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Cumulative Perinatal Steroids: Child Development of Preterm Infants

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Abstract

The development of premature infants may be altered due to exposure to high cumulative doses of the perinatal corticosteroid dexamethasone during critical growth periods. To compare child behavioral development of prematurely born infants who were exposed to higher perinatal steroids (PNS; ≥ 0.2 mg/kg) with that of infants exposed to lower PNS (≤ 0.2 mg/kg), we used the Vineland Adaptive Behavioral Scales to assess school-age behavioral outcomes of a historical cohort of 45 prematurely born infants. Children who had received higher PNS treatment were more likely to have lower overall behavioral developmental scores, especially lower social skills ($p < .05$). Higher PNS plus higher severity of illness during the first day of life based on the Clinical Risk Index for Babies ($p = .016$) and lower birth head size ($p = .015$) were linked with poorer behavioral outcomes among participants. Nursing practice includes promotion of quality care and should include closer evaluation of cumulative steroid therapy, severity of illness, and promotion of long-term follow-up support for premature infants.

Keywords

Perinatal steroids; Dexamethasone; Preterm infants; Neurodevelopment

PRETERM DELIVERY, ESTIMATED to occur in 7–11% of all North American births, is responsible for 75% of neonatal deaths (National Institutes of Health [NIH] Consensus Development Conference Statement, 1994). The outcomes of preterm infant survival are often dependent upon the provision of high-quality perinatal care, prior to 40 weeks' postconceptual age, as this is a vulnerable time in development. Over the past 30 years, synthetic or exogenous steroids have increasingly been prescribed before and after birth with the intent to improve infant lung maturity and outcomes. The 1994 NIH consensus panel recommendation for antenatal steroids (before birth) consisted of two doses of 12 mg of betamethasone given intramuscularly at 24-hour intervals or four doses of 6 mg of dexamethasone given intramuscularly at 12-hour intervals. In 2000, the panel revisited this recommendation and discouraged the use of multiple-course antenatal steroids because studies identified associations between steroids and impaired infant head growth and neurodevelopmental outcomes (National Institutes of Health, 2000). Then, early in 2002, a joint statement of the American Academy of Pediatrics (AAP) and the Canadian Paediatric Society called for limitation in the use of postnatal corticosteroids because of concerns regarding risk of neuromorbidity (AAP, Committee on Fetus and Newborn, 2002). Postnatal steroid use with premature infants rose between 1990 and 1998 (8–28%) and began to

decline in 1999; however, approximately 8% of very low birth weight infants continue to receive postnatal steroid treatment (Walsh et al., 2006).

Although commonly given for a variety of therapeutic reasons in perinatal care, the risks may not outweigh the benefits of either higher antenatal or postnatal steroid exposure. Perinatal steroids (PNS) are primarily administered for the promotion of infant lung maturation and reduction of respiratory distress syndrome and mortality (Huang, Dunlop, & Harper, 1999). Many premature infants have received multiple doses of therapeutic steroid drugs while in utero as well as in the postnatal period.

Studies have retrospectively examined either antenatal or postnatal steroid effects (Doyle et al., 2000). This study was the first to retrospectively identify the precise milligram amount of cumulative PNS dosed prior to 40 weeks and prospectively examine relationships with neurodevelopment of premature infants. The primary aim of this study was to examine the relationships between the infants' cumulative PNS exposure measured in milligrams per kilogram of body weight and childhood neurodevelopmental outcomes measured at school age using the Vineland Adaptive Behavioral Scales (VABS) (2001).

THEORETICAL FRAMEWORK

The theoretical framework for this research was formulated from a combination of three models that evolved into the Preterm Infant Vulnerability to Neuromorbidity Model (Figure 1) that focused on health status, relative risks, and resource availability (Als, 1986; Flakerud & Winslow, 1998; Matthews, 2000, 2001). This theoretical framework highlights corticosteroids as one of many perinatal risk factors that can positively or negatively influence preterm infant development and long-term health status. The Conceptual Model of Matthews (2000, 2001) described the sensitivity of the fetal neuroendocrine system, especially the hypothalamic–pituitary–adrenal axis, to increased amounts of glucocorticosteroids during critical stages of development prior to 40 weeks' gestational age as having lifelong effects on behavior and neuroendocrine function. Synactive theory (Als, 1986) added a bioevolutionary view of infant neurodevelopment and provides the central figure of the developing fetus/infant in the study model. PNS pose an environmental risk on the developing fetus/infant (Als, Lester, & Brazelton, 1979). A premature infant's health status, supportive care, and environmental exposures, before and after birth, can, in combination or alone, alter the fetus'/infant's neurodevelopmental subsystems such as communication, motor, and social skills (Als, 1986). The Vulnerable Populations Model (Flakerud & Winslow, 1998) defined a *vulnerable population* as a social group that is at increased susceptibility to adverse health outcomes as evidenced by increased comparative morbidity and premature mortality. Although PNS aid lung maturity, higher doses may be harmful to the long-term developmental health of the vulnerable premature infant whose susceptibility can be multidimensional (e.g., neurosensory, immune, neuromuscular, etc.) depending on the delicate balance between resources and risks. Together, these models provided a framework for this biobehavioral research to examine preterm infant relative risk (cumulative steroid exposures and Clinical Risk Index for Babies [CRIB] scores), resource availability (parental education and prenatal and follow-up care), and associations with adverse health status (VABS and infant health outcomes).

REVIEW OF THE LITERATURE

More than 30 years have passed since antenatal corticosteroids were first shown to increase pulmonary surfactant and, thus, decrease the incidence of respiratory distress syndrome in prematurely born infants (Liggins, 1969; Liggins & Howie, 1972). In very low birth weight infants, the wide use of PNS increased from 19.1% in 1991 to 26.5% in 1999 (Horbar et al., 2002). Repeated antenatal steroid treatments are given to women at risk of premature

delivery and when premature labor recurs. Additional steroids can also be directly administered to the premature infant in the neonatal intensive care unit (NICU) to reduce pulmonary inflammation leading to lung injury and decrease the risk of bronchopulmonary dysplasia (BPD; Jobe & Ikegami, 2000) and chronic lung disease (Barrington, Denson-Lino, Bloch, & Finer, 2001; Bhuta & Ohlsson, 1998).

Long-term steroid tapering regimens were not uncommon in the past two decades. They were used to aid in decreasing infant dependence on ventilators and on oxygen (Halliday & Ehrenkranz, 2001a, 2001b). At school-age follow-up, preterm infants whose chronic lung disease was treated with long-term steroid tapering doses were identified to have poor neurodevelopmental outcomes (Yeh et al., 2004).

Earlier studies with animals found a variety of alterations in neurobehavioral outcome following PNS exposure (Benesova & Pavlik, 1989; Meaney & Stewart, 1981; Weichsel, 1977). Studies on sheep found that greater exposure to early steroid decreased fetal growth (Jobe, Wadda, Berry, Ikegami, & Ervin 1998). Primate studies suggested dose-dependent relationships with decreased growth and impaired neurodevelopment (Coe & Lubach, 2000).

More recent clinical trials have associated steroid exposures to an increase in neurodevelopmental deficits seen among preterm infants (French, Hagan, Evans, Godfrey, & Newnham, 1999; O'Shea & Doyle, 2001; Perlman, 2001; Shinwell et al., 2000; Stark et al., 2001; Yeh et al., 2004). Animal and human studies seem to be identifying similar concerns, but it is difficult to extrapolate from findings of animal and human studies because of the wide variations in drug dosage and administration schedule duration, infant age, birth weights, and severity of illness. Infants who were exposed to high cumulative doses of PNS may show no neurologic side effects until examined later in life.

Kopelman, Moise, Holbert, and Hegemier (1999) showed in their study that, compared to controls, preterm infants less than 28 weeks' gestational age who received postnatal dexamethasone treatment at 0.2 mg/kg had a higher mortality rate (27% vs. 15%, $p = .23$) and higher incidence of Grade III/IV intraventricular hemorrhage (IVH; 22% vs. 12%, $p = .26$). However, nearly 80% of their sample had received additional antenatal steroids. Peabody (2000) commented that these results, albeit not statistically significant, are of such clinical importance that the routine early use of dexamethasone (even at the low level of 0.2 mg/kg) in the neonatal period should be banned. This low dose was equivalent to twice that of the approved estimated fetal exposure (0.1 mg/kg) from a single course of antenatal steroids. During the months prior to delivery, the brain is highly vulnerable to hazardous drugs, stressors, infections, or malnutrition that can disrupt the normal central nervous system organization, thereby placing the infant at greater risk for neurologic adversity (Schonkoff & Phillips, 2000).

In 2002, the Committee on Fetus and Newborn of both the AAP and the Canadian Paediatric Society jointly advised against the routine use of systemic dexamethasone for the prevention of chronic lung disease in preterm infants. The need for neonatal follow-up research was well supported by experts, suggesting that there are many unanswered questions regarding associations between early steroid treatment and delays in infant behavioral development. The consensus view has shifted toward less PNS use.

Concern continues to exist for those children previously exposed to higher steroid treatment. To accurately evaluate steroid exposure, clinical researchers need to look back and quantify doses administered to infants during the perinatal period to identify childhood neurodevelopmental outcomes that potentially reflect mixed blessings. This study was unique in that it retrospectively evaluated cumulative PNS exposure in milligrams per kilogram (before 40 weeks' postconceptual age) to determine associations with

developmental outcomes and to identify potential covariates such as neonatal complications, infant diet, and stress. The study hypothesized that children (ages 5–13) who had been born prematurely and exposed to higher PNS (>0.2 mg/kg) would have lower scores on VABS composite and domain scores than those exposed to no or lower PNS (≤ 0.2 mg/kg).

METHODOLOGY

Design

This descriptive study prospectively examined the relationships between cumulative PNS exposure and childhood neurodevelopmental outcomes measured at school age with the VABS overall composite and individual developmental skill domains (e.g., Motor, Communication, Daily Living, and Social) among a nonrepresentative sample from a historical hospital-based cohort of prematurely born infants. Background characteristics at time of parent report of child's development were prospectively collected to evaluate potential confounders (e.g., parental education, race, post-NICU infant supportive services, breast-feeding, etc.). Background characteristics at time of delivery and NICU stay were retrospectively collected to evaluate potential covariates of interest (e.g., infant gender, growth, and severity of illness at birth).

Instruments/Measures

Child Behavioral Development—The VABS is a well-developed, parent-reported psychometric tool that has established validity and reliability for measuring behavioral development against the normal population. VABS provides an overall behavioral development summary (composite) and includes subcomponent domains (Rosenbaum, Saigal, Szatmari, & Hoult, 1995). The VABS covers the following four domains of adaptive behavior. The Communication subscale covers expressive, receptive, and written language to determine what a child understands, says, reads, and writes. The Daily Living Skills (DLS) domain looks at practical skills a child needs in the provision of personal, domestic, and community skillfulness and aptitude. The Socialization domain identifies coping skills, interpersonal relationships, and play and leisure time competence. The Motor Skills subscale evaluates a child's fine and gross motor movements and coordination.

Strong to moderate correlations between VABS subscale and total scores were previously reported with a variety of other screening tools used to test child development of premature infants (Sparrow, Balla, & Cicchetti, 1984). Using a sample of 3,000 individuals divided into 15 age groups of 200 individuals from a national standardization program, Sparrow et al. (1984) reported that VABS had good intraclass correlation coefficients for test–retest reliability (.95–.99) and interrater reliability (.93–.99) for each domain and subdomain as well as for the composite (.99 and .98, respectively). Criterion-related validity is reported with correlations (.58) between VABS and other adaptive behavioral and intelligence scales such as the Adaptive Behavior Inventory for Children (Mercer & Lewis, 1978). Internal consistency reliability coefficients for the VABS composite (tested with Guilford's formula for reliability) and for VABS domains (tested with Spearman–Brown formula for split-half coefficients) were very good across all age groups and the following behavioral domains: Communication ($Mdn = .89$), DLS ($Mdn = .90$), Socialization ($Mdn = .86$), Motor Skills ($Mdn = .83$), and Adaptive Behavior Composite ($Mdn = .94$).

Sparrow et al. (1984) provided a variety of derived scoring (e.g., standard scores, percentile ranks, stanines, and adaptive levels), all based upon a national standardization. They recommended that the VABS raw scores were not directly interpretable because the same raw score may signify different levels of performance depending upon the individual's age. Due to the wide age range of prematurely born children in this sample, the standard scores, percentile ranks, stanines, and adaptive levels were analyzed and the raw scores were not

examined. VABS standard scores are expressed in standard deviation units and have a mean of 100 ($SD = 15$). The following categories of adaptive levels correspond to the standard scores: high (131 to 160), moderately high (116 to 130), adequate (85 to 115), moderately low (70 to 84), and low (<70 to 69). Data cut points for behavioral scores were set at 1 SD or below the mean for all derived scores, as this corresponded with the moderately low category.

Infant Severity of Illness—The CRIB has the ability to discriminate and weigh perinatal risk factors suggestive of severity of illness that can significantly influence preterm infant outcomes (Gagliardi et al., 2004; Richardson, Tarnow-Mordi, & Escobar, 1998). The CRIB was identified as a valid and reliable measure of severity of illness beyond the first 12 hours of life, with strong interrater reliability (.96; 95% confidence interval [CI] = 0.94–1.00), intrarater reliability (.97; 95% CI = 0.94–1.00), and intraclass reliability (.93; 95% CI = 0.82–1.00) identified using correlation coefficients and 95% CIs (Fowlie, Gould, Tarnow-Mordi, & Strang, 1997). The CRIB consists of the following six items identified during the first day of life: birth weight, gestational age, highest and lowest fractions of inspired oxygen (FiO_2), worst base excess, and congenital anomalies (Bührer, Grimmer, Metze, & Obladen, 2000; Gagliardi et al., 2004). Scores of greater than 7 (range = 0–23) were considered high and representative of high biophysiologic stress or severity of illness at birth. Bührer et al. (2000) identified that scores greater than 7 were associated with poorer neurodevelopment at 1-year corrected age in very low birth weight infants.

Anthropomorphic Data—The Colorado Intrauterine Growth Charts are well-recognized tools utilized for measuring prenatal growth based upon gestational age at birth (Lubchenco, Hansman, & Boyd, 1966). The Infant Health and Development Program (IHDP) low birth weight growth charts are well recognized by the Centers for Disease Control and Prevention as standardized growth tools for the assessment of preterm infants who were less than 2,500 g and less than or equal to 37 weeks' gestational age when they were born (Guo, Roche, Chumlea, Casey, & Moore, 1997; Sherry, Zuguo, Grummer-Strawn, & Dietz, 2003). These low birth weight growth chart measurements were developed from a study of 867 preterm infants in the IHDP, a randomized clinical trial that included various ethnic groups at eight sites. Guo et al. (1997) report that two thirds of the infant birth weights were less than 2,000 g, and one third had birth weights between 2,000 and 2,500 g. Scales for estimates of head circumference (HC), length, and weight from 36 weeks' postconception to 36 months of gestation-adjusted age were developed from a statistical model fitted to serial data measurements taken at birth, at 40 weeks of postconceptional age, and at 4, 8, 12, 18, 24, 30, and 36 months of gestation-adjusted age.

Procedures of Conducting Study

Child Development Data—The dependent variable was developmental scores on the parent-reported VABS. During 2001–2003, VABS scores were obtained during a 45-minute interview in the parent's home or by telephone with a professional developmental specialist trained in VABS developmental interviews and scoring. She was unaware of the children's steroid exposure levels. She was fluent in written and spoken Spanish and English. Parents reported their perceptions of their child's display of particular behaviors according to the VABS questions. Parent summary letters were provided after the information was computer scored to standard scores, percentile ranks, stanines, and adaptive levels.

Additional Parent and Child Data—Demographic information was prospectively obtained at time of parent interview. Parental education and marital status, child's current age and educational level, and ethnicity were recorded on the VABS sheets and an investigator-prepared form filled out by the parent, which included post-NICU home

medications or equipment, breast milk feedings or formula feedings, and receipt of developmental or other supportive therapies.

The principal investigator collected and retrospectively examined the following background data abstracted from the maternal labor and delivery record and the infant's hospital records. This included the following information for cumulative PNS dose, CRIB score, and maternal and infant characteristics during the child's NICU stay.

Cumulative PNS Data—The independent variable (exposure of interest) was the cumulative PNS dose of dexamethasone received by the infant prior to 40 weeks' post-conceptual age. Perinatal dexamethasone doses were identified from chart reviews of the mother's labor and delivery records and the child's birth and NICU records. PNS dose was calculated according to the amount received by the fetus based on a reported dose administered to the mother (Coe & Lubach, 2000), then adjusted for the 30% fetal absorption rate (Ballard & Ballard, 1995). Total cumulative exposure to PNS was estimated by adding the amount of the fetal dose to the calculation of the infant's total postnatal dose prior to 40 weeks' postconceptual age. Participants were then dichotomized based on total PNS received: higher PNS-dexamethasone (>0.2 mg/kg) and lower PNS-dexamethasone (≤ 0.2 mg/kg), to compare children based upon the differences between these two steroid levels. Peabody's argument against the routine early use of even 0.2 mg/kg dexamethasone justified the study of this dosage for scrutiny of associations that minimal steroid exposure has with developmental outcomes.

Background Characteristics

General Characteristics Data—Parental education, infant race, post-NICU infant supportive services, and data on breast milk feeding or formula feeding were obtained by parent report at time of developmental interviews.

Medical Characteristics Data—Maternal pregnancy and delivery characteristics and infant medical and anthropomorphic characteristics were retrospectively gathered from medical chart review for descriptive analysis by the principal investigator. Maternal medical background data included delivery type, hypertension, fever, prenatal care, maternal smoking, weight, age, laboratory test results, and chorioamnionitis. Infant medical background data that could be potential covariates were gathered and included gestational age at birth, Apgar scores, laboratory test results, NICU length of stay, time on mechanical ventilation, sepsis, length of time to full enteral feeds, BPD, degree of IVH, discharged home on medications, oxygen, sepsis, seizures, retinopathy of prematurity (ROP) staging, and necrotizing enterocolitis (NEC). Infant severity of illness during the first day of life was retrospectively gathered from medical chart information and scored on the CRIB sheet. Anthropomorphic measurements (HC, length, and weight) were plotted by the principal investigator and randomly double checked by the developmental specialist on the Colorado Intrauterine Growth Charts (Lubchenco, Hansman, & Boyd, 1966) and the Ross low birth weight growth charts.

Locating Participants

Participants were selected from a historical hospital-based cohort of children who were born prematurely before 32 weeks' gestation between 1990 and 1998. These children were born prior to the national PNS alerts published in 2000 and cared for in a single public tertiary NICU where postnatal use of artificial surfactant was a standard of care. Two hundred eighty-one potential participants were identified from logbooks of neonatal births during that period. National and local proprietary searches were utilized to locate 213 (86%) potential participants' addresses for the mailing of invitations to participate. Of these, 26 (11%) were

lost to follow-up when they went to foster or other care. Only 51 (27.3%) of the remaining 187 families contacted the research staff by telephone or return self-addressed prestamped postcards; of these, 45 joined (88%, or 24% of the initial recruited sample).

Analysis

Statistical analyses were performed using SAS 8.02 (1999–2001) and STATA 8 (2003) to examine and estimate the associations between VABS scores, CRIB scores, background characteristics, and PNS dosage. Descriptive analyses, frequency distribution, cross tabulation, Fisher's Exact Test, Mantel–Haenszel odds ratios (ORs), and chi-square tests were used for analyzing categorical data. Continuous data were analyzed using Student's *t* test and analysis of variance and regression analysis with post hoc testing with Hosmer–Lemeshow goodness-of-fit test using a .05 level of significance. Murphy et al. (2001) supported the use of several regression techniques to analyze dexamethasone exposure and associations with brain development. Similarly, this study identified predictor variables, each with the potential to act as a confounder to others; thus, multivariate analytic methods were used to cope with these during the analysis phase to better assess the independent contributions of predictor variables. Linear regressions for continuous variables and logistic regression for dichotomous variables were used to examine any statistically significant relationships with, first, the independent variable and, then, with the dependent variables to identify avenues for future research.

Participants

All children admitted to the study were preterm singleton births between 24 and 32 weeks' gestation, as determined by Ballard score. Children who resided with a parent or legal guardian who could read English or Spanish and provide informed consent were eligible for the study. Children excluded from the study were those who were of multiple births or diagnosed with congenital anomalies. The reported characteristics of the parents and children are presented in Tables 1–4. Most mothers were married (51%) or living with a significant other (9%). The mean maternal age was 30 years. Data on age and education are listed in Table 1. Most mothers had greater than high school education (58%), 18% had a high school education, and 24% had an eighth-grade education or less. Only 30% of the fathers had greater than high school education, 45% had a high school education, and 25% had an eighth-grade education or less.

Background characteristics of the children in this study provide information about the early health status of this sample and are depicted in Tables 2 and 3. At the time of parent report of development, the children had a mean age of 8 years (range = 5–13, *SD* = 2.3). Their mean gestational age at birth was 28 weeks (*SD* = 2.2), and their mean birth weight was 1,066 g (*SD* = 327; 47% female, 53% male). The data on NICU health status suggested a wide range of medical vulnerability and neuromorbidity risk among this sample. Mean length of NICU hospitalization was 68 days (*SD* = 28). Nearly all the children (>95%) had some form of health care insurance resource at time of birth, mostly state medical assistance.

Table 4 displays the other resource characteristics of these children after hospital discharge. Less than half (42%) of the children were discharged home with some medical equipment, and less than a quarter (22%) required prescription medications. Two thirds of the sample received developmental support or a combination of other services provided by a regional center.

RESULTS

VABS Results for Study Sample

The frequency distributions for the study sample were similar across the variety of derived VABS scoring methods (e.g., national standard, national percentile ranks, stanines, and adaptive levels). The sample's VABS national standard scores are provided here, and additional information is listed in Table 5. The mean of VABS composite scores was 87 ($SD = 16$). The mean of VABS Communication scores was 89 ($SD = 18$). The mean of VABS Motor scores was 100 ($SD = 17$). The mean of VABS DLS scores was 90 ($SD = 17$). The mean of VABS Social Skills scores was 88 ($SD = 15$). Figure 2 shows the percentages of children who scored low on VABS outcomes (national standard scores 1 SD or below the mean) between the two PNS treatment groups, and Table 6 displays the data comparisons.

PNS and VABS Composite Scores

General findings in this study were that across all derived scores, prematurely born children who were exposed to higher PNS (>0.2 mg/kg) were more likely to have lower scores on VABS overall developmental composite and subscale domains than prematurely born children who were exposed to lower PNS (≤ 0.2 mg/kg). When VABS composite standard scores for overall adaptive behavior were cut at the mean and evaluated, the data suggested that children in the higher dose PNS group were almost twice as likely to score below the mean for the sample population (i.e., 60% vs. 44%, $OR = 1.9$, confidence limits [CL] = 0.5, 6.5). Of the perinatal factors examined in multivariate regression analysis, those strongly associated with lower VABS composites were lower mean HC at birth ($p = .013$, $CL = -0.65, -0.08$) and the clustered variable of both higher PNS and higher CRIB score ($p = .016$, $CL = 0.04, 0.42$).

PNS and DLS Scores

Table 6 shows that the higher PNS group was approximately twice as likely to have lower scores on VABS DLS (i.e., 35% vs. 20%, $OR = 2.2$, $CL = 0.6, 8.3$).

PNS and Communication Scores

Across all analyses and VABS-derived scores, the children treated with higher PNS were found more likely to score lower on communication skills. Table 6 depicts that the children exposed to higher PNS were nearly three times as likely to have lower VABS expressive and receptive language scores as the children exposed to lower PNS (i.e., 50% vs. 28%, $OR = 2.6$, $CL = 0.7, 8.9$). Although most families reported themselves to be of Hispanic descent (62%), only 42% of the children resided in households where Spanish was spoken.

PNS and VABS Social Scores

In the VABS subscale scores, the strongest associations were noted between children treated with >0.2 mg/kg cumulative dexamethasone who were found to be at least two to three and a half times more likely to have lower social scores than those treated with ≤ 0.2 mg/kg cumulative dexamethasone. Table 6 shows that children in the group treated with higher PNS (55% vs. 36%) were more likely to score greater than or equal to 1 SD below the mean on social skills compared to those in the group treated with lower PNS ($OR = 2.2$, $CL = 0.7, 7.2$). A negative association was also noted with social scores and cumulative PNS; for every unit increase in PNS, there was approximately a 9-point reduction in VABS social standard score ($p = .04$, $CL = -18, -0.67$). Length of NICU stay was also a significant factor ($p = .001$, $CL = 0.004, 0.01$). Regression analysis of social standard scores found that higher dose PNS exposures had a strong negative influence on social skills ($p = .006$, $CL =$

−19, −3), whereas breast milk feeding had a strong positive influence on social skills ($p = .001$, $CL = 6, 22$).

PNS and VABS Motor Scores

Children treated with >0.2 mg/kg PNS were approximately two times more likely to have deficits in standard motor scores. Examination of VABS national standard scores identified that 50% of the children treated with higher PNS had motor skill deficits compared to 32% of the children who were either not treated or treated with lower PNS ($OR = 2.1$, $CL = 0.6, 7.4$).

PNS and Infant Characteristics at Time of NICU Discharge

Background characteristic differences between the two steroid exposure groups are provided in Table 7. Duration of hospitalization was longer in infants who had BPD, prolonged mechanical ventilation, and receipt of the higher PNS dose. Compared to the lower PNS group, children in the higher PNS group were more likely to be male. Sepsis occurred more commonly in children in the higher PNS group. Parental concern ($p = .007$, $CL = 0.1, 0.7$) was strongly linked to lower VABS composite scores.

Anthropomorphic Outcomes, Growth, and Nutrition

Children in the higher PNS group were smaller at NICU discharge than children in the lower PNS group. Table 7 includes comparisons of the means of anthropomorphic measures between the two PNS groups at NICU discharge using the Fisher's Exact Test (F test). The mean HC (33 cm; $SD = 1.7$) was significantly smaller between the higher PNS group compared to the lower PNS group (32.2 vs. 33.4; $p = .02$, $CL = 0.04, 0.73$) at time of NICU discharge. The mean length was 44 cm ($SD = 3$), and mean weight was 2,312 g ($SD = 442$) at discharge. The means of infants' lengths were 2.3 cm shorter, and weight percentiles (16% vs. 32%) were plotted lower comparatively for the children in the higher PNS group at hospital discharge ($p = .01$, $CL = 0.02, 0.5$).

A lower NICU discharge weight and HC percentile and decreased length in centimeters were noted among the higher PNS group, despite the fact that children in this group tended to have a longer NICU hospitalization and were more likely to have received breast milk feedings (45% vs. 28%). In the multivariate analysis, significant predictors of lower overall VABS composite scores were birth HC ($p = .015$, $CL = 0.02, 0.15$) and the combination of higher PNS and a higher CRIB score ($p = .016$, $CL = 0.05, 0.43$). Regression analyses suggested that maternal background characteristics were nonsignificant in relation to higher PNS and growth.

DISCUSSION

Developmental delay in latent child behavioral outcomes remains an important and adverse complication among low birth weight premature infants. Using a biobehavioral approach, we provide in this study insight into evaluation of cumulative PNS dexamethasone exposure prior to 40 weeks' postconceptual age as a potential risk factor along with severity of illness and associations with poorer growth and developmental outcomes of children born premature. Examining cumulative PNS exposure may clarify some of the ambiguity and uncertainty that surround similar research that refers to percentage of the sample contaminated by postnatal or antenatal steroids. Without assessment of the actual total steroid dose, there is an increased risk of biased and inaccurate predictions of the exposure and relationships to neonatal outcomes data.

PNS and VABS Overall Composite Outcomes

The higher PNS group was more likely than the no-low PNS group in this sample to be at risk for deficits in the following skill domains: Social, Communication, Motor, and DLS. Although these findings may present some level of clinical significance, it is important to note that most of these findings did not reach a level of statistical significance. Neurobehavioral problems at school age among children born prematurely may be linked to perinatal influences (Hack, Flannery, Schluchter, Cartar, & Klein, 2002; Hack, Taylor, Klein, & Mercuri-Minich, 2000). Specifically, French et al. (1999), Perlman (2001), and Smith, Qureshi, and Chao (2000) cited multiple steroid exposures as a potential risk factor for neurodevelopmental deficits seen among preterm infants.

Gathering data on children's behavior by parent report can be complex and challenging for parents of children who had more chronic health conditions or involved neonatal histories. For some parents, it may be the first time they are describing or recognizing the unique differences of their child. This may result in parents' misreporting of developmental skills.

Although children who were exposed to higher PNS were more likely to be sicker infants with longer mechanical ventilation time and hospital stays, these potential covariates were not identified as strong predictors of adverse behavioral outcomes in the regression analyses. Most maternal and infant background characteristics, developmental resources, and clinical NICU health status of these children (e.g., BPD, NEC, IVH, NICU stay, and mechanical ventilation) were also tested and found to not be significantly associated with adverse behavioral outcomes. The exception was that lower overall VABS composite scores were associated with lower birth HC and the combination of higher PNS and high severity of illness noted on the CRIB score. This suggests that other factors beyond higher PNS, such as fetal growth and severity of illness during the first 24 hours of life, also influenced the behavioral outcomes of this study group.

PNS, VABS Composite, Growth, and CRIB Score Outcomes

It was not surprising that lower head sizes at birth were significantly associated with lower overall VABS composite scores in children who had higher cumulative PNS and high CRIB scores at birth. These findings were consistent with studies that suggested that PNS effects decreased preterm infant size and subsequent growth (French et al., 1999) and that preterm infant subnormal head size impacts cognitive abilities at school age (Hack et al., 1991). This is also consistent with findings in animal studies that suggested a dose-dependent steroid relationship with decreased fetal growth (Coe & Lubach, 2000; Jobe et al., 1998).

Adaptive behavioral development is complex and can be influenced by a variety of factors that either disrupt or balance outcomes. For example, greater severity of illness at birth (e.g., higher CRIB scores) may be a proxy for elevated stress causing higher endogenous steroid levels. Elevated stress can alter lipid and glucose metabolism, adversely influencing growth and neurodevelopment (Matthews, 2001). However, much debate has evolved around differences in infant nutrition and the associations with early growth and neurobehavioral outcomes (Beliakov, Kashin, & Popova, 2003; Dobbing & Sands, 1978; Feldman & Eidelman, 2003). Similarly, other studies have reported better social skills in breast-milk-fed versus formula-fed infants who had lower weight and height growth (Beliakov et al., 2003; Feldman et al., 2003).

PNS and Social Outcomes

Although these higher PNS levels were strongly associated with adverse social outcomes, it is possible that the lower social skills of these children were additionally influenced by factors not collected in this study (e.g., parental attachment, support, and employment

status). Social deficits after steroid treatment were a concern of the 1994 NIH consensus panel that set limits on antenatal steroid dosing, warning that long-term studies were needed because of findings in earlier steroid studies in small animals (Benesova & Pavlik, 1989; Meaney & Stewart, 1981).

PNS and Communication Outcomes

Communication disorders are commonly classified as receptive (disorder of input) and expressive (disorder of production), and any language deficit can have far-reaching meaning for overall child development (Spreen, Risser, & Edgell, 1995). A pervasive trend exists whereby immigrant parents reinforce their ancestral culture in their homes by speaking their elders' language (Weiss & Van Haren, 2003). Cultural differences influencing language development, such as growing up in a bilingual speaking home, should not be diagnosed as communication disorders (Weiss & Van Haren, 2003). Although lower communication skills were identified among the children in the higher dose PNS group, receipt of speech therapy for language delays or disorders was not significantly different between steroid groups. Many of the children (62%) were from bilingual or monolingual Spanish-speaking households. This may have placed them at a lingual disadvantage. Ethnicity did not influence this outcome across groups but may have a role in influencing individual children.

PNS and Motor Outcomes

There have been concerns about the incidence of cerebral palsy (CP) and motor delays among infants treated with higher PNS levels (Bos, Dibiasi, Tiessen, & Bergman, 2002; Esplin, Fausett, & Smith, 2000). Several systematic reviews identified an increased incidence of CP among children who had received postnatal steroids, and this has led to current PNS warnings (Barrington, 2001a, 2001b, 2001c; Doyle & Davis, 2000). CP, a general term applied to a variety of motor disorders, is commonly linked with anoxic episodes and complications of prematurity. There were clinically significant differences in the motor skills of the steroid exposure groups in this study, but incidence of CP was not found to be significantly related to higher PNS exposure as noted in prior studies (Shinwell et al., 2000).

Limitations

The major limitation of this study is its small sample size. This study involved a nonrepresentative sample. These findings are specific to these children. This study did not evaluate the entire accessible population; therefore, it may be at risk of sampling biases. A variety of approaches were used to reduce the bias of nonparticipation. Despite exhaustive efforts, it was not feasible to locate a larger sample; thus, data on nonparticipating families were lost to follow-up. Sample size limited how the statistical analyses could be conducted and limited the power to detect modest relationships among the covariates evaluated. Findings were not adjusted for the effect of running multiple tests and inflating experiment-wise error. Limits on data requested were related to parent demographics. It was not clear whether the father living in the household was the biological father. Evaluation of maternal employment status was not conducted to determine any differences between the groups. The child behavioral measurement tool was based on parent report, and the possibility exists that individual parents were inclined to mischaracterize or misreport current developmental information.

Implications for Nursing and Future Directions

This descriptive study is the first study to examine the relationship between PNS dose and latent developmental outcomes of preterm infants. Research guided by evidence-based literature reviews and national guidelines identified important information for better follow-

up of PNS treatment among premature infants. Developmental follow-up of cumulative PNS exposure is clinically relevant as well as scientifically important to preterm infant care as prescribing steroids continues. The benefits of higher dexamethasone doses have not outweighed the risk of adverse outcomes; hence, trends are shifting toward other steroid treatments such as hydrocortisone. This study provides one method of clarifying cumulative exposure for purposes of high-risk infant follow-up and early intervention as needed. Monitoring infant treatments and outcomes for quality improvement initiatives is within the role of nursing. Nurses can advocate for interdisciplinary team and parent awareness of steroid risks and benefits.

One area that should be explored further in future PNS research is the effects steroids play on early growth measurements. Another is to evaluate associations with nutritional interventions (i.e., earlier breast milk feeding or exclusive breast milk feeding when possible). Additionally, little research has been done to explore the long-term outcomes of the combined exposure to perinatal stress (endogenous steroids) and exogenous steroid treatments among preterm infants. Larger sample sizes will be needed to adequately speak to the interactions of stress, steroids, and growth as causal factors along the pathway that influence functional behavioral outcomes. Prospective randomized control trials of steroid treatments are superior for comparisons of children's development at the same points in time. Future clinical trials of lower dose regimens including variables assessed in this study may provide better data about optimal timing and cumulative dosage relevant to neurodevelopment.

SUMMARY

Within a small cohort study, it is unwise to make broad conclusions based upon preliminary findings. Future research should consider the fetus/infant in a state of evolution that is on a continuum from uterine life throughout the NICU stay. By conceptualizing cumulative PNS exposures and examining relationships with severity of illness and latent development of preterm infants, this study sought to add to the body of scientific knowledge in this area and challenge conventional wisdom. Concern should continue to exist for those children previously exposed to higher steroid treatment. To accurately evaluate steroid exposure, clinical researchers need to look back and quantify doses offered to patients to identify childhood outcomes that reflect potentially mixed blessings. The moratorium on PNS may have already altered clinical practice and limited usage of dexamethasone or led to substituting another steroid, hydro-cortisone, about which even less is known. Thus, it seems that the search should continue for safer minimal dose steroid guidelines with a focus on cumulative exposure and close assessment of infant development throughout childhood.

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Figure 1. Preterm infant vulnerability to neuromorbidity. Revision of central diagram of fetal/infant derived with permission from A Synactive Model of Neonatal Behavioral Organization (Als, 1986).

Figure 2.

Comparisons of PNS exposures among prematurely born children who scored low on VABS. † ≥ 1 SD below the mean on national standard scores. *Social standard scores ($p = .04$, $CL = -18, -0.07$).

Table 1

Self-Report for Characteristics of Parents of Child Participants

Characteristic	<i>n</i>	%
Maternal age, in years (<i>N</i> = 45)		
<25	9	20
25–35	29	64
>35	7	16
Maternal education (<i>N</i> = 45)		
Eighth grade or less	11	24
High school	8	18
Partial college or graduate	26	58
Paternal highest education* (<i>n</i> = 40)		
Eighth grade or less	18	45
High school education	10	25
Partial college or graduate	12	30
Marriage status (<i>n</i> = 45)		
Nonmarried, living alone	18	40
Married or with significant other	27	60

* Missing data for five fathers.

Table 2Demographic and Specific Health Characteristics of Child Participants ($N = 45$)

Characteristic	<i>n</i>	%
Gestational age (weeks)		
24–26	12	27
27–29	30	67
30–32	3	7
Ethnicity		
African American	9	20
Hispanic/Latino	28	62
Caucasian	5	11
Other	3	7
Gender		
Female	21	47
Male	24	53
NICU medical diagnoses*		
IVH, any grade	11	24
IVH, Grade III/IV	4	9
ROP	12	27
NEC	6	14
BPD	21	48
Sepsis	17	38
>28 days on ventilation	14	31

* Infants could have more than one medical diagnosis.

Table 3

Anthropometric and Treatment Characteristics at Birth and at the Time of Hospital Discharge of 45 Child Participants

Parameter	<i>M</i>	<i>SD</i>	Range
Birth weight (g)	1,066	327.2	526–1,975
Birth length (cm)	36	3.2	30–43
Birth HC (cm)	25	2.6	21–31.5
Discharge weight (g)	2,312	442	1,292–3,495
Discharge HC (cm)	33	1.7	27.5–36
Discharge length (cm)	44	3	37–50
Days to full enteral feed	25	22	1–97
Length of NICU stay	68	28	15–138

Table 4

Parent-Reported Child Resource Characteristics for Period Following Hospital Discharge for 45 Child Participants

Variable	<i>n</i>	%
Breast milk fed	16	36
Formula fed	42	93
Discharged home on medical equipment	21	42
Discharged home on prescribed medications	10	22
Developmental follow-up	29	64
Speech follow-up	12	27
Physical therapy follow-up	20	44
Other therapy follow-up	20	44
Readmission to hospital more than one time	24	53

Table 5
Frequency Distribution of VABS National Standard Scores Based Upon Parent Report of Their Child's Behavior

VABS Standard Scores	<i>M</i>	<i>SD</i>	<i>Mdn</i>	Minimum	Maximum
Composite	87	16	85	60	126
Communication	89	18	90	52	127
Motor	100	17	70	47	113
DLS	90	17	93	7	115
Social	88	15	88	53	118

Table 6

Child Participants ($N = 45$) Identified for High Versus “Low or No” Cumulative PNS Exposure Who Scored Low on VABS National Standard Scores

Children ≥ 1 SD Below the Mean VABS Standard Score by Cumulative PNS Exposure Levels				
Scales	>0.2 mg/kg[†] ($n = 20$), n (% affected)	≤ 0.2 mg/kg[‡] ($n = 25$), n (% affected)	cOR*	95% CL
Composite	11 (55)	11 (44)	1.6	(0.5, 5.1)
Motor	6 (30)	5 (20)	1.7	(0.4, 6.7)
DLS	7 (35)	5 (20)	2.2	(0.6, 8.3)
Communication	10 (50)	7 (28)	2.6	(0.7, 8.9)
Socialization	11 (55)	9 (36)	2.2	(0.7, 7.2)

* Mantel–Haenszel Crude OR.

[†] Cumulative exposure to high dose dexamethasone (>0.2 mg/kg).

[‡] Cumulative exposure to no dose/low-dose dexamethasone (≤ 0.2 mg/kg).

Table 7
Comparison of Perinatal Physiologic and Background Characteristics of Children Classified Between Cumulative PNS Exposure Groups

	No-Low PNS (≤ 0.2 mg/kg)		High PNS (> 0.2 mg/kg)		M	n	Test	p
	n	M	n	M				
Male (%)	25	40	20	70			χ^2	.04*
5-minute Apgar score < 5 (%)	25	7.28	20	5.7			t test	.03*
Sepsis (%)	25	24	20	55			χ^2	.03*
BPD (%)	24	29	20	70			χ^2	.007*
ROP (%)	25	20	20	35			χ^2	.26
NEC (%)	24	13	20	20			χ^2	.50
IVH (%)	25	20	20	15			χ^2	.66
Length of stay (days)	25	54	20	82.6			t test	.001*
Discharge HC (cm) 24	24	32.2	20	33.4			F test	.02*
Discharge weight (percentile) 25	25	31.5	20	15.5			F test	.01*
Discharge length (cm) 24	24	45.6	20	43.3			F test	.01*
Any breast milk feeds (%)	25	28	20	45			χ^2	.24
Developmental follow-up (%)	25	64	20	65			χ^2	.94
Maternal smoke (%)	25	16	18	6			χ^2	.29
CP (%)	25	12	20	5			χ^2	.41
GA [†] antenatal steroid (weeks)	21	27.4	15	26.4			t test	.13
Chorioamnionitis (%)	25	12	20	10			χ^2	.83
Maternal age at delivery (years)	25	29.4	20	29.9			t test	.77
Prenatal care (%)	25	76	20	85			χ^2	.45
PROM > 24 hours (%) [‡]	25	20	18	6			χ^2	.18

* Statistically significant at $p < .05$.

[†] Gestational age at time of delivery of antenatal steroids.

[‡] Premature rupture of membranes greater than 24 hours prior to time of delivery.