Published in final edited form as:

Biol Res Nurs. 2013 January ; 15(1): 86–95. doi:10.1177/1099800411420134.

A Psychoneuroimmunologic Examination of Cumulative Perinatal Steroid Exposures and Preterm Infant Behavioral Follow-Up

Isabell B. Purdy, PhD, NNP, CPNP¹, Lynne Smith, MD¹, Dorothy Wiley, PhD², and Lina Badr, DNSc., CPNP²

¹Department of Pediatrics, Neonatology, David Geffen School of Medicine at University of California, Los Angeles, CA, USA

²UCLA School of Nursing, Los Angeles, CA

Abstract

Purpose—This study's aim was to explore relationships between preterm infant behavioral outcomes and maternal/infant glucocorticoid (dexamethasone [DEX]) treatments using a psychoneuroimmunologic approach. Research questions were (a) do relationships exist between infant cumulative perinatal steroid (PNS) exposure and child behavioral problems? and (b) do maternal/infant characteristics (e.g., immune markers and biophysiological stressors) influence these relationships?

Methods—The convenience sample comprised 45 mother–child dyads in which the children (mean age 8 years $\pm$ 2.3) had been born at a mean postconceptional age of 28 weeks ($\pm$ 4.2). We used the Child Behavior Checklist (CBCL) to assess behavior, the Clinical Risk Index for Babies (CRIB) to score stress at birth, and retrospective record review to identify additional perinatal factors (PNS dosage, sepsis, and maternal and infant complete blood counts near delivery).

Results—Children were dichotomized into high ($> 0.2\text{mg/kg}$; $n = 20$) versus low–no ($\leq 0.2\text{mg/kg}$; $n = 25$) PNS exposure groups. Significant relationships existed between CBCL Total Problems score and sepsis, PNS exposure, timing of initial PNS, and infant length percentile at discharge. Competence problems were significantly associated with PNS, neonatal intensive care unit (NICU) infant length percentile, CRIB score, sepsis, retinopathy of prematurity, hearing deficit, and immunity markers (i.e., maternal lymphocyte percentage and infant band/seg ratio). Children in the higher PNS group exhibited more behavioral problems (e.g., withdrawn, attention, conduct, social, and rule breaking problems), but there were no significant differences. The findings are reassuring regarding long-term effects of this PNS dose on preterm infant behavioral outcomes.

© The Author(s) 2011

Corresponding Author: Isabell B. Purdy, Department of Pediatrics, Neonatology, David Geffen School of Medicine at University of California, 10833 Le Conte Avenue, MDCC, Room B2-375 Mailcode 175217, Los Angeles, CA 90096, USA, ipurdy@mednet.ucla.edu.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Keywords

steroids; dexamethasone; psychoneuroimmunology; preterm infant; behavior; neurodevelopment; childhood; stress

Nearly 40 years have passed since Liggins and Howie (1972) identified the benefits that glucocorticoids offer for premature infant lung development. These initial findings led to further research and promotion of the use of antenatal steroids by the National Institutes of Health (2000). Clinicians administered repeated antenatal steroid treatments like dexamethasone (DEX) to women at risk of premature delivery prior to 32 weeks' postconceptional age (PCA) and with the recurrence of premature labor. Initially, the recommended standard of care for single-course antenatal DEX was to administer four individual 6-mg doses intramuscularly (IM) 12 hr apart (National Institute of Health [NIH], 1994). At the same time, postnatal steroids were primarily administered in the neonatal intensive care unit (NICU) to reduce pulmonary inflammation leading to lung injury and to decrease the risk of bronchopulmonary dysplasia ([BPD] Jobe & Ikegami, 2000). Additionally, clinicians used long-term steroid-tapering regimens to aid in decreasing infant dependence on ventilators and oxygen (Halliday & Ehrenkranz, 2001a, 2001b).

Glucocorticoids are essential for normal hypothalamic–pituitary–adrenal (HPA) axis activity; however, many researchers have warned that exposure to excess endogenous or synthetic glucocorticoids like DEX during a vulnerable period of fetal development, prior to 40 weeks' PCA adversely affects the HPA axis, immunity, and behavioral outcomes (Ng et al., 1999). For example, Shoener, Baig, and Page (2006) found an association between late-gestation DEX exposure in rats and persistent changes in modulating HPA axis activity and mediated response to stress. Experts have also expressed concerns that increased steroid dosing may lead to neurologic problems, as additional animal studies have shown (Dunlap, Archer, Quinlivan, Beazley, & Newnham, 1997). Animal studies have also suggested that antenatal DEX might decrease immune responsiveness, resulting in prolonged effects post-birth (Coe & Lubach, 2005). While animal studies raise concerns, it is difficult to extrapolate their findings to humans because of the wide variations in drug dosage and duration, infant age, birth weights, and severity of illness. In fact, human infants exposed to higher cumulative perinatal steroid (PNS) may show no neurologic side effects until later in life. Clinical trials have associated steroid treatment with stunted growth, cerebral atrophy, neurobehavioral deficits, and endocrine disruption (Benesova & Pavlik, 1989).

Due to these concerns, experts began to discourage the use of multiple-course antenatal steroids in 2000. In 2002, the American Academy of Pediatrics and the Canadian Paediatric Society Committees on Fetus and Newborn jointly advised against the routine use of systemic DEX for the prevention of chronic lung disease (CLD) in preterm infants. They based their recommendations on data-based evidence that antenatal or postnatal steroids were linked to increased risk of impaired growth and development and identified the need for long-term follow-up research (Barrington, 2001; Doyle & Davis, 2000; French, Hagan, Evans, Godfrey, & Newnham, 1999; Stark et al., 2001; Yeh et al., 2004). Even the minimal postnatal DEX treatment at 0.2 mg/kg was under scrutiny due to research identifying higher

infant mortality rate, more intraventricular hemorrhage (IVH) Grades 3 and 4, and more necrotizing enterocolitis (NEC) in infants exposed to this dose compared to control infants (Kopelman, Moise, Holbert, & Hegemier, 1999; Peabody, 2000).

Most basic science studies of steroid exposure conducted in the laboratory have examined the effects either on the body or on the brain but not both. Biophysiologic stress and immunity are more complex in the NICU than in the laboratory setting and both impact health outcomes. Psychoneuroimmunology (PNI) focuses on the interactions among the central nervous system, the endocrine system, and the immune system and is a useful framework for studying biophysiologic stress that may alter the HPA system (Adler, Felten, & Cohen, 2001; Daruna, 2004). Matthews (2001) described potential influences of steroids on the fetal brain that can lead to altered behavior and immunity beyond infancy. However, no human preterm infant studies to date have used a PNI approach to evaluate associations among DEX as a source of cumulative PNS exposure, early immunity, biophysiologic stress, and factors that could affect behavioral outcomes.

Our primary aim in the present study was to examine relationships among preterm infant behavioral outcomes and maternal/infant DEX treatments while considering other potential factors such as immune markers at birth and neonatal sepsis. We asked the following research questions: (a) Do relationships exist between preterm infant cumulative PNS exposure and childhood behavioral problems? (b) Do maternal/infant characteristics (e.g., immune markers, sepsis, and biophysiologic stress) influence these relationships? We hypothesized that greater premature infant exposure to PNS and higher levels of biophysiologic stress at birth might underpin relationships with early immunity and life events associated with childhood behavioral problems.

Material and Method

The present investigation was a prospective follow-up study in which we evaluated preterm infant behavioral development using a convenience sample. The university institutional research review boards approved this study.

Participants

Preterm delivery, estimated to occur in 7–11% of all North American births, was responsible for 75% of neonatal deaths in the early 1990s (Mathews, Menacker, & MacDorman, 2004; NIH, 1994). Clinical use of DEX in infants at risk of preterm birth was also at its apex during that decade. Accordingly, behavioral development among preterm infant survivors born during that decade and exposed to DEX is of acute interest.

Using NICU log books, we identified a cohort of 281 premature infants (< 32 weeks' PCA) who had been cared for at a single tertiary NICU between January 1990 and December 1998. Inclusion criteria for the mothers included no medical history of drug or alcohol abuse. Inclusion criteria for infants were preterm singleton birth at 24–32 weeks' gestation, as determined by Ballard score. Infants were excluded if they had fetal congenital or chromosomal abnormalities. We conducted national and local searches to locate current maternal contact information to mail study invitations to 213 (86%) potential participants

who met the inclusion criteria. Of these, 26 (11%) were lost to follow-up because they had gone to foster or other care. Only 51 (27.3%) of the remaining 187 families responded to the invitation. Of those, we identified 45 eligible participants (88%) based on the additional criteria that the child resided with a parent or legal guardian who could read English or Spanish and provide informed consent. We reimbursed mothers \$20 for their participation.

Data Collection

The principal investigator (PI) gathered maternal pregnancy and delivery characteristics and infant medical and anthropomorphic characteristics retrospectively via medical chart review. In addition, each mother completed a demographic questionnaire and the Child Behavior Checklist (CBCL) at home. These forms were either delivered and completed during a home visit from our developmental specialist or mailed to the home and completed during telephone interviews with the specialist.

Measures

Maternal characteristics—The PI reviewed maternal medical records for medical background data, including delivery type, hypertension, fever, prenatal care, maternal smoking, weight, age, complete blood count (CBC) at time of delivery, chorioamnionitis, exposures to and types of antenatal steroids, and maternal background characteristics that may influence infant behavioral outcomes, including age, education (via maternal self-report on the demographic form), and pregnancy complications.

Infant characteristics—The PI gathered PCA, initial infant CBC, and neonatal diagnoses from review of the medical records. We defined BPD using compatible chest radiograph findings and oxygen requirements at 28 days of life. We also recorded incidence of severe (Grade 3 or 4) IVH, NEC, retinopathy of prematurity (ROP), and hearing deficit as well as breast milk feeds, length of NICU stay and time on mechanical ventilation, home equipment and medication needs, and receipt of early intervention services via maternal self-report.

Cumulative PNS exposure—The PI retrospectively identified perinatal DEX doses from chart reviews of the mother's labor and delivery records and the child's birth and NICU records. We estimated total PNS exposure by adjusting the reported doses administered to the mother (Coe & Lubach, 2000) for the 30% fetal absorption rate (Ballard & Ballard, 1995) and adding that amount to the infant's total postnatal exposure prior to 40 weeks' PCA.

Immune measures—White blood count (WBC) and its components (i.e., lymphocytes and neutrophils) serve as useful immune markers in research. Segmented neutrophils are the body's primary defense against bacterial infection and physiologic stress. Normally, most of the neutrophils circulating in the bloodstream are in the mature form known commonly as segs. The less mature neutrophils, "bands," are released on demand from the bone marrow. The bands-segs ratio (BS ratio) and total neutrophil level are sensitive predictors of immune system function in neonates. Lymphocytes are the source of serum immunoglobulins and of cellular immune response. A decreased lymphocyte count increases the risk of infections,

especially viral infections. The PI retrospectively identified CBCs, manual differentials, and absolute neutrophil counts from medical chart review.

Instruments

Preterm infants are at increased risk of early mortality and acute and chronic morbidity due to both biophysiologic factors and limited financial, social, and health resources (Hack et al., 2002). Even though advances in technology have increased the survival rate among infants born at low birth weight ([LBW] <2500 g) and very low birth weight (<1500 g), little improvement has been noted in the overall morbidity of survivors. Major risk factors that predispose this population to higher rates of morbidity include birth weight, PCA, race, gender (males are often at higher risk), CLD, IVH, and socioeconomic risk (Piecuch, Leonard, Cooper, & Sehring, 1997), hypoxia and increased number of ventilator days (Perlman, 2001), toxic exposures and maternal infection (Brazy, Eckerman, Oehler, Goldstein, & O'Rand, 1991), and prolonged neonatal physiologic stressors (Mattia & deRegnier, 1998). We used the Clinical Risk Index for Babies (CRIB), Score for Acute Neonatal Physiology, Perinatal Edition (SNAPPE-II), and Neurobiologic Risk Score (NBRS) to identify and score risk factors for neuromorbidity. The PI abstracted data from the medical charts and completed these instruments as proxies for assessing biophysiologic stress in the study population (Brazy et al, 1991; Richardson, Corcoran, Escobar, & Lee, 2001). To ensure accuracy, a research study nurse rechecked the data.

Preterm infants also have increased rates of hospital readmittance and risk of neurodevelopmental problems, including difficulties with language and school. We used the CBCL for examining longer-term outcomes in the at-risk infants in our study. Using this instrument, Hille et al. (2001) examined preterm infant outcomes in four countries and identified more frequent total behavioral problems among preterm infants than in the normative population. In the present study, mothers filled out the CBCL along with a demographic form at their homes.

CRIB—We used the CRIB to examine severity of illness data as a proxy for biophysiologic stress in the first 12 hr of life, including birth weight, PCA, maximum and minimum fraction of inspired oxygen (FiO_2), maximum base excess, and presence of congenital malformations. Validity and reliability have been previously established (Lodha, Sauvé, Chen, Tang, & Christianson, 2009). Scores range from 0 to 23, with scores above 10 having specificity and predictive positive value as indicators for severity of illness.

SNAPPE-II—We used the SNAPPE-II to score the level of physiologic instability during the first 24 hr of life. Validated and widely used, this tool offers a quantifiable means of describing severity of infant illness as a proxy for biophysiologic stress (Gagliardi et al., 2004). The score is based on variations in physiology during the first day of life, including lowest mean blood pressure, lowest temperature, $\text{PaO}_2/\text{FiO}_2$ (ratio of partial pressure of arterial oxygen and the fraction of inspired O_2), lowest pH, seizures, urine output (cc/kg/hr), birth weight, small for gestational age, and 5 min APGAR score. Scores range from 0 to 63, with the cut point for high scores set at 30. Higher scores represent greater instability.

NBRS—We used the NBRS to assess biophysiological stress over the entire NICU stay, as represented by degree of illness in several categories, including IVH or periventricular hemorrhage, prolonged time on ventilation, lowest pH level of blood, hypoxia, hypoglycemia, and sepsis or meningitis. The instrument sums four monotonically weighted risk categories to provide summary scores ranging from 0 to 28 (Brazy et al., 1991). Lefebvre, Grégoire, Dubois, and Glorieux (1998) correlated NBRS scores to developmental quotients, with scores >5 (medium risk) being strongly predictive of neuromorbidity and scores >8 indicate high risk.

CBCL and demographic questionnaire—We measured childhood behavioral development with the CBCL for ages 4–14 years, a well-known psychiatric screening tool for parent report of childhood behavior (Achenbach & Ruffle, 2001). Test–retest reliability for the internalizing, externalizing, and total problems subscales range from .89 to .93, and internal consistency (Cronbach's α) of the three scales ranges from .89 to .96. The instrument also includes Diagnostic and Statistical Manual (DSM)-oriented Syndrome and Competence scales. The Syndrome scales are grouped into Externalizing Behaviors (i.e., aggressive and anxious) and Internalizing Behaviors (anxious/depressed, somatic complaints, and withdrawn). Three of the Syndrome scores (Social, Thought, and Attention Problems) are independent. *T* scores distinguish the normative population from those who fall in the borderline-to-clinical range. The Total Problem score is a sum of all problem items. For the present study, we determined cut points for scores based on the borderline-to-clinical cut points for the CBCL Syndrome, Competence, and Total Problems scales, as recommended, to appropriately discriminate referred behaviors.

We designed a demographic questionnaire to gather information about parent education, marital status, child's current age and educational level, ethnicity, post-NICU home medications or equipment, breast or formula feedings, and receipt of developmental or supportive therapies.

Data Analysis

The independent variable for the present study was cumulative infant PNS exposure to DEX prior to 40 weeks' PCA. The dependent variables were CBCL behavioral outcome scores. We dichotomized subjects for data analysis into a high PNS (>0.2mg/kg, twice the common dose given for preterm delivery) and low-no PNS ($\leq$ 0.2mg/kg) groups. The steroid data were not normally distributed, and we did not remove outliers. We used SAS 8.02 (SAS Institute, NC) and STATA 8 (STATA Corp., TX) to conduct the analyses. A power analysis revealed that we would need a sample size of 45 subjects to detect a 90% difference between the two steroid exposure groups. We used descriptive analyses, frequency distribution, cross-tabulation, Fisher's exact test, Mantel–Haenszel odds ratios (ORs), and chi-square tests for analyzing categorical data and Student's *t* test, analysis of variance and regression analysis for analyzing continuous data, with post hoc testing with Hosmer–Lemeshow goodness-of-fit test using a .05 level of significance. Because we identified predictor variables, each with the potential to act as a confounder to others, we used multivariate analytic methods to better assess the independent contributions of these variables. We used linear regressions for continuous variables and logistic regressions for dichotomous variables to examine any

statistically significant relationships with, first, the independent variables and, then, the dependent variables to identify avenues for future research.

Results

Maternal Characteristics

Table 1 provides demographic characteristics of the participating mothers dichotomized by infant PNS exposure. At the time of data collection, the majority of mothers were married (51%) or living with a significant other (9%) and received state-supported medical insurance for their child (95%). At the time of delivery, the mean maternal age was 30 years. The mean cumulative PNS exposure level was 1.8 mg/kg (*SD* 2.7). There was no statistically significant group difference for maternal WBC count (mean 13.7 10e9/L, *SD* 4.3, *n* = 33) or infant WBC (mean 11.8 10e9/L, *SD* 10.5, *n* = 43) near the time of delivery.

Infant Characteristics at the Time of NICU Discharge

Table 2 displays the NICU medical diagnostic characteristics of this sample dichotomized by PNS exposure group. Compared to the lower PNS group, infants in the high PNS group were more likely to be male. The mean PCA at birth of all infants was 28 weeks (range 24–32, *SD* 4.2) and mean birth weight was 1066 g (*SD* 327). The data on NICU health status suggest a wide range of medical vulnerability and risk of neuromorbidity. Interestingly, sepsis occurred more commonly among the high PNS group compared to the low–no PNS group. The high PNS group also had lower mean Apgar scores at 1 and 5 min. However, there were no significant differences between groups in the biophysiologic stress scores at birth using the CRIB and SNAPPE-II.

Likewise, there were no significant group differences on the NBRS as a proxy for biophysiologic stress during the entire NICU stay. Mean length of NICU hospitalization for the entire sample was 68 days (*SD* 28). Duration of hospitalization was longer in infants who had BPD, prolonged mechanical ventilation, and received higher PNS dose. Children in the high PNS group were smaller at NICU discharge than children in the low–no PNS group, with smaller mean head circumference (24th percentile vs 28th percentile, respectively), weight (16th percentile vs 23rd percentile) and length (mean length for high PNS group was 2.3 cm <mean length for no–low group). In the regression analyses, length percentile at the time of NICU discharge was significantly related to CBCL scores.

Child Characteristics at Time of Behavioral Assessment

At the time of parent report of behavioral development, the children had a mean age of 8 years (range 5–13, *SD* 2.3). Less than half (42%) of the children had been discharged from the NICU with some medical equipment and less than a quarter (22%) required prescription medications any time after NICU discharge. Two thirds of the sample received developmental support or a combination of other services provided by a regional center. There were no significant differences between the PNS groups on any of these measures.

In addition, there were no statistically significant differences between the PNS groups in the mean scores for behavioral problems on the Internalizing, Externalizing and Total Problems

scales, Competence scales, DSM-Oriented scales, and Syndrome scales (Table 3). Table 4 lists the ORs of scoring in the CBCL borderline-to-clinical range dichotomized by group. More children in the high PNS group scored in the borderline-to-clinical range on several CBCL problem areas (i.e., withdrawn, attention deficit, social issues, rule breaking, conduct, and school activity). These differences were not statistically significant but they are clinically interesting.

Child Behavioral Development and Associations Between Sample Characteristics

In univariate analyses, we found the following factors to be individually related to scores on the CBCL Internalizing Problems scale: maternal marital status at the time of birth, infant NICU sepsis, discharge length percentile, and rehospitalization for surgery. These variables were also the strongest predictors in the multivariate regression models. We also noted associations between CBCL Competence scores and PNS exposure, ROP, hearing problems, CRIB scores, and several maternal and infant immune factors: sepsis, BS ratio, and maternal lymphocyte percentage. The strong predictors related to CBCL Total Problems Score included sepsis, PNS exposure, infant age at the time of PNS exposure, and discharge length percentile. Table 5 includes a summary of clinically or statistically significant variables for these regression analyses. We noted no strong associations between CBCL outcomes and maternal variables of fever, hypertension, smoking, premature rupture of membranes, chorioamnionitis, and education.

Discussion

As research moves from the bench to bedside and beyond, this exploratory study of a historic hospital-based cohort demonstrates that there are many variables to consider regarding assessment of long-term behavioral outcomes of prematurely born infants. In this study, we examined long-term neurobehavioral outcomes in children who had been born prematurely and had been exposed to relatively high versus relatively low doses of the glucocorticoid DEX. Prior research has demonstrated that antenatal glucocorticoids as well as prenatal stress are linked to permanent reprogramming of endocrine function and brain alterations even in lower doses in animals (Owen, Andrews, & Matthews, 2005; Slotkin, Kreider, Tate, & Seidler, 2006) and humans (Bos, Dibiasi, Tiessen, & Bergman, 2002; Doyle et al., 2000; Esplin, Fausett, & Smith, 2000; Stark et al., 2001).

We expected to see differences between the two steroid groups in CBCL scores in the cross-tabulation analyses but found no statistically significant differences. The multivariate regressions suggest that cumulative PNS exposure was strongly associated with CBCL Internalizing, Competency, and Total Problem Scores. Crowther et al. (2007) examined the associations between repeat courses of antenatal steroids and infant behavioral outcomes at 2 years of age in a randomized controlled study of 1085 children. Similar to the present study, they found no significant differences in CBCL scores at 2 years of age between steroid exposure groups; however, they did not quantify fetal steroid exposure in mg/kg or examine the influences of postnatal steroids or neonatal medical diagnoses. Of interest, though, is their finding that children exposed to repeat antenatal steroid doses were more likely than those in the placebo group to have attention problems at age 2 ($p = .04$). Though

we did not find a relationship between PNS exposure and attention problems in the present study, we did find links between overall CBCL Internalizing Problem scores and other perinatal variables (e.g., maternal marital status at the time of birth, infant rehospitalization for surgery, sepsis, and infant discharge length percentile).

Contrary to CBCL scores, we did find a significant difference in infant length at the time of NICU discharge between the two groups. The mean length of the higher PNS exposure group was about 2 cm shorter than that of the low–no PNS group. Moss, Harding, and Newnawn (2002) found that lambs exposed to multiple antenatal steroid doses compared to those exposed to a single dose had reduced skeletal growth during early postnatal life. Suppression of growth is a frequent complication in infants who receive prolonged corticosteroid treatment. French et al. (1999) noted delayed head and weight growth in neonates exposed to higher doses of steroids. In the present study, our regression models suggested that infant length percentile at NICU discharge was strongly linked with CBCL Total Problem Scores, while factors such as BPD, home oxygen, and NICU length of stay were not.

Most prior research on the effects of PNS exposure has focused on assessing the influences of IVH, CLD, and neurosensory impairments such as hearing and vision deficits on long-term developmental outcomes. It is not surprising that diagnoses of ROP and hearing deficits were linked with competency problems, as these disabilities can be challenging. Hearing loss during early development can lead to speech and cognitive delays and be emotionally isolating. ROP can result in detached retinas, nearsightedness, eye misalignment, and blindness. Smolkin et al. (2008) found that the incidence of ROP was higher in neonates who received late postnatal systemic steroids. They suggested that steroids may alter insulin growth factor 1 (IGF-1) and vascular endothelial growth factor (VEGF) expression, which might contribute to the pathogenesis of ROP. Anti-VEGF monoclonal antibody clinical trials are underway to investigate its efficacy with ROP (Fleck & McIntosh, 2009).

While we found vision (ROP) and hearing deficits to influence scores on the CBCL Competency Problems scale, additionally influential were higher levels of newborn biophysiologic stress (i.e., higher CRIB scores) and immune markers such as sepsis, the initial newborn BS ratio, and maternal lymphocyte percentage near time of delivery. These findings are consistent with animal studies that reported corticosteroids can markedly decrease the body's lymphocyte supply and alter lymphocyte function and behavior later in life (Coe & Lubach, 2000). These potentially interrelated findings support our speculation that there may be interplay among the maternal/infant immune markers, PNS exposure, and behavioral outcomes.

Saigal, Pinelli, Houtl, Kim, and Boyle (2003) noted a higher incidence among adolescents who were born with very low birth weight and premature of borderline and clinical problems as reported on the CBCL with anxious/depressed, withdrawn/depressed, social, and conduct issues that can lead to later academic problems. Mason et al. (2004) noted a four-fold increase in depressive episodes among children at 10–11 years of age and reported concerns that such episodes may be predictive of risks of depression, social phobia, and

violence in early adulthood. Saigal et al. (2003) conducted multivariate analyses on parent-reported behavioral subscale scores and found a variety of variables that were significant predictors of behavioral outcomes among adolescents who had been of extremely LBW, including family connectedness, social practices, stressors, biologic risks, and developmental and physical disabilities. Clearly developmental assessment of the interplay between behavioral problems and motor, cognitive, and/or language skills is valuable to this research. In the present study, we examined developmental scores from our prior research with the Vineland Adaptive Behavioral Scales in our current regressions (see Table 5) and found no statistically significant associations (Purdy et al., 2008; Sparrow, Balla, & Cicchetti, 1984).

The present study aligns with PNI theories (Glazer & Kiecolt-Glaser, 2005) in suggesting that early infant stress, sepsis, and perinatal immune markers may play bigger roles than previously thought in influencing long-term behavioral outcomes in infants exposed to PNS. We found biophysiologic stress identified on the CRIB at birth to be more influential on behavioral outcomes than scores on the NBRS, which assesses stress over the entire NICU stay. Perhaps the greater influence of the CRIB scores reflects sensitivity to the timing of stress related to exogenous steroid exposure that is as influential on child development as is the early timing of synthetic steroid dosing. This suggestion aligns with the theories of Matthews (2001) about the influences of exogenous steroids on behavioral and immune system outcomes beyond infancy. Regarding the role of sepsis in long-term outcomes in these infants, it is significant to note that, during the 1990s, sepsis posed significant threats to neonates, with estimates of up to 30% of LBW preterm infants developing infections prior to discharge (Stoll, Gordon, & Korones, 1996). The immaturity of the preterm infant's immune system may be the cause of the overwhelming impact of sepsis, a condition that warrants early recognition and prompt treatment. These findings about stress, sepsis, and immune markers suggest that medical, biophysiologic stress, and social factors may interact in preterm infants to strongly influence behavioral outcomes.

Limitations

We used a variety of approaches to reduce the bias of nonparticipation. Despite exhaustive efforts, it was not feasible to locate a larger sample, and we do not have data on the nonparticipant portion of this population. Unfortunately there was a high loss to follow-up in this population, which was born in a hospital located in a region of Los Angeles with a highly transient population. Thus, these findings must be interpreted with caution as this nonrandom loss to follow-up increases the risk of sampling biases. The smaller sample size also limited our options for statistical analyses as well as the power to detect modest relationships among the covariates evaluated. It may not be a sufficient size to detect differences (Type II error). Further, we did not adjust findings for potential effects of multiple tests inflating experiment-wise error. Larger sample sizes are thus needed to adequately explore the interactions of the multiple influences on preterm infants' childhood behavioral outcomes.

In addition, we did not capture some parental demographic factors that may also have an influence on child behavioral problems (e.g., socioeconomic status, home environment and

acculturation). Also, the possibility exists that individual parents were inclined to mischaracterize or misreport child behaviors on the CBCL. Earlier studies, however, have reported no group differences in long-term follow-up studies of preterm infants that evaluated parent report versus self-report by young adult controls (Hack et al., 2002; Saigal et al., 2003).

Conclusions

This exploratory study is the first to quantify preterm infants' exposure to cumulative doses of PNS 0.2 mg/kg and investigate the combined influence of PNS exposure and other infant and maternal perinatal factors on child behavioral outcomes. Follow-up of the neurobehavioral outcomes of PNS exposure is scientifically important, as clinicians are still using PNS treatments to minimize RDS and CLD in preterm infants (Walsh et al., 2006). Our findings are clinically relevant to nursing science, as nurses play a key role at every level of maternal-child health care promotion.

Overall, the findings of this small study offer reassuring information about the levels of steroid exposure represented in this sample. Although parents of the children in the high PNS exposure group reported more behavioral syndrome problems (particularly withdrawn/depressed, attention, social, rule breaking, and conduct problems), differences between the groups did not reach a level of statistical significance.

Even though the consensus view has now shifted toward less PNS use in the NICU, there is a need for researchers and clinicians to explore the effects of even minimal cumulative steroid exposure in order to improve the mind-body connection and neurobehavioral outcomes in vulnerable infants. It is often difficult to compare studies examining either antenatal or postnatal steroid exposure as vital information regarding the actual cumulative PNS exposure and important medical predictors are often missing. In the present study, we addressed these limitations using a PNI approach and conceptualizing cumulative PNS exposure. The model for future research in this area should place the fetus and infant on a continuum from uterine life throughout the NICU stay and beyond.

Acknowledgments

We wish to acknowledge additional support provided by Vital Research and the UCLA's Graduate School of Education & Information Studies and the Cousins Center for Psychoneuroimmunology. We are grateful to the parents whose children were born prematurely for sharing their time to participate in this study. We also gratefully acknowledge the support of the Department of Pediatrics/Division of Neonatology and David Geffen School of Medicine at UCLA.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Funding for this study was provided by postdoctoral NIH grant funding T32 NR0070077 from the University of California, Los Angeles (UCLA), School of Nursing.

References

- Achenbach T, Ruffle T. The child behavior checklist and related forms for assessing behavioral/emotional problems and competencies. *Pediatrics in Review*. 2001; 21:265–271. [PubMed: 10922023]

- Adler, R.; Felten, D.; Cohen, N., editors. *Psychoneuroimmunology*. 3. San Diego, CA: Academic Press; 2001.
- American Academy of Pediatrics, Committee on Fetus and Newborn & the Canadian Paediatric Society, Fetus and Newborn Committee. Postnatal corticosteroids to treat or prevent chronic lung disease in preterm infants. *Pediatrics*. 2002; 109:330–338. [PubMed: 11826218]
- Ballard P, Ballard R. Scientific basis and therapeutic regimens for use of antenatal glucocorticoids. *American Journal of Obstetrics and Gynecology*. 1995; 181:709–717. [PubMed: 10486488]
- Barrington KJ. The adverse neuro-developmental effects of postnatal steroids in the preterm infant: A systematic review of RCTs. *BMC Pediatrics*. 2001; 1:1. [PubMed: 11248841]
- Benesova O, Pavlik A. Perinatal treatment with glucocorticoids and the risk of maldevelopment of the brain. *Neuropharmacology*. 1989; 28:89–97. [PubMed: 2927582]
- Bos A, Dibiasi J, Tiessen A, Bergman K. Treating preterm infants at risk for chronic lung disease with dexamethasone leads to an impaired quality of general movements. *Biology of the Neonate*. 2002; 82:155–158. [PubMed: 12373065]
- Brazy J, Eckerman C, Oehler J, Goldstein R, O'Rand A. Nursery neurobiologic risk score: Important factors in predicting outcome in very low birth weight infants. *Journal of Pediatrics*. 1991; 118:783–792. [PubMed: 2019935]
- Coe C, Lubach G. Prenatal influences on neuroimmune set points in infancy. *Annals of the New York Academy of Sciences*. 2000; 917:468–477. [PubMed: 11268374]
- Coe C, Lubach G. Prenatal origins of individual variation in behavior and immunity. *Neuroscience and Biobehavioral Reviews*. 2005; 29:39–49. [PubMed: 15652253]
- Crowther CA, Doyle LW, Haslam RR, Hiller JE, Harding JE, Robinson JS, for the ACTORDS Study Group. Outcomes at 2 years of age after repeat doses of antenatal corticosteroids. *New England Journal of Medicine*. 2007; 357:1179–1189. [PubMed: 17881750]
- Daruna, JH. *Introduction to psychoneuroimmunology*. San Diego, CA: Elsevier; 2004.
- Doyle L, Davis P. Postnatal corticosteroids in preterm infants: Systematic review of effects on mortality and motor function. *Journal of Paediatric Child Health*. 2000; 36:101–107.
- Doyle L, Ford G, Rickards A, Kelly A, Davis N, Callanan C. Antenatal corticosteroids and outcome at 14 years of age in children with birth weight less than 1501 grams [Abstract]. *Pediatrics*. 2000; 106:e2. [PubMed: 10878171]
- Dunlap S, Archer M, Quinlivan J, Beazley L, Newnham J. Repeated prenatal corticosteroids delay myelination in the ovine central nervous system. *Journal of Maternal and Fetal Medicine*. 1997; 6:309–313.
- Esplin M, Fausett M, Smith S. Multiple courses of antenatal steroids are associated with delay in long-term psychomotor development in children with birth weights < 1500 grams. *American Journal of Obstetrics and Gynecology*. 2000; 182:S24.
- Fleck B, McIntosh N. Retinopathy of prematurity. Recent developments. *NeoReviews*. 2009; 10:20–30.
- French N, Hagan R, Evans S, Godfrey M, Newnham J. Repeated antenatal corticosteroids: Size at birth and subsequent development. *American Journal of Obstetrics and Gynecology*. 1999; 180:114–121. [PubMed: 9914589]
- Gagliardi L, Cavazza A, Brunelli A, Battaglioli M, Merzzi D, Tandoi F, Bellu R. Assessing mortality risk in very low birthweight infants: A comparison of CRIB, CRIB-II, and SNAPPE-II. *Archives of Disease in Children, Fetal Neonatal Edition*. 2004; 89:F419–F422.
- Glazer R, Kiecolt-Glaser R. Stress-induced immune dysfunction: Implications for health. *Nature Reviews: Immunology*. 2005; 5:243–251.
- Hack M, Flannery D, Schluchter M, Cartar L, Borawski E, Klein N. Outcomes of young adulthood for very-low-birth-weight infants. *New England Journal of Medicine*. 2002; 346:149–157. [PubMed: 11796848]
- Halliday HL, Ehrenkranz RA. Delayed (> 3 weeks) postnatal corticosteroids for chronic lung disease in preterm infants [online]. *Cochrane Database of Systematic Reviews*. 2001a; 2:CD001145. [PubMed: 11405975]

- Halliday HL, Ehrenkranz RA. Early postnatal (< 96 hours) corticosteroids for preventing chronic lung disease in preterm infants [online]. Cochrane Database of Systematic Reviews. 2001b; 1:CD001146. [PubMed: 11279706]
- Hille E, den Ouden A, Saigal S, Wolke D, Lambert M, Whitaker A, Feldman J. Behavioural problems in children who weigh 1000 g or less at birth in four countries. *Lancet*. 2001; 357:1641–1643. [PubMed: 11425366]
- Jobe A, Ikegami M. Beyond the NIH consensus conference for antenatal glucocorticoids. *Neonatal Respiratory Diseases*. 2000; 10:1–8.
- Kopelman A, Moise A, Holbert D, Hegemier S. A single very early dexamethasone dose improves respiratory and cardiovascular adaptation in preterm infants. *Journal of Pediatrics*. 1999; 135:345–350. [PubMed: 10484801]
- Lefebvre F, Grégoire M, Dubois J, Glorieux J. Nursery neurobiologic risk score and outcome at 18 months. *Acta Paediatrica*. 1998; 87:751–757. [PubMed: 9722248]
- Liggins G, Howie R. A controlled trial of antepartum glucocorticoid treatment for prevention of respiratory distress syndrome in premature infants. *Pediatrics*. 1972; 50:515–525. [PubMed: 4561295]
- Lodha A, Sauvé R, Chen S, Tang S, Christianson H. Clinical risk index for babies score for the prediction of neurodevelopmental outcomes at 3 years of age in infants of very low birth-weight. *Developmental Medicine and Child Neurology*. 2009; 51:895–900. [PubMed: 19416333]
- Mason W, Koserian R, Hawkins J, Herrenkohl T, Lengua L, McCauley E. Predicting depression, social phobia, and violence in early adulthood from child behavior problems. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2004; 43:307. [PubMed: 15076264]
- Mathews T, Menacker F, MacDorman M. Infant mortality statistics from 2002 period. *Monthly Vital Statistics Report*. 2004; 53:1–29.
- Matthews SG. Antenatal glucocorticoids and the developing brain: Mechanisms of action. *Seminars in Neonatology*. 2001; 6:309–317. [PubMed: 11972432]
- Mattia F, deRegnier A. Chronic physiologic instability is associated with neurodevelopmental morbidity at one and two years in extremely premature infants. *Pediatrics*. 1998; 102:1–14.10.1542/peds.102.3.e35 [PubMed: 9651405]
- Moss TJ, Harding R, Newnham JP. Lung function, arterial pressure and growth in sheep during early postnatal life following single and repeated prenatal corticosteroid treatments. *Early Human Development*. 2002; 66:11–24. [PubMed: 11834344]
- National Institute of Health. Consensus development conference statement. Effect of corticosteroids for fetal maturation on perinatal outcomes, February 28–March 2, 1994. *American Journal of Obstetrics and Gynecology*. 1994; 173:246–252.
- National Institutes of Health. Report of the consensus development conference on antenatal corticosteroids revisited: Repeat courses. Bethesda, Maryland: National Institute of Child Health and Human Development; 2000.
- Ng P, Wong G, Lam C, Lee C, Fok T, Wong M, Ma K. Effect of multiple courses of antenatal corticosteroids on pituitary-adrenal function in preterm infants. *Archives of Disease in the Child, Fetal and Neonatal Edition*. 1999; 80:F213–F216.
- Owen D, Andrews M, Matthews S. Maternal adversity, glucocorticoids and the programming of neuroendocrine function and behavior. *Neuroscience and Biobehavioral Reviews*. 2005; 29:209–226. [PubMed: 15811494]
- Peabody J. Interpreting risks of steroids for preterm infants. *Journal of Pediatrics*. 2000; 137:590–592. [PubMed: 11035850]
- Perlman JM. Neurobehavioral deficits in premature graduates of intensive care—Potential medical and neonatal environmental risk factors. *Pediatrics*. 2001; 108:1339–1348. [PubMed: 11731657]
- Piecuch R, Leonard C, Cooper B, Sehring S. Outcome of extremely low birth weight infants (500 to 999 grams) over a 12-year period. *Pediatrics*. 1997; 100:633–639. [PubMed: 9310517]
- Purdy IB, Smith LM, Wiley D, Howes C, Gawlinski A, Robbins W, Badr L. Cumulative perinatal steroids: Child development of preterm infants. *Journal of Pediatric Nursing*. 2008; 23:210–214.
- Richardson D, Corcoran J, Escobar G, Lee S. SNAP-II and SNAPPE-II: Simplified newborn illness severity and mortality risk scores. *Journal of Pediatrics*. 2001; 138:92–100. [PubMed: 11148519]

- Saigal S, Pinelli J, Houtl L, Kim M, Boyle M. Psychopathology and social competencies of adolescents who were extremely low birth weight. *Pediatrics*. 2003; 111:969–975. [PubMed: 12728073]
- Shoener J, Baig R, Page K. Prenatal exposure to dexamethasone alters hippocampal drive on hypothalamicpituitary-adrenal axis activity in adult male rats. *American Journal of Physiology—Regulatory, Integrative and Comparative Physiology*. 2006; 290:R1366–R1373.
- Slotkin T, Kreider M, Tate M, Seidler F. Critical prenatal and postnatal periods for persistent effects of dexamethasone on serotonergic and dopaminergic systems. *Neuropsychopharmacology*. 2006; 31:904–911. [PubMed: 16160705]
- Smolkin T, Steinberg M, Sujov P, Mezer E, Tamir A, Makhoul I. Late postnatal systemic steroids predispose to retinopathy of prematurity in very-low-birth-weight infants: A comparative study. *Acta Paediatrica*. 2008; 97:322–326. [PubMed: 18298780]
- Sparrow, S.; Balla, D.; Cicchetti, D. Vineland adaptive behavior scales survey form manual. Circle Pines, MN: American Guidance Incorporated; 1984.
- Stark A, Carlo W, Tyson J, Papile L, Wright L, Shankaran S, Stevenson D, for the National Institute of Child Health Human Development Neonatal Research Network. Adverse effects of early dexamethasone in extremely-low-birth-weight infants. National Institute of Child Health and Human Development Neonatal Research Network. *New England Journal of Medicine*. 2001; 344:95–101. [PubMed: 11150359]
- Stoll BJ, Gordon T, Korones SB. Early-onset sepsis in very low birth weight neonates: A report from the National Institute of Child Health and Human Development Neonatal Research Network. *Journal of Pediatrics*. 1996; 129:63–80. [PubMed: 8757564]
- Walsh M, Yao Q, Horbar J, Carpenter J, Lee S, Ohlsson A. Changes in the use of postnatal steroids for bronchopulmonary dysplasia in 3 large neonatal networks. *Pediatrics*. 2006; 118:1328–1335.
- Yeh TF, Lin YJ, Lin HC, Huang CC, Hsieh WS, Lin CH, Tsai CH. Outcomes at school age after postnatal dexamethasone therapy for lung disease of prematurity. *New England Journal of Medicine*. 2004; 350:1304–1313. [PubMed: 15044641]

Table 1Maternal Demographic Characteristics, *n* (%), by Dichotomous Perinatal Steroid (PNS) Exposure Group

Characteristic	Total (<i>N</i> = 45)	Low–No PNS (<i>n</i> = 25)	High PNS (<i>n</i> = 20)
Maternal age at the time of birth			
<25 years of age	9 (20)	6 (24)	3 (15)
25–35 years of age	29 (64)	16 (64)	13 (65)
>35 years of age	7 (16)	3 (12)	4 (20)
Maternal education at the time of study			
Eighth grade	11 (24)	7 (28)	4 (20)
High school	8 (18)	4 (16)	4 (20)
At least some college	26 (58)	14 (56)	12 (60)
Marital status at the time of study			
Single/living alone	18 (40)	10 (40)	8 (40)
Married/significant other	27 (60)	15 (60)	12 (60)
Ethnicity			
African American/Black	9 (20)	4 (16)	5 (25)
Hispanic/Latina	28 (62)	16 (64)	12 (60)
Caucasian	5 (11)	2 (8)	3 (15)
Other	3 (7)	3 (12)	0

Note. The low–no PNS group was exposed to 0.2 mg/kg dexamethasone (DEX) prior to 40 weeks' postconceptional age (PCA); the high PNS group was exposed to >0.2 mg/kg DEX prior to 40 weeks' PCA.

Infant and Parental Medical, Physiologic, and Demographic Characteristics (mean or %) by Dichotomous Perinatal Steroid (PNS) Exposure Group

Table 2

Characteristic	Low-No PNS		High PNS		P Value
	n	Mean or %	n	Mean or %	
Chorioamnionitis (%)	25	12	20	10	.83
Maternal age at delivery (mean years)	25	29.4	20	29.9	.77
Prenatal care (%)	25	76	20	85	.45
PROM >24 hr (%)	25	20	18	6	.18
Maternal smoking during pregnancy (%)	25	16	18	6	.29
1-min Apgar score < 5 (mean)	25	5.68	20	3.55	.007*
5-min Apgar score < 5 (mean)	25	7.28	20	5.7	.03*
PCA first ACS (weeks)	21	27.4	15	26.4	.13
Male (%)	25	40	20	70	.04*
Sepsis (%)	25	24	20	55	.03*
BPD (%)	24	29	20	70	.007*
ROP (%)	25	20	20	35	.26
NEC (%)	24	13	20	20	.50
IVH (%)	25	20	20	15	.66
PCA (weeks; mean)	25	28.4	20	27.4	.15
Length of stay (days; mean)	25	54	20	82.6	.001*
Discharge head circumference (cm; mean)	24	32.2	20	33.4	.02*
Discharge weight (percentile; mean)	25	31.5	20	15.5	.01*
Discharge length (cm; mean)	24	45.6	20	43.3	.01*
Any breast milk feeds (%)	25	28	20	45	.24
Developmental follow-up (%)	25	64	20	65	.94
Maternal education 12th grade at data collection (%)	25	74	9	27	.70
Paternal education 12th grade at data collection (%)	23	68	11	32	.47
Cerebral palsy (%)	25	12	20	5	.41

Note. The low-no PNS group was exposed to 0.2 mg/kg dexamethasone (DEX) prior to 40 weeks' postconceptional age (PCA); the high PNS group was exposed to > 0.2 mg/kg DEX prior to 40 weeks' PCA. BPD = bronchopulmonary dysplasia; IVH = intraventricular hemorrhage; NEC = necrotizing enterocolitis; PCA = postconceptional age; PCA first ACS = postconceptional age at time of delivery of first dose of antenatal corticosteroids; PROM > 24 hr = premature rupture of membranes > 24 hr prior to time of delivery; ROP = retinopathy of prematurity.

* Statistically significant at $p < .05$

Table 3

Child Behavior Checklist (CBCL) Scores at School Age by Dichotomized Perinatal Steroid (PNS) Group

Outcome	Low-No PNS Mean $\pm$ SD (<i>n</i> = 25)	High PNS Mean $\pm$ SD (<i>n</i> = 20)	<i>F</i>	<i>P</i>
Internalizing, Externalizing Total Problems scale				
Total Problems	55.5 $\pm$ 11.8	52.1 $\pm$ 11.0	1.0	.32
Internalizing	54.8 $\pm$ 11.9	52.2 $\pm$ 10.1	.63	.43
Externalizing	53.0 $\pm$ 10.2	49.0 $\pm$ 10.9	1.5	.23
DSM-oriented scale				
Affective problems	56.6 $\pm$ 8.0	54.8 $\pm$ 7.14	.62	.43
Anxiety problems	59.4 $\pm$ 8.1	55.2 $\pm$ 6.8	3.4	.07
Somatic problems	56.1 $\pm$ 7.4	55.7 $\pm$ 7.1	.04	.84
Attention deficit/hyperactivity problems	58.4 $\pm$ 8.6	58.3 $\pm$ 7.6	.32	.57
Oppositional defiant problems	55.4 $\pm$ 6.2	53.7 $\pm$ 6.8	.06	.81
Conduct problems	55.4 $\pm$ 5.0	53.8 $\pm$ 7.0	.69	.41
Syndrome scale				
Anxious/depressed	57.3 $\pm$ 8.2	53.2 $\pm$ 5.3	3.68	.06
Withdrawn/depressed	58.2 $\pm$ 9.0	58.0 $\pm$ 9.1	.01	.94
Somatic complaints	55.3 $\pm$ 8.0	58.0 $\pm$ 7.3	.04	.83
Social problems	56.7 $\pm$ 8.2	57.0 $\pm$ 8.6	.01	.93
Thought problems	58.2 $\pm$ 9.2	54.6 $\pm$ 6.2	1.87	.18
Attention problems	58.0 $\pm$ 7.9	58.9 $\pm$ 7.9	.12	.73
Rule-breaking problems	56.0 $\pm$ 5.9	53.9 $\pm$ 7.1	1	.32
Aggressive behavior	56.0 $\pm$ 8.0	54.0 $\pm$ 6.9	.74	.39

Note. The low-no PNS group was exposed to 0.2 mg/kg dexamethasone (DEX) prior to 40 weeks' postconceptional age (PCA); the high PNS group was exposed to > 0.2 mg/kg DEX prior to 40 weeks' PCA. DSM = Diagnostic and Statistical Manual.

Table 4

Odds Ratios of Scoring in the Child Behavior Checklist (CBCL) Borderline-to-Clinical Range by Dichotomous Perinatal Steroid (PNS) Exposure Group

	% Scoring in Borderline-to-Clinical Range		
CBCL Scale	Low-No PNS(<i>n</i> = 25)	High PNS(<i>n</i> = 20)	MH cOR
Internalizing, Externalizing			
Total Problems scale ^a			
Externalizing	28	20	0.6
Internalizing	32	20	0.5
CBCL total	32	20	0.5
Competence scale ^b			
Social	25	22	0.9
School	15	28	2.2
Activities	40	47 ^c	1.3
Total competence	40	44	1.3
Syndrome scale ^d			
Anxious/Depressed	24	10	0.4
Withdrawn/Depressed	20	25	1.3
Somatic problems	16	15	0.9
Attention problems	20	25	1.3
Aggressive behavior	12	10	0.8
Social problems	15	22	1.6
Thought problems	25	11	0.4
Rule-breaking	10	17	1.8
DSM-oriented scale ^d			
Affective problems	16	15	0.9
Anxiety problems	32	15	0.4
Somatic Problems	17 ^c	15	0.8
ADHD problems	28	20	0.6
Oppositional defiant	4	5	1.3
Conduct problems	5	17	3.8

Note. The low–no PNS group was exposed to 0.2 mg/kg dexamethasone (DEX) prior to 40 weeks' postconceptional age (PCA); the high PNS group was exposed to >0.2 mg/kg DEX prior to 40 weeks' PCA. MH cOR = Mantel–Haenszel crude odds ratio (none reached a level of statistical significance); DSM = Diagnostic and Statistical Manual; ADHD = Attention-deficit hyperactivity disorder.

^aBorderline-to-clinical range for CBCL Total Problems scales is >59.

^bBorderline-to-clinical range for CBCL Competence scale is <35.

^cOne parent refused to answer.

^dBorderline-to-clinical range for CBCL Syndrome Problems and Diagnostic and Statistical Manual-Oriented Problems scales is >64.

Table 5

Summary of Multivariate Regression Analyses for Variables Predicting Scores in the Borderline-to-Clinical Range on the Child Behavior Checklist (CBCL)

CBCL Scale and Variables	Coef.	SE Coef.	p
CBCL internalizing problems			
Marriage	1.36	.55	.02
Sepsis	5.93	2.76	.04
Rehospitalized for surgery	9.50	3.19	.005
Infant length percentile at NICU discharge	7.98	2.75	.006
Cumulative PNS exposure	.22	.12	.07
CBCL competency total score			
Cumulative PNS exposure	.29	.12	.03
Retinopathy of prematurity	-.86	.15	<.001
Hearing deficits	-.56	.17	.005
Higher CRIB scores	.59	.15	.001
Sepsis	.55	.17	.004
Infant band/seg ratio	1.07	.19	<.001
Maternal lymphocyte %	.21	.04	<.001
Total CBCL problem scores			
Sepsis	.42	.11	.004
Cumulative PNS exposure	.10	.04	.007
Timing of 1st PNS exposure	-.02	.006	.01
Infant length percentile at NICU discharge	.43	.11	<.001
VABS developmental composite ^a	-.01	.007	.08

Note. Regression for Internalizing Problems scale: $R^2 = .51$, $R^2 = .42$; for Total Competence scale: $R^2 = .84$, $R^2 = .73$; and for Total Problems scale: $R^2 = .950$, $R^2 = .92$. CRIB = Clinical Risk Index for Babies; NICU = neonatal intensive care unit; PNS = perinatal steroid; VABS = Vineland Adaptive Behavior scales.

^aVABS data from prior study (Purdy, 2008).