Perinatal Neuroprotection for Extremely Preterm Infants

Alexis S. Davis, MD, MS Epi[1] Victoria K. Berger, MD[2] Valerie Y. Chock, MD, MS Epi[1]

[1] Division of Neonatal-Developmental Medicine, Stanford University, Palo Alto, California
[2] Division of Maternal-Fetal Medicine, University of California, San Francisco, San Francisco, California

Address for correspondence Alexis Davis, MD, MS Epi, 750 Welch Road Suite 315 Palo Alto, CA 94304 (e-mail: alexis.davis@stanford.edu).

Am J Perinatol 2016;33:290–296.

Abstract

The preterm brain is vulnerable to injury through multiple mechanisms, from direct cerebral injury through ischemia and hemorrhage, indirect injury through inflammatory processes, and aberrations in growth and development. While prevention of preterm birth is the best neuroprotective strategy, this is not always possible. This article will review various obstetric and neonatal practices that have been shown to confer a neuroprotective effect on the developing brain.

Keywords

- very low-birth-weight
- brain injury
- neuroprotection
- outcomes
- premature infant

Despite improvements in the rate of preterm birth in the last several years, the proportion of very low-birth-weight (VLBW) infants in 2013 remained steady in the United States at 1.4% of live births.[1] In absolute numbers, this translates into approximately 55,000 infants born at risk for neurologic injury each year. Risk factors for adverse neurodevelopmental outcome in this vulnerable population include direct neurologic injury such as intraventricular and intraparenchymal hemorrhage,[2,3] and indirect harm resulting from inflammation or infection.[4,5] Up to 30% of extremely low-birth-weight (ELBW) infants with normal neuroimaging may be at risk for adverse outcome,[6] suggesting a role for insult at the cellular level with alterations in growth[7] and connectivity[8] in the developing brain.

Early attempts to improve neurologic outcomes in preterm infants were targeted at preventing injury by reducing the rate of intraventricular hemorrhage (IVH). While the initial effects of antenatal phenobarbital and indomethacin prophylaxis seemed favorable in the neonatal period, they did not have a significant impact on subsequent neurodevelopmental outcomes.[9,10]

Prevention of preterm birth and extension of gestation through antenatal progesterone, prophylactic cerclage, and judicious application of artificial reproductive technology is the ultimate strategy to reduce the rates of infants surviving with neurologic sequelae.[11] If preterm birth cannot be prevented, however, several interventions exist to reduce the risk of adverse outcome in extremely preterm infants. This review will describe strategies in the antepartum period, during resuscitation and transition to extrauterine life, and postnatal therapies to reduce the risk of adverse outcome (►**Table 1**).

Antenatal Strategies for Neuroprotection

Antenatal Corticosteroids

Antenatal corticosteroid (ACS) use in the setting of suspected premature birth was first described 1972 by Liggins and Howie, who demonstrated the effectiveness of corticosteroids in reducing respiratory distress syndrome and IVH among premature babies.[12] Following the introduction of ACS, more studies emerged showing similar favorable outcomes.[13,14] A Cochrane review showed a significant reduction in those that received ACS prior to preterm delivery.[15] Given the important role of ACS, the National Institutes of Health published a consensus statement in 1995 recommending that ACS be offered to patients at risk for delivery between 24 and 34 weeks.[16] A more recent study that evaluated outcomes of extremely preterm infants born at less than 29 weeks concluded that IVH was less likely among those that received ACS.[17] Administration of ACS to women at risk for preterm birth is thought to be the most beneficial intervention

received
November 18, 2015
accepted
November 24, 2015
published online
January 22, 2016

DOI http://dx.doi.org/10.1055/s-0035-1571148.
ISSN 0735-1631.

Table 1 Proposed checklist for neuroprotective strategies in the preterm infant

Antepartum
Antenatal steroids[18] • Gestational age <34 wk • Recommended dosing: betamethasone 12 mg q24h × 2 doses or dexamethasone 6 mg q12h × 4 doses • Consider rescue course if undelivered and preterm delivery <34 wk expected Magnesium sulfate[33] • Gestational age <32 wk • Dosing recommendations vary
Delivery and initial care
Delayed cord clamping[42] • For preterm infants, specific gestational age criteria not specified • 30–60 s recommended • Position infant at or below the level of the placenta
NICU care considerations[34,55,59]
• Midline head positioning • Delay procedures requiring excessive handling, e.g., lumbar puncture • Avoid sodium bicarbonate infusions • Near-infrared spectroscopy monitoring of cerebral oxygenation
Convalescent care in the NICU
Prophylactic indomethacin[61] • Consider in high-risk populations • Suggested dose: 0.1 mg/kg q24h × 3 doses Caffeine[71] • Infants <1,250 g • Loading dose 20 mg/kg followed by maintenance 5–10 mg/kg daily Erythropoiesis stimulation agents: erythropoietin or darbepoetin • Optimal population and dosing not well established

available to obstetricians in reducing neonatal respiratory and neurologic morbidity.[18]

Although short-term benefits of ACS administration have been widely appreciated, the long-term neurodevelopmental effects have been questioned, and studies have shown variable results. Lower rates of death or neurodevelopmental impairment at 18 to 22 months' corrected age were reported by the Neonatal Research Network among infants born at 23 to 25 weeks, including significant improvements in the rates of death, IVH, and periventricular leukomalacia.[19] In a 30-year follow-up of the Auckland steroid trial, there was no difference in cognitive outcomes between infants exposed to ACS and those exposed to placebo,[20] and this was true in the Cochrane meta-analysis.[15] However, a more recent meta-analysis, which included 14 studies on long-term neurodevelopmental effects of ACS, showed a favorable outcome, with a reduction in cerebral palsy among infants born before 34 weeks.[21] Importantly, a decrease in risk of severe disability was demonstrated in the most premature infants, born at less than 28 weeks, with 34% prevalence of severe disability in the steroid exposure group compared with 44% in those untreated.[21]

Given the documented decreased risk of respiratory and neurologic morbidity when ACS are administered, current practice guidelines recommend a course of ACS when preterm birth is suspected, with either two 12-mg betamethasone intramuscular injections given 24 hours apart or four 6-mg dexamethasone intramuscular injections given 12 hours apart.[18] Emerging evidence suggests that consideration should be given to one rescue course if the mother, who originally received ACS but was undelivered, is again at risk for delivery before 34 weeks.[18,22] Repeat doses beyond one rescue course are not recommended, as repeat doses have been associated with decrease in fetal growth and head circumference.[23,24]

Magnesium Sulfate

An association of magnesium sulfate with improved neurologic outcomes was first recognized through studies of infants born to preeclamptic mothers exposed to magnesium sulfate demonstrating lower rates of IVH and cerebral palsy (CP).[25–27] In 2003, a trial showed a nonsignificant trend toward decrease rates of CP with magnesium sulfate exposure among infants delivered before 30 weeks.[28] More recently, a trial of infants born between 24 and 31 weeks demonstrated a significant reduction in the rate of CP for infants exposed to magnesium sulfate (1.9 vs. 3.5%).[29] A Cochrane review published in 2009 concluded that although there was no decrease in mortality, there was a reduction in CP and gross motor dysfunction among infants exposed to magnesium sulfate, with the number of mothers needed to treat of 63.[30] The precise mechanism by which magnesium sulfate exerts a neuroprotective benefit is not known, but it is speculated that it possess anti-inflammatory and anti-excitotoxic effects while also improving cerebral blood flow and stabilizing fluctuations in blood pressure in the newborn

infant.[31] A recent study of infants ≤30 weeks' gestational age using near infrared spectroscopy (NIRS) showed that those exposed to antenatal magnesium sulfate had lower cerebral fractional tissue oxygen extraction in the first 24 hours of life compared with nonexposed infants.[32] The authors speculated that magnesium sulfate exerted a neuroprotective effect by reducing cerebral metabolic demand. In response to the growing evidence demonstrating reduction in CP rates, the American College of Obstetricians and Gynecologists (ACOG) with the Society for Maternal Fetal Medicine issued a statement in support of magnesium sulfate for neuroprotection in women at risk for delivery under 32 weeks' gestation.[33]

Delivery Room Management and Care during the Transition to Postnatal Life

Specific strategies and interventions in the delivery room to preserve long-term neurodevelopment of the preterm infant remain an important goal. Several areas of current research include ideal oxygen saturation targets in the first few minutes of life, optimal approaches to ventilation and initial lung-distending pressures, practices to best avoid hypothermia, and efforts to minimize the need for cardiac compressions and extensive resuscitation.[34] We will not focus on delivery-room-specific interventions, as this will be addressed in another companion article in this series, aside from addressing the practice of delayed umbilical cord clamping as it pertains to preterm infants.

Delayed Cord Clamping

Delayed cord clamping (DCC), also known as timed umbilical cord clamping or placental transfusion, has experienced several eras of research interest and definitional shifts.[35] In the premodern era of medicine, "early" cord clamping was defined as occurring at approximately 1 minute of life, and delayed clamping occurring at or after 5 minutes. Modern operational definitions seem to equate early with immediate clamping, in the first 15 seconds of life; the timing of DCC varies by study, between 30 seconds and up to 1 to 5 minutes of life. In the 1960s and 1970s, DCC was demonstrated to reduce the incidence of RDS in preterm infants, an observation initially noted by veterinarians as the "Barker Foal Syndrome" and borne out in other animal models. DCC lost favor in the postsurfactant era, as the emphasis in care for extremely preterm infants was redirected toward initiating resuscitative efforts as soon as possible and due to concerns about hyperbilirubinemia and hyperviscosity in those exposed to DCC.

We have come full circle, and interest in DCC has been renewed with multiple clinical trials in preterm infants aimed at the prevention of anemia of prematurity. A Cochrane Review in 2004 reviewed seven studies conducted largely in the 1980s and 1990s and affirmed the benefit of DCC in infants less than 37 weeks by reducing the need for red blood cell transfusions, improving blood pressure, and decreasing the rate of IVH.[36] More trials and meta-analyses have confirmed the hematologic and physiologic benefits of DCC, generally without adverse effects such as low Apgar scores, acidosis, or hypothermia.[37–40] There is speculation that DCC may confer additional immunologic and regenerative benefits through transfer of stem cells to ameliorate various neonatal morbidities as well as age-related diseases.[41] Due to the mounting body of literature, ACOG published a Committee Opinion in 2012 that recommended DCC up to 60 seconds for preterm infants but cited that areas requiring additional investigation included determining the optimal timing by mode of delivery (vaginal vs. cesarean section) and risks and benefits conferred to the most premature infants (defined as <28 weeks' gestational age).[42] Reports of the long-term benefits of DCC in preterm infants are sparse and have yet to demonstrate a significant benefit on neurodevelopmental outcomes.[39] However, a 4-year outcomes study of DCC in a low-risk, term infant population demonstrated improvements in fine motor and social domains, particularly in boys.[43]

DCC is most effective when onset of respirations has already occurred, thereby permitting the pulmonary vascular bed to fill with blood.[44] Additional variables to optimize placental transfusion include the position of the infant relative to the placenta to permit optimal gravitational flow and the presence of uterine contractions, including the administration of oxytocin.[45] Current areas of active research include (1) umbilical cord milking, either to enhance placental transfusion or when resuscitation efforts need to be initiated before DCC can occur,[46,47] and (2) the development of mobile trolleys to initiate resuscitation and provide respiratory support prior to clamping the umbilical cord.[48] Further, additional data on the long-term outcomes to support or refute the benefits of DCC are needed.

Resuscitation Practices and Neuromonitoring after Birth

Neuromonitoring in the delivery room with NIRS may help to guide resuscitation to improve neurodevelopmental outcomes. NIRS is a noninvasive method to continuously monitor cerebral tissue oxygenation and can feasibly be applied to preterm infants during resuscitation in the first few minutes of life.[49] Preterm infants requiring respiratory support in the delivery room have been shown to have lower cerebral tissue oxygenation levels compared with those requiring no intervention.[50] Furthermore, effective ventilatory resuscitation after birth in preterm infants results first in increased cerebral tissue oxygenation, followed by a subsequent increase in systemic oxygen saturation (SpO_2) levels.[51] Therefore cerebral NIRS measures may be a better reflection than SpO_2 alone to guide adequate cerebral oxygen delivery during the immediate transition period. Cerebral NIRS measures will be decreased not only with inadequate systemic oxygenation, but also by hemodynamic stability, anemia, and hypocarbia. Addressing these factors may have implications in improving cerebral oxygenation, and limited data have demonstrated an association between early cerebral oxygenation measures and the development of IVH[52] and longer-term neurodevelopmental outcomes.[53] Further research is required to establish normative cerebral oxygenation values for the preterm infant and to minimize differences in absolute oxygenation values between various types of NIRS devices.[54]

Early stabilization of the preterm infant in the neonatal intensive care unit has further implications for neurodevelopment. Potentially better practices for the prevention of IVH and ischemia in the preterm infant have been promoted[34,55] however, the long-term neurologic benefit of adopting such practices has not been extensively studied. Avoiding stressful conditions and limiting handling and excessive noise may be of benefit.[56] A consequence of this practice would be to avoid routine lumbar punctures in the immediate newborn period, although no direct neurologic benefit of this practice has been demonstrated.[34] Similarly, midline head positioning has been advocated so as not to impede jugular venous flow and thereby reduce fluctuations in intracranial pressure and maintain a more constant cerebral blood flow.[57,58] Routine sodium bicarbonate infusion for correction of metabolic acidosis should also be avoided or used with extreme caution in the preterm infant due to risks of IVH.[59] By reducing the risk of IVH, these practices may improve neurodevelopmental outcomes, but further research must be conducted to confirm long-term benefit.

Postnatal Therapies and Interventions

Indomethacin

The administration of prophylactic indomethacin has been a well-studied, but controversial, practice for the preterm infant. Prophylactic indomethacin has been shown in multiple studies to reduce the incidence of severe IVH in preterm infants,[60–62] possibly by decreasing cerebral blood flow.[63] Further rationale for use of prophylactic indomethacin is to close the persistent patent ductus arteriosus (PDA), a common complication in ELBW infants.[64] A hemodynamically significant PDA increases the risk of prolonged ventilation and bronchopulmonary dysplasia,[65] and diastolic steal from a PDA may contribute to altered cerebral blood flow and ensuing ischemia or IVH.[66] These consequences in turn put an infant at higher risk for neurodevelopmental impairment. Surgical ligation of a PDA has further been associated with neurosensory impairment.[67] Thus, avoiding the potential adverse outcomes of a significant PDA by early closure with prophylactic indomethacin would appear to be a logical strategy.

The Trial of Indomethacin Prophylaxis in Preterms Study (TIPPS) was a large, randomized multicenter study conducted through the NICHD Neonatal Research Network to investigate the utility of indomethacin prophylaxis and enrolled >1,200 ELBW infants. This trial found that use of prophylactic indomethacin resulted in a lower rate of severe IVH, but no difference in survival without neurosensory impairment at 18 months corrected age.[61] Several other smaller, randomized controlled trials and a meta-analysis also demonstrated a reduction in severe IVH, but no change in long-term survival without neurosensory impairment.[9,62]

Given the controversy surrounding the benefit of prophylactic indomethacin, some practitioners have advocated for limiting its use to a high-risk population. VLBW infants whose mothers did not receive ACS or those with chorioamnionitis might have greater benefit from prophylactic indomethacin.[34] Others have used a risk prediction model for severe IVH to target a population for prophylactic indomethacin.[68] Early PDA closure with prophylactic indomethacin may have further benefit in centers that transport a significant number of infants out for PDA ligation. Concerns about the use of prophylactic indomethacin in early feeding of ELBW infants and the development of spontaneous intestinal perforation were not borne out in a recent multicenter retrospective study.[69] Given the relative safety but lack of long-term neuroprotective effect, centers must make individualized decisions about the utility of prophylactic indomethacin for their preterm population.

Caffeine

Caffeine has widely been used for the treatment of apnea of prematurity, with early studies demonstrating positive effects on apnea and need for ventilator support but lacking in safety data and assessment of long-term outcomes.[70] The Caffeine for Apnea of Prematurity (CAP) Trial was the first randomized controlled trial to document a beneficial effect on longer-term outcomes for infants 500 to 1,250 g birth weight, with reduced death or disability at 18 to 21 months' corrected age.[71] In surviving infants, there was a significant reduction in the rates of CP and cognitive delay, without adverse consequences on growth. Magnetic resonance imaging (MRI) of subset of CAP Trial participants demonstrated improved white matter microstructure, with a decrease in apparent diffusion coefficient and axial and radial diffusivity, independent of improvements in respiratory morbidity.[72] Follow-up studies have investigated whether higher doses of caffeine might confer additive beneficial effects, with mixed results. One study compared high-dose regimen (40 mg/kg caffeine load, 20 mg/kg maintenance therapy compared with 20 and 10 mg/kg, respectively) and demonstrated no adverse short-term effects, with lower rates of extubation failure.[73] Another study using an even higher dose of caffeine (80 mg/kg loading dose compared with 20mg/kg) raised concern about higher rates of cerebellar hemorrhage on MRI and abnormal neurologic exam at term equivalent.

Biologic Agents: Erythropoietin and Darbepoetin

Erythropoiesis-stimulating agents (ESAs), such as erythropoietin (Epo) and darbepoetin, are beginning to show promise not only as a therapy for reducing transfusions for anemia of prematurity, but also for their potential neuroprotective effects. The specific mechanism of ESAs is not completely understood, but animal studies support a role in neurogenesis and white matter maturation, along with antiapoptotic, anti-inflammatory, and antioxidant properties. An early trial of Epo for the treatment of anemia of prematurity showed no improvement in the rates of cerebral palsy or cognitive function at 18 to 22 months' corrected age.[74] However, a small single-center study using the same dosing regimen (400 U/kg three times per week) showed that infants who achieved higher Epo concentrations (>500 mU/mL) had higher Mental Developmental Index scores.[75] Recent studies are showing a more consistent association between ESAs and improved neurodevelopmental outcomes. One historical

cohort study that examined participants at 10 to 13 years of age showed an overall protective effect of Epo; further analysis concluded that the effects were attributable to a benefit in those infants with IVH.[76] A phase I/II study of early, high-dose Epo (500, 1,000, or 2,500 U/kg) demonstrated improved cognitive and motor outcomes without adverse side effects.[77] Another trial comparing Epo (400 U/kg three times per week) or darbepoetin (10 U/kg weekly) resulted in improved cognitive outcomes and reduced CP compared with placebo.[78] The Swiss EPO group has shown reduced brain injury and improved white matter development in infants treated with early, high-dose Epo (3,000 U/kg), substantiating previously published animal studies[79,80]; long-term effects on neurologic outcomes have not yet been reported. Enthusiasm about ESAs, particularly those given early in postnatal life, to improve neurocognitive and motor outcomes for extremely preterm infants must be tempered with concern about higher rates of retinopathy of prematurity,[81] though this was not substantiated in the Swiss EPO study.[82] The Preterm Erythropoietin Neuroprotection Trial (PENUT Trial, NCT01378273) will provide additional evidence to support or refute the safety and efficacy of ESAs for neuroprotection.

Conclusion

When preterm birth is inevitable, a series of interventions exist to protect against potential neurologic injury and to enhance repair of the injured preterm brain. Neuroprotection efforts begin before birth and continue through delivery, resuscitation, and continuing care in the neonatal intensive care unit. Much like processes documented to improve catheter-associated bloodstream infections[83] and delivery room resuscitation,[84] the measures described in this article could be incorporated into a "neuroprotection bundle," with use of a checklist to ensure consistent use. Successful implementation of all of these neuroprotective interventions will require a coordinated effort between obstetricians and neonatologists to achieve the most optimal outcome.

References

1 Osterman MJ, Kochanek KD, MacDorman MF, Strobino DM, Guyer B. Annual summary of vital statistics: 2012-2013. Pediatrics 2015; 135(6):1115–1125

2 O'Shea TM, Allred EN, Kuban KC, et al; ELGAN Study Investigators. Intraventricular hemorrhage and developmental outcomes at 24 months of age in extremely preterm infants. J Child Neurol 2012;27(1):22–29

3 Tsai AJ, Lasky RE, John SD, Evans PW, Kennedy KA. Predictors of neurodevelopmental outcomes in preterm infants with intraparenchymal hemorrhage. J Perinatol 2014;34(5):399–404

4 Stoll BJ, Hansen NI, Adams-Chapman I, et al; National Institute of Child Health and Human Development Neonatal Research Network. Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. JAMA 2004;292(19):2357–2365

5 Kuban KC, O'Shea TM, Allred EN, et al; ELGAN Study Investigators. The breadth and type of systemic inflammation and the risk of adverse neurological outcomes in extremely low gestation newborns. Pediatr Neurol 2015;52(1):42–48

6 Laptook AR, O'Shea TM, Shankaran S, Bhaskar B; NICHD Neonatal Network. Adverse neurodevelopmental outcomes among extremely low birth weight infants with a normal head ultrasound: prevalence and antecedents. Pediatrics 2005;115(3): 673–680

7 Young JM, Powell TL, Morgan BR, et al. Deep grey matter growth predicts neurodevelopmental outcomes in very preterm children. Neuroimage 2015;111:360–368

8 Smyser CD, Inder TE, Shimony JS, et al. Longitudinal analysis of neural network development in preterm infants. Cereb Cortex 2010;20(12):2852–2862

9 Ment LR, Vohr B, Oh W, et al. Neurodevelopmental outcome at 36 months' corrected age of preterm infants in the Multicenter Indomethacin Intraventricular Hemorrhage Prevention Trial. Pediatrics 1996;98(4, Pt 1):714–718

10 Shankaran S, Papile L-A, Wright LL, et al. Neurodevelopmental outcome of premature infants after antenatal phenobarbital exposure. Am J Obstet Gynecol 2002;187(1):171–177

11 McCabe ER, Carrino GE, Russell RB, Howse JL. Fighting for the next generation: US prematurity in 2030. Pediatrics 2014;134(6): 1193–1199

12 Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. Pediatrics 1972; 50(4):515–525

13 Amorim MM, Santos LC, Faúndes A. Corticosteroid therapy for prevention of respiratory distress syndrome in severe preeclampsia. Am J Obstet Gynecol 1999;180(5):1283–1288

14 Garite TJ, Rumney PJ, Briggs GG, et al. A randomized, placebo-controlled trial of betamethasone for the prevention of respiratory distress syndrome at 24 to 28 weeks' gestation. Am J Obstet Gynecol 1992;166(2):646–651

15 Roberts D, Dalziel S. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev 2006;(3):CD004454

16 NIH Consensus Development Panel on the Effect of Corticosteroids for Fetal Maturation on Perinatal Outcomes. Effect of corticosteroids for fetal maturation on perinatal outcomes. JAMA 1995; 273(5):413–418

17 Wong D, Abdel-Latif M, Kent A; NICUS Network. Antenatal steroid exposure and outcomes of very premature infants: a regional cohort study. Arch Dis Child Fetal Neonatal Ed 2014;99(1): F12–F20

18 American College of Obstetricians and Gynecologists; Committee on Practice Bulletins—Obstetrics. ACOG practice bulletin no. 127: management of preterm labor. Obstet Gynecol 2012;119(6): 1308–1317

19 Carlo WA, McDonald SA, Fanaroff AA, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Association of antenatal corticosteroids with mortality and neurodevelopmental outcomes among infants born at 22 to 25 weeks' gestation. JAMA 2011; 306(21):2348–2358

20 Dalziel SR, Lim VK, Lambert A, et al. Antenatal exposure to betamethasone: psychological functioning and health related quality of life 31 years after inclusion in randomised controlled trial. BMJ 2005;331(7518):665

21 Sotiriadis A, Tsiami A, Papatheodorou S, Baschat AA, Sarafidis K, Makrydimas G. Neurodevelopmental outcome after a single course of antenatal steroids in children born preterm: a systematic review and meta-analysis. Obstet Gynecol 2015;125(6): 1385–1396

22 Garite TJ, Kurtzman J, Maurel K, Clark R; Obstetrix Collaborative Research Network. Impact of a 'rescue course' of antenatal corticosteroids: a multicenter randomized placebo-controlled trial. Am J Obstet Gynecol 2009;200(3):248.e1–248.e9

23 Wapner RJ, Sorokin Y, Thom EA, et al; National Institute of Child Health and Human Development Maternal Fetal Medicine Units

Network. Single versus weekly courses of antenatal corticosteroids: evaluation of safety and efficacy. Am J Obstet Gynecol 2006; 195(3):633–642
24 French NP, Hagan R, Evans SF, Godfrey M, Newnham JP. Repeated antenatal corticosteroids: size at birth and subsequent development. Am J Obstet Gynecol 1999;180(1, Pt 1):114–121
25 van de Bor M, Verloove-Vanhorick SP, Brand R, Keirse MJ, Ruys JH. Incidence and prediction of periventricular-intraventricular hemorrhage in very preterm infants. J Perinat Med 1987;15(4): 333–339
26 Leviton A, Kuban KC, Pagano M, Brown ER, Krishnamoorthy KS, Allred EN. Maternal toxemia and neonatal germinal matrix hemorrhage in intubated infants less than 1751 g. Obstet Gynecol 1988;72(4):571–576
27 Kuban KC, Leviton A, Pagano M, Fenton T, Strassfeld R, Wolff M. Maternal toxemia is associated with reduced incidence of germinal matrix hemorrhage in premature babies. J Child Neurol 1992; 7(1):70–76
28 Crowther CA, Hiller JE, Doyle LW, Haslam RR; Australasian Collaborative Trial of Magnesium Sulphate (ACTOMg SO4) Collaborative Group. Effect of magnesium sulfate given for neuroprotection before preterm birth: a randomized controlled trial. JAMA 2003; 290(20):2669–2676
29 Rouse DJ, Hirtz DG, Thom E, et al; Eunice Kennedy Shriver NICHD Maternal-Fetal Medicine Units Network. A randomized, controlled trial of magnesium sulfate for the prevention of cerebral palsy. N Engl J Med 2008;359(9):895–905
30 Doyle LW, Crowther CA, Middleton P, Marret S, Rouse D. Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus. Cochrane Database Syst Rev 2009;(1): CD004661
31 Marret S, Doyle LW, Crowther CA, Middleton P. Antenatal magnesium sulphate neuroprotection in the preterm infant. Semin Fetal Neonatal Med 2007;12(4):311–317
32 Stark MJ, Hodyl NA, Andersen CC. Effects of antenatal magnesium sulfate treatment for neonatal neuro-protection on cerebral oxygen kinetics. Pediatr Res 2015;78(3):310–314
33 American College of Obstetricians and Gynecologists Committee on Obstetric Practice; Society for Maternal-Fetal Medicine. Committee Opinion No. 455: magnesium sulfate before anticipated preterm birth for neuroprotection. Obstet Gynecol 2010;115(3): 669–671
34 Carteaux P, Cohen H, Check J, et al. Evaluation and development of potentially better practices for the prevention of brain hemorrhage and ischemic brain injury in very low birth weight infants. Pediatrics 2003;111(4, Pt 2):e489–e496
35 Philip AGS, Saigal S. When should we clamp the umbilical cord? NeoReviews 2004;5(4):e142–e154
36 Rabe H, Reynolds G, Diaz-Rossello J. Early versus delayed umbilical cord clamping in preterm infants. Cochrane Database Syst Rev 2004;(4):CD003248
37 Mercer JS, Vohr BR, McGrath MM, Padbury JF, Wallach M, Oh W. Delayed cord clamping in very preterm infants reduces the incidence of intraventricular hemorrhage and late-onset sepsis: a randomized, controlled trial. Pediatrics 2006;117(4): 1235–1242
38 Baenziger O, Stolkin F, Keel M, et al. The influence of the timing of cord clamping on postnatal cerebral oxygenation in preterm neonates: a randomized, controlled trial. Pediatrics 2007; 119(3):455–459
39 Ghavam S, Batra D, Mercer J, et al. Effects of placental transfusion in extremely low birthweight infants: meta-analysis of long- and short-term outcomes. Transfusion 2014;54(4):1192–1198
40 Backes CH, Rivera BK, Haque U, et al. Placental transfusion strategies in very preterm neonates: a systematic review and meta-analysis. Obstet Gynecol 2014;124(1):47–56
41 Sanberg PR, Park DH, Borlongan CV. Stem cell transplants at childbirth. Stem Cell Rev 2010;6(1):27–30
42 Committee on Obstetric Practice, American College of Obstetricians and Gynecologists. Committee Opinion No.543: timing of umbilical cord clamping after birth. Obstet Gynecol 2012;120(6): 1522–1526
43 Andersson O, Lindquist B, Lindgren M, Stjernqvist K, Domellöf M, Hellström-Westas L. Effect of delayed cord clamping on neurodevelopment at 4 years of age: a randomized clinical trial. JAMA Pediatr 2015;169(7):631–638
44 Lakshminrusimha S, Van Meurs K. Better timing for cord clamping is after onset of lung aeration. Pediatr Res 2015;77(5):615–617
45 Yao AC, Lind J. Placental transfusion. Am J Dis Child 1974;127(1): 128–141
46 Katheria AC, Truong G, Cousins L, Oshiro B, Finer NN. Umbilical cord milking versus delayed cord clamping in preterm infants. Pediatrics 2015;136(1):61–69
47 Krueger MS, Eyal FG, Peevy KJ, Hamm CR, Whitehurst RM, Lewis DF. Delayed cord clamping with and without cord stripping: a prospective randomized trial of preterm neonates. Am J Obstet Gynecol 2015;212(3):394.e1–394.e5
48 Thomas MR, Yoxall CW, Weeks AD, Duley L. Providing newborn resuscitation at the mother's bedside: assessing the safety, usability and acceptability of a mobile trolley. BMC Pediatr 2014;14:135
49 Fuchs H, Lindner W, Buschko A, Almazam M, Hummler HD, Schmid MB. Brain oxygenation monitoring during neonatal resuscitation of very low birth weight infants. J Perinatol 2012;32(5):356–362
50 Binder C, Urlesberger B, Avian A, Pocivalnik M, Müller W, Pichler G. Cerebral and peripheral regional oxygen saturation during postnatal transition in preterm neonates. J Pediatr 2013;163(2): 394–399
51 Fuchs H, Lindner W, Buschko A, Trischberger T, Schmid M, Hummler HD. Cerebral oxygenation in very low birth weight infants supported with sustained lung inflations after birth. Pediatr Res 2011;70(2):176–180
52 Baik N, Urlesberger B, Schwaberger B, Schmölzer GM, Avian A, Pichler G. Cerebral haemorrhage in preterm neonates: does cerebral regional oxygen saturation during the immediate transition matter? Arch Dis Child Fetal Neonatal Ed 2015; 100(5):F422–F427
53 Verhagen EA, Van Braeckel KNJA, van der Veere CN, et al. Cerebral oxygenation is associated with neurodevelopmental outcome of preterm children at age 2 to 3 years. Dev Med Child Neurol 2015; 57(5):449–455
54 Schneider A, Minnich B, Hofstätter E, Weisser C, Hattinger-Jürgenssen E, Wald M. Comparison of four near-infrared spectroscopy devices shows that they are only suitable for monitoring cerebral oxygenation trends in preterm infants. Acta Paediatr 2014;103(9):934–938
55 McLendon D, Check J, Carteaux P, et al. Implementation of potentially better practices for the prevention of brain hemorrhage and ischemic brain injury in very low birth weight infants. Pediatrics 2003;111(4, Pt 2):e497–e503
56 Bada HS, Hajjar W, Chua C, Sumner DS. Noninvasive diagnosis of neonatal asphyxia and intraventricular hemorrhage by Doppler ultrasound. J Pediatr 1979;95(5, Pt 1):775–779
57 Emery JR, Peabody JL. Head position affects intracranial pressure in newborn infants. J Pediatr 1983;103(6):950–953
58 Pellicer A, Gayá F, Madero R, Quero J, Cabañas F. Noninvasive continuous monitoring of the effects of head position on brain hemodynamics in ventilated infants. Pediatrics 2002;109(3): 434–440
59 Aschner JL, Poland RL. Sodium bicarbonate: basically useless therapy. Pediatrics 2008;122(4):831–835
60 Ment LR, Oh W, Ehrenkranz RA, et al. Low-dose indomethacin and prevention of intraventricular hemorrhage: a multicenter randomized trial. Pediatrics 1994;93(4):543–550
61 Schmidt B, Davis P, Moddemann D, et al; Trial of Indomethacin Prophylaxis in Preterms Investigators. Long-term effects of

indomethacin prophylaxis in extremely-low-birth-weight infants. N Engl J Med 2001;344(26):1966–1972
62 Fowlie PW, Davis PG, McGuire W. Prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants. Cochrane Database Syst Rev 2010;(7):CD000174
63 Yanowitz TD, Yao AC, Werner JC, Pettigrew KD, Oh W, Stonestreet BS. Effects of prophylactic low-dose indomethacin on hemodynamics in very low birth weight infants. J Pediatr 1998;132(1): 28–34
64 Koch J, Hensley G, Roy L, Brown S, Ramaciotti C, Rosenfeld CR. Prevalence of spontaneous closure of the ductus arteriosus in neonates at a birth weight of 1000 grams or less. Pediatrics 2006; 117(4):1113–1121
65 Oh W, Poindexter BB, Perritt R, et al; Neonatal Research Network. Association between fluid intake and weight loss during the first ten days of life and risk of bronchopulmonary dysplasia in extremely low birth weight infants. J Pediatr 2005;147(6): 786–790
66 Osborn DA, Evans N, Kluckow M. Hemodynamic and antecedent risk factors of early and late periventricular/intraventricular hemorrhage in premature infants. Pediatrics 2003;112(1, Pt 1):33–39
67 Kabra NS, Schmidt B, Roberts RS, Doyle LW, Papile L, Fanaroff A; Trial of Indomethacin Prophylaxis in Preterms Investigators. Neurosensory impairment after surgical closure of patent ductus arteriosus in extremely low birth weight infants: results from the Trial of Indomethacin Prophylaxis in Preterms. J Pediatr 2007; 150(3):229–234, 234.e1
68 Luque MJ, Tapia JL, Villarroel L, et al; Neocosur Neonatal Network. A risk prediction model for severe intraventricular hemorrhage in very low birth weight infants and the effect of prophylactic indomethacin. J Perinatol 2014;34(1):43–48
69 Kelleher J, Salas AA, Bhat R, et al; GDB Subcommittee, Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Prophylactic indomethacin and intestinal perforation in extremely low birth weight infants. Pediatrics 2014;134(5):e1369–e1377
70 Henderson-Smart DJ, Steer P. Methylxanthine treatment for apnea in preterm infants. Cochrane Database Syst Rev 2001;(3): CD000140
71 Schmidt B, Roberts RS, Davis P, et al; Caffeine for Apnea of Prematurity Trial Group. Long-term effects of caffeine therapy for apnea of prematurity. N Engl J Med 2007;357(19):1893–1902
72 Doyle LW, Cheong J, Hunt RW, et al. Caffeine and brain development in very preterm infants. Ann Neurol 2010;68(5):734–742
73 Mohammed S, Nour I, Shabaan AE, Shouman B, Abdel-Hady H, Nasef N. High versus low-dose caffeine for apnea of prematurity: a randomized controlled trial. Eur J Pediatr 2015;174(7):949–956
74 Ohls RK, Ehrenkranz RA, Das A, et al; National Institute of Child Health and Human Development Neonatal Research Network. Neurodevelopmental outcome and growth at 18 to 22 months' corrected age in extremely low birth weight infants treated with early erythropoietin and iron. Pediatrics 2004;114(5):1287–1291
75 Bierer R, Peceny MC, Hartenberger CH, Ohls RK. Erythropoietin concentrations and neurodevelopmental outcome in preterm infants. Pediatrics 2006;118(3):e635–e640
76 Neubauer AP, Voss W, Wachtendorf M, Jungmann T. Erythropoietin improves neurodevelopmental outcome of extremely preterm infants. Ann Neurol 2010;67(5):657–666
77 McAdams RM, McPherson RJ, Mayock DE, Juul SE. Outcomes of extremely low birth weight infants given early high-dose erythropoietin. J Perinatol 2013;33(3):226–230
78 Ohls RK, Kamath-Rayne BD, Christensen RD, et al. Cognitive outcomes of preterm infants randomized to darbepoetin, erythropoietin, or placebo. Pediatrics 2014;133(6):1023–1030
79 O'Gorman RL, Bucher HU, Held U, Koller BM, Hüppi PS, Hagmann CF; Swiss EPO Neuroprotection Trial Group. Tract-based spatial statistics to assess the neuroprotective effect of early erythropoietin on white matter development in preterm infants. Brain 2015; 138(Pt 2):388–397
80 Leuchter RH, Gui L, Poncet A, et al. Association between early administration of high-dose erythropoietin in preterm infants and brain MRI abnormality at term-equivalent age. JAMA 2014; 312(8):817–824
81 Ohlsson A, Aher SM. Early erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants. Cochrane Database Syst Rev 2014;4(4):CD004863
82 Fauchère JC, Koller BM, Tschopp A, Dame C, Ruegger C, Bucher HU; Swiss Erythropoietin Neuroprotection Trial Group. Safety of early high-dose recombinant erythropoietin for neuroprotection in very preterm infants. J Pediatr 2015;167(1):52–7.e1, 3
83 Schulman J, Stricof R, Stevens TP, et al; New York State Regional Perinatal Care Centers. Statewide NICU central-line-associated bloodstream infection rates decline after bundles and checklists. Pediatrics 2011;127(3):436–444
84 Katheria A, Rich W, Finer N. Development of a strategic process using checklists to facilitate team preparation and improve communication during neonatal resuscitation. Resuscitation 2013;84(11):1552–1557