the appropriateness of resuscitation efforts at the lowest gestational ages.

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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 2 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 articles²⁻⁴ concluded that antenatal steroid (ANS) exposure reduces neonatal mortality and various morbidities, including respiratory distress syndrome (RDS), necrotizing

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enterocolitis (NEC), and intracranial hemorrhage (ICH) supporting the conclusions of investigators outside the NRN.⁵⁻⁷ Data from the NRN Generic DataBase (GDB) suggested that antenatal corticosteroids improved blood pressure stability in the first 24 h 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 neonates, 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.¹⁵ 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). Subgroup 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 the possible deleterious effects on the fetus and newborn including

increased risk for necrotizing enterocolitis and intraventricular hemorrhage (IVH). Doyle et al.¹³ used the NRN GDB to compare outcomes of very low birth weight (VLBW) who were exposed to antenatal indomethacin versus those that were not. 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 this therapy was adopted in hopes of preventing preterm labor.

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 the need for ventriculoperitoneal shunt, as well as subsequent adverse neurologic outcomes such as cerebral palsy and mental retardation.^{17,18} Several non-NRN studies suggested that antenatal phenobarbital might reduce the frequency of intracranial hemorrhage and death in premature neonates.¹⁹⁻²¹ 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 24-33-week pregnant and who were expected to deliver their infants within the next 24 h were enrolled. Disappointingly, the incidence of ICH or death within 72 h after birth was comparable between the phenobarbital and placebo groups (24% versus 23% $p = NS$, relative risk ratio of 1.1, 95% CI: 0.8-1.4).²² 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.²³ 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 versus 86), or median Psychomotor Developmental Index (91 versus 91) was found for the phenobarbital versus placebo group.²⁴ The findings from the NRN antenatal phenobarbital studies are consistent with the conclusion of a recent meta-analysis by Crowther et al.,²⁵ which does not support the administration of maternal phenobarbital to prevent neonatal ICH or to protect the infant from neurologic disability in childhood.

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, preeclampsia, and more recently neuroprotection of the newborn.^{26,27} 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 End points Trial (MagNET)

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