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Prematurity and Perinatal Adversity Effects Hypothalamic-Pituitary-Adrenal Axis Reactivity to Social Evaluative Threat in Adulthood

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Abstract

This study examined the long-term effects of prematurity and perinatal adversity on individual differences in stress-related reactivity and regulation of the HPA axis. A prospective sample of 155 infants born preterm and healthy (*n*=20), medical illness (*n*=48), neurological illness (n = 26), and small for gestational age (n = 24) and full-term (*n*=37) were recruited between 1985–1989. At age 23 years, multiple saliva samples were collected before and after participation in the Trier Social Stress Test and later assayed for cortisol. Results reveal that at age 23 years, infants born premature with neurological complications showed higher cortisol reactivity to social evaluative threat compared to either their full-term, small for gestation age, medically ill or healthy preterm peers. Findings are discussed in terms of implications for contemporary theories that propose effects of early adversity on biological sensitivities and susceptibilities, which translate experience into developmental outcomes related to poor health and risk for disease.

Keywords

TSST; Cortisol; Stress; Prematurity; Pre-perinatal Adversity

Contemporary theories originating from several different disciplines place key emphasis on the experience of early life adversity for long-term developmental outcomes (Barker, 1995; Boyce & Ellis, 2005; Gottlieb, 1992; Shonkoff, Garner, & The Committee on Psychosocial Aspects of Child and Family Health, 2012). Substantial empirical effort has applied these

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theories to explore the consequences of a wide range of pre- and peri-natal stress on later adjustment, including for instance prenatal drug exposure (Eiden, Veira, & Granger, 2009), child maltreatment (Cicchetti & Rogosch, 2001; Cicchetti & Rogosch, 2012), poverty (Blair et al., 2011), and interpartner violence (Levandosky et al., 2016). Among the most intense experiences of adversity for infants is premature birth, defined as delivery before 37 weeks gestational age (World Health Organization, 2016). In the United States, one of every ten births is premature.

The U.S. Institute of Medicine reported that infant complications of prematurity greatly vary across neonatal centers (Behrman & Butler, 2007). While neonatal care has improved, 40% of small birth weight infants (500–1500 grams) experience one or more serious morbidities (Horbar et al., 2017). Infants born prematurely who have neurological and medical complications are especially at risk, especially with smaller birth weights. In 2007, 80% of premature infants born less than 27 weeks experience acute respiratory distress syndrome (RDS), and 3–43% suffer the chronic respiratory illness of bronchopulmonary dysplasia (BPD; Behrman & Butler, 2007). The immature capacity for gas exchange and lung function can lead to hypoxic-ischemic episodes that may lead to brain tissue damage. Necrotizing enterocolitis (NEC), an acute injury to the intestines causing inflammation and injury, is experienced by 3–7% or premature infants, almost all have feeding difficulties that may affect growth, and almost 65% will have at least one infection during their hospitalization. Up to 11% of premature infants suffer intraventricular hemorrhage (IVH), which begins with bleeding into the germinal matrix below the lateral ventricles of the brain. The bleeding can fill the ventricles and dilate them. Of those with germinal matrix bleeding, 10–15% have blood return obstructed causing infarction of brain tissue.

A comprehensive U.S. study representing 90% of U.S. neonatal intensive care units reported on the change in complications for infants with birth weight < 1500 grams from 2005–2014 (Horbar et al., 2017). Late onset sepsis infection diminished from 21.9% to 10.1%, severe IVH from 9.4% to 7.9%, NEC from 7.1% to 5.2%, and chronic lung disease from 31.6% to 28.6%. Stoll and colleagues (2015) illustrated the rise and fall in neonatal morbidities over a 20 year period (1993–2013) for infants with birth weight 401–1500 grams from 26 neonatal centers. While there were minimal changes in morbidity rates over two decades for sepsis (8–54%), NEC (7–13%), and IVH (11–19%), the rate of BPD increased from 32% to 45%.

More difficult to diagnose is white matter central nervous system (CNS) injuries, from focal cystic necrotic lesions to more extensive bilateral lesions, or cerebral atrophy. Periventricular leukomalacia (PVL), a distinct injury of white matter that is often un- or under-diagnosed, compromises connectivity (Volpe, 2009). The Stoll study (Stoll et al., 2015) reported 4–8% PVL for infants < 1500 grams. These neonatal complications and treatments are associated with increased sensitivity to pain and other stimuli. The preterm infant responds to these stimuli with increases in cortisol and endorphin levels as early as 23 weeks of gestation, but the neurotransmitters that attenuate pain develop later (Franck et al., 2000). Thus, these painful experiences could lead to structural and functional alterations of their nervous system and subsequent altered pain responses (Grunau, Whitfield, & Petrie, 1998).

The preterm infant is at risk for adverse outcomes across the lifespan and the sequelae may be singular or multiple, severe or mild, and vary with age. Infants born at lower gestational age and birth weight have greater risk for adverse outcomes and methodological issues make outcome estimates challenging (Saigal, 2014). For premature infants less than 1500 grams, 17–48% had neuromotor impairment during infancy (Behrman & Butler, 2007; Vohr, Wright, Poole, McDonald, & for the NICHD Neonatal Research Network Follow-Up Study, 2005). As adults, 6–9% have cerebral palsy (Hack et al., 2002; Moster, Lie, & Markstad, 2008; Saigal, 2014; Saigal et al., 2006), 1.6–4% have severe vision problems (Hack et al., 2002; Moster et al., 2008), and refraction errors are common. In a Canadian adult cohort born less than 1000 grams, 64% reported refraction errors (Saigal, 2014). Several meta-analyses reveal long-term neurocognitive (Kerr-Wilson, Mackay, Smith, & Pell, 2012), academic (Aarnoudse-Moens, Weisglad-Kuperus, van Goudoever, & Oosterlaan, 2009), and mental health (Aarnoudse-Moens et al., 2009) sequelae directly associated with prematurity (Lemola, 2015).

Among the many mechanisms hypothesized to translate differential experience with adversity in early life into risk later in life are environmentally sensitive biological systems such as the hypothalamic-pituitary-adrenal (HPA) axis (Chrousos & Gold, 1992). The HPA axis is one of the major components of the psychobiology of the stress response and considerable empirical attention is focused on the correlates and concomitants of individual differences in the reactivity and regulation of its primary product (cortisol). At birth, the HPA axis is not fully developed, and during the early years its set-point and threshold for reactivity, as well as its recovery after reactivity, is heavily influenced by the social buffering capacity of the early caregiving environment (Gunnar & Donzella, 2002; Gunnar & Quevedo, 2007). That is, studies show that infants who have more available, predictable, sensitive, and nurturing caregivers show distinctly different HPA reactivity and regulation than those who do not (Blair et al., 2011; Gunnar & Quevedo, 2008).

In the short run, HPA axis reactivity is considered adaptive, especially when adverse environmental events are novel or unfamiliar (e.g., Weiner,1992). Upon repeated exposure, as once novel events become familiar, the expectation is that the magnitude of the HPA response attenuates (Wiener, 1992). By contrast, circumstances that present challenges that are very intense, of long duration, repetitive and unpredictable are associated with chronic or frequent HPA axis activation. In the long run, chronic HPA axis activation has the potential to cause considerable downstream problems linked to the effect of cortisol on target cells and tissues in multiple body systems (McEwen, 1998; McEwen & Seeman, 1999).

For premature infants born with neurological problems we hypothesize a triple-hazard model. That is, they are exposed to frequent, intense medical procedures in a unpredictable environment; they spend considerable time in the hospital separated from caregivers who would provide social buffering; and neurological or medical complications at birth may amplify or attenuate biological sensitivities and susceptibilities to context.

Taken together, it appears that early adversity associated with premature birth has the potential to alter the set-point of the reactivity of the HPA axis creating a more vulnerable phenotype. Two studies illustrate this possibility (Quesada, Tristao, Pratesi, & Wolf, 2014;

Winchester, Sullivan, Roberts, & Granger, 2016). Quesada and colleagues (Quesada et al., 2014) studied 30 preterm children in middle childhood (ages 6–10 years). They reported that preterm children, compared to full-term controls, showed higher cortisol concentrations at awakening, a flattened cortisol awakening response (CAR) and an exaggerated response to the Trier Social Stress Test (TSST-C) for children. Interesting, these alterations were more pronounced in girls. In the second study, reported by our study group Sullivan and colleagues (Winchester et al., 2016) employed a prospective, case-controlled design of 180 preterm and full-term infants who had been enrolled at birth. Of these, 149 young adults, 34 formerly full-term and 115 formerly preterm (22 healthy preterm, 48 with medical complications, 21 with neurological complications, and 24 small for gestational age) donated five saliva samples from a single day that were assayed for cortisol to assess diurnal variation of the hypothalamic-pituitary-adrenal (HPA) axis. Perinatal circumstances associated with prematurity influenced the activity of this environmentally sensitive physiological system. These findings have implications for the theory of Developmental Origins of Health and Disease and highlight a possible mechanism for the link between prematurity and health disparities later in life.

Present Study

The present study extends the prior findings of Quesada and colleagues (Quesada et al., 2014) in important ways. The study employs a prospective rather than retrospective design, the sample size is considerably larger, the sample reflects individual differences in key circumstances of premature birth (e.g., healthy preterm, small for gestational age, full-term), and the follow up is at early adulthood (age 23 years compared to ages 6–10 years). The analyses also extend our previous findings. Here we focus on the effects of prematurity on acute reactivity and recovery to social evaluative threat (TSST), as opposed to our prior reports (Winchester, Sullivan, Roberts, Bryce, & Granger, in press), which focused on metrics linked to the diurnal rhythm of cortisol production (CAR, diurnal slope). We hypothesized that stress-related cortisol reactivity to the TSST at age 23 years would be different for the preterm group with neurological complications at birth than for their healthy full term peers. Importantly, this case-control design enabled us to determine the extent to which this difference is specifically due to neurological problems at birth by comparing the preterm group with neurological complications to infants born healthy but premature (HPT), infants born small size for gestational age and premature (SGA), and infants born premature with medical complications (MPT).

Materials and Methods

Study Sample at Recruitment

Two hundred and fifteen infants were recruited at birth from a specialty hospital between 1985–1989. The recruitment criteria were chosen a priori and included neonatal diagnoses, birth weight, absence of maternal mental illness, and English as a primary language. Full-term infants (FT; n=55) were born from mothers with uncomplicated labor and delivery, absent of neonatal diagnoses, ≥ 2,450 grams birth weight, ≥ 38 weeks gestational age, and recruited from the same medical center within the same time period as the preterm infants.

All preterm infants were less than 37 weeks gestational age and classified by neonatal illness. Healthy preterm infants (HPT; $n = 33$) had no medical or neurological illness. Medical Preterm infants (MPT; $n = 60$) had medical illnesses of RDS, BPD, NEC, and/or sepsis. Neurological Preterm infants (NPT; $n = 36$) had IVH (Grade III & IV), meningitis or shunted hydrocephalus. Approximately half of the small for gestational age preterm infants had neonatal illness (Lubchenco, Hansman, & Boyd, 1966); SGA; $n = 31$) Socioeconomic status was equally distributed within and across all groups at recruitment. The sample was representative the infant population in the regional neonatal center at the time of recruitment.

Study Sample at Age 23 Years

One hundred and eighty (N=180, 84%) completed a comprehensive assessment protocol at age 23 years. Of these, 155 (86%) were able to complete the social stress protocol (72% of the infancy sample). No differences were found between those who dropped out from the study and those who participated at age 23 years on neonatal illness (birth weight, gestational age, neonatal acuity, total hospitalized days, oxygen duration, BPD, NEC, sepsis, IVH, meningitis, hydrocephalus, SES, parent education, marital status, or race). The only differentiating factor was that more males (n =23) than females (n =12) dropped from the study at age 23 years, X^2 (1) = 4.25, p =0.04.

Procedures

Participants and their parent(s) were assessed in repeated research protocols since birth for additional detail see Miller, Sullivan, Hawes, & Marks, 2009; Sullivan, Msall, & Miller, 2012). At age 23 years, a health assessment was performed and all participants were subject to the Trier Social Stress Test (TSST: Kirschbaum, Pirke, & Hellhammer, 1993), which began promptly at one o'clock on testing day. The TSST involved 10 minutes of preparation, followed by two public speaking tasks of 5 minutes each (mock job interview, mental arithmetic task). Salivary samples were collected at 8 intervals: 2 samples prior to the tasks and 20, 30, 45, 60 75, and 90 minutes after task completion. Participants placed a 1 × 4 cm foam swab (SalivaBio LLC, Carlsbad, CA) under the tongue for 2 minutes. After 2 minutes, the swab was returned to a storage tube. The entire TSST and saliva sampling were strictly timed.

Each participant spent a full day at the hospital laboratory as part of a day-long research protocol, which assured a non-stressful period prior to the TSST. Cell phones and iPads were not permitted, and non-stressful reading materials were available. In addition, potential confounders were reduced and eliminated including the timing and type of food and drink, vigorous exercise, smoking, use of steroids and medications, sleep patterns, mood, and menstrual cycle (females only). Urine was screened for toxicology, and all females were screened for pregnancy with the OSOM hcG Combo Pregnancy Kit (Sekisui Diagnostics LLC, 2012). If the pregnancy test was positive, female participants were re-scheduled until a minimum of 3 months post-pregnancy (Granger et al., 2009).

A research assistant (RA) escorted the participant through the TSST protocol and followed strict guidelines for verbal direction and minimal conversation. The TSST began in an interview room for baseline salivary samples, then moved to a plain assessment room

outfitted with a one-way mirror where the participant was introduced to the three confederates seated as the audience behind a long table. The confederate 'judges', unknown to the participant, wore plain white lab coats, held clipboards and maintained a neutral face with no verbal or non-verbal communication during the TSST. The RA identified the three confederates as 'three experienced judges', then instructed the participant that s/he had 10 minutes to prepare for a job interview for their chosen occupation. They returned to the interview room where paper and pen were provided for interview notes. After 10 minutes, the notes were taken away and the participant was led back to the laboratory room. The Lead Confederate directed the participant to stand behind a microphone on the 'X' marked on the floor, and gave the single directive to begin speaking for the interview. For the mental arithmetic task, the participant was asked to 'subtract 13 from 1,022 as quickly and as accurately as possible. If a mistake was made, the participant was directed to begin again at 1,022. While a mock video-camera was focused on the subject, the lead confederate activated a 5-minute timer for each task and a noisy wall clock ticked throughout both tasks. The TSST was video-recorded from behind the one-way mirror.

At the conclusion of the tasks, the participant returned to the interview room with the RA to complete the remaining salivary samples. Additional measures taken during the TSST but not presented in this report were heart rate, blood pressure, a visual analog scale, and Adverse Symptoms Checklist (completed 30 minutes prior and 30 minutes after the start of the TSST, and 75 minutes after the start of the TSST). Full Institutional Review Board approvals were obtained from university and hospital.

Measures

Saliva collection—Participants collected eight saliva specimens: 2 samples prior to the task and 20, 30, 45, 60 75, and 90 minutes after participating in the TSST. Specimens were frozen at or below −20°C within 1 hour of collection. Salivary specimens were stored at −40c or below until shipped with dry ice overnight for assay.

Determination of salivary cortisol—On the day of assay, samples were thawed, centrifuged to remove mucins, and tested in duplicate for cortisol using a commercially available enzyme immunoassay without modification to the manufacturer's protocol (Salimetrics LLC, Carlsbad, CA). The test volume was 25 μL, range of sensitivity from .007 to 3.0 ug/dL, and on average, inter- and intra-assay coefficients of variation were less than 15 and 10% respectively. Cortisol values below the lower limit of sensitivity were recoded to the value of the lowest calibrator (0.012 ug/dL, n=3) and greater than 4.0 ug/dL (n=1) were recoded to missing since these values are physiologically implausible (Jacobson, Bihun, & Chiodo, 1999). Anticipatory response was computed by taking the average between the first and second cortisol samples. Reactivity response included both the slope, calculated as the change per minute to reach peak cortisol levels, and area under the curve with respect to increase (AUCi), calculated as the increase in cortisol over baseline. Last, recovery response was computed using the slope (change per minute from peak to last sample).

Analytic Strategy

All analyses were conducted using SPSS 23. Prior to analyses, data were screened for outliers. Outliers greater than 3 standard deviations from the mean were screened and winsorized to reduce outliers (Gunnar, Brodersen, Krueger, & Rigatuso, 1996; Tukey, 1977). Preliminary analyses were conducted both with the whole sample and by group to examine descriptive statistics on study variables. All descriptive statistics by group are presented in Table 1. Variables that were not within the recommended range of a normal distribution (i.e., skewness < 2 and kurtosis < 7; (Tabachnick & Fidell, 2012) underwent a natural log transformation. These transformed variables were then used in all analyses. A priori group comparisons and independent samples t-tests were conducted to test the main hypotheses.

Results

Group differences in cortisol reactivity to the TSST are plotted in Figure 1 (see Figure 1). A priori contrasts (e.g., independent samples t-tests) compared cortisol levels in anticipation, in response, and in recovery to the TSST between the Neurological Preterm (NPT) group and the Full-Term (FT) group. The NPT group had significantly higher cortisol AUCi (M = 10.78, SD = 12.90) than the FT group (M = 4.61, SD = 10.41, t (55) = −2.00, p = 0.05). Next, we examined if the NPT differed from either the HPT and SGA groups on cortisol variables of interest. In terms of reactivity response, the NPT group had significantly higher AUCi (M = 10.78, SD = 12.90) than the HPT group (M = 3.89, SD = 7.77, t (36.86) = −2.14, p = 0.04). There were no group differences on reactivity slope, and anticipatory or recovery responses. The NPT and HPT did not show any significant differences on anticipatory response or AUCi, but there were significant group differences in both reactivity and response slopes. Specifically, the NPT group had significantly higher reactivity slope (M = 2.50, SD = .31) than the SGA group (M = 2.24, SD = .41, t (40.91) = −2.52, p = 0.02). Conversely, the NPT group had significantly lower recovery slope (M = −.95, SD = .27) than the SGA group (M = −1.23, SD = .48, t (40.91) = −2.52, p = 0.02), indicating a more rapid decline to baseline in the SGA compared to the NPT group. To further probe group differences, we compared the MPT and the NPT groups. There were no significant group differences on any cortisol variables. For completeness, we also tested group differences between the MPT group and the full-term group on anticipatory, reactivity, and recovery responses. There were no significant group differences.

Discussion

In a prospective case-controlled study of the effects of prematurity, we reveal that infants born prematurely with neurological complications show higher HPA reactivity to acute social evaluative threat in young adulthood. These effects appear to be specifically related to neurological complications suffered after birth, as infants born healthy preterm, small for gestational age preterm, and preterm with medical complications show HPA reactivity profiles similar to those of the full-term healthy group. The findings have several noteworthy implications.

Premature infants at the lowest birth weights are more likely to have neonatal illness and later neurodevelopmental difficulties. The infants in the NPT and SGA groups had the

lowest birth weights, but the acuity measured by the Hobel Scores was higher in the NPT group. One of the most serious neurological morbidities is intraventricular hemorrhage (IVH), which is more likely to occur with preterm infants born < 1500 grams. Infants in the NPT group had Grades 3 and 4 IVH, which involved more substantial bleeding in the brain. Grade 3 is marked by bleeding in the ventricles pressing on brain tissue, while Grade 4 is characterized by bleeding directly into brain tissue (Papile, Burstein, Burstein, & Koffler, 1978).

Cortisol concentrations has been a research focus for the very small premature infants because they are a particularly high risk group who have difficulty responding to inflammatory insult due to adrenal insufficiency. In a secondary analysis of 350 infants with birth weight < 1000 grams requiring mechanical ventilation, great variability in cortisol concentrations at both 12–48 hours and days 5–7 after birth were found with lower concentrations at 5–7 days. When cortisol concentrations were examined by quartiles, severe IVH grades 3/4 was found for infants in the highest quartile (OR 3.96, 95% CI 1.91–8.21 at 12–48h; OR 3.63 95% CI 1.63–8.12 at 5–7d), and those in the lower quartile were not associated with increased morbidity and mortality (OR 1.80, 95% CI 0.71–4.60 at 12–48h; OR 2.49, 95% CI 0.91–6.82 at 5–7d). The most severe morbidities, severe IVH, PVL, gastrointestinal perforation and death, were found in infants with cortisol concentrations in the 90th percentile (Aucott, Watterberg, Shaffer, Donohue, & the PROPHET Study Group., 2008).

The infants in this study were hospitalized in a bay-style NICU with 8–12 infants per bay where there was constant stimulation of caregivers, machinery, noise and light. They were born at a time when NICU technologies and care had improved survival rates. As a result, the infants received cutting edge care in the regional, tertiary neonatal center that was also the site for U.S. neonatal clinical trials. Since the onset of modern intensive care, premature infant survival has improved where more than 75% of infants at the point of viability survive. However, the infant outcomes continue to reveal medical, behavioral, neurocognitive and functional problems, as well as more severe disability such as cerebral palsy (Kerr-Wilson et al., 2012; Lemola, 2015).

The NPT group might be more biologically susceptible and perhaps, more likely to be influenced by adversity or enrichment. Due to their illness acuity, preterm infants in the NPT group had the longest length of stay in the neonatal intensive care unit (NICU) averaging more than two months (M = 67 days, SD = 22, range 23–107). Given the biological sensitivity of premature infants, features of caregiving environments have been studied in an effort to prevent developmental trajectories of concern. There are ongoing efforts to evaluate caretaking modifications aimed at reducing stressors for the premature infant and parents in NICUs (White-Traut, 2015). Instead of the traditional NICU bay-style pods, recent trends include the single family room NICU that features a serene space with in-room accommodation for parents enabling individual care and privacy for parental involvement. Surprisingly, the early evidence on single family room NICUs and infant outcomes is incongruent (Lester et al., 2014; Pineda et al., 2014).

Smith and colleagues (Smith et al., 2011) recorded infant stress exposures in the NICU to examine stress as a modifier to brain development in a sample of 55 premature infants < 30 weeks gestation. The MRI scans near term age confirmed that the many stressors to which premature infants are exposed was associated with decreased brain size in the frontal and parietal regions, and altered functional connectivity in the temporal lobes. Thus, the triple hazard model which we hypothesized involving early birth + environmental intensive care stress + separation from primary caregiver seems plausible.

It may be of more than passing interest that the effects of pre-perinatal adversity were manifest as individual differences in acute HPA reactivity to social stress in young adulthood. Is this observation the result of a difference in the effects of pre-perinatal adversity on the set point of HPA reactivity to novelty generally? Or is this effect related to HPA reactivity to social evaluative threat specifically? Alternatively, is the effect a manifestation of the HPA axis failing to habituate or attenuate to stress? Each of these possibilities has inferences for our interpretation of the significance and implications of these findings. Clearly, additional studies to address and untangle these possibilities are warranted. Regardless of the mechanism, higher levels of HPA reactivity to stress, if experienced on a chronic basis throughout childhood and early adulthood, are in the bodies of individuals exposed to pre-perinatal adversity on a more regular basis than their peers. This suggests that the chemical signals related to the psychobiology of the stress response are activated. Increased exposure to these signaling molecules has been associated with wear and tear on downstream biological processes (McEwen & Seeman, 1999) that result in negative consequences (allostatic load) for aspects of learning/memory, mental health, and immune function. In the context of prematurity and pre-perinatal adversity, changes in the HPA axis initiated early in life may serve as a mechanism involved in translating experiences with stress, threat, and challenge experienced throughout life into differential outcomes or developmental trajectories.

Concluding Comment

The findings have implications for theoretical perspectives linked to Toxic Stress, Developmental Origins of Health and Disease (DOHaD), and Biological susceptibility theories. In fact, in this instance, it would appear that these models have a significant degree of overlap. Toxic stress (premature and neurological problems) sets the stage from the outset for individuals to be more sensitive and susceptible to adversities, which in combination could be viewed as a DOHaDs. There is a need to reconcile these theories, and unify them into a working model from which specific hypotheses can be forwarded and tested in an effort to harness this knowledge to make a difference in the lives of children born prematurely.

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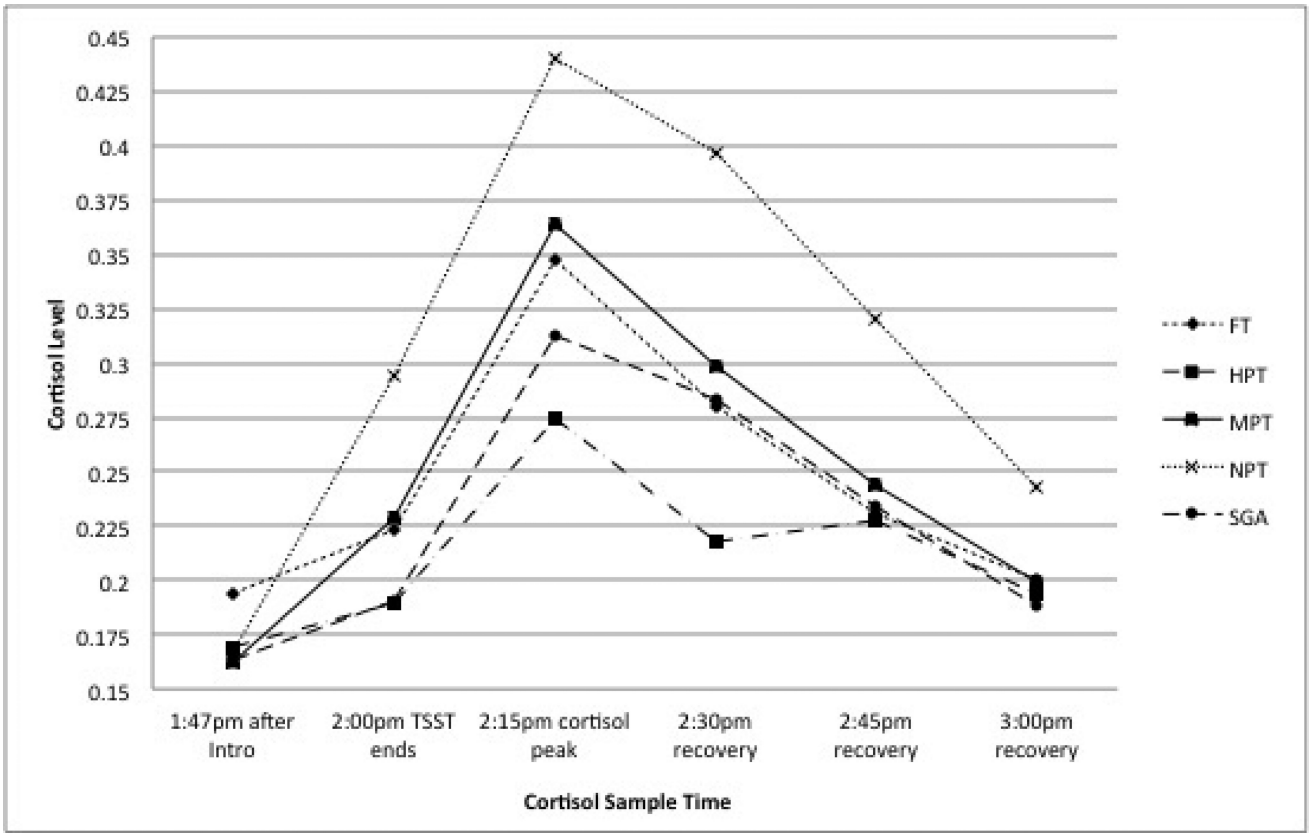

Figure 1.

Table 1

Neonatal Demographics of Study Sample at Age 23 Years (N=155)

	FT (*n*=37)			HPT (*n*=20)			MPT (*n*=48)			NPT (*n*=26)			SGA (*n*=24)			*F*	*df*
	M	*SD*	*Min-Max*	*M*	*SD*	*Min-Max*	*M*	*SD*	*Min-Max*	*M*	*SD*	*Min-Max*	*M*	*SD*	*Min-Max*		
Birth weight (grams)	[a]3397	438	2495–4370	[b]1468	209	900–1690	[c]1271	318	710–1800	[c]1192	281	720–1670	[c]1144	371	640–1915	276‡	4, 154
Gestational Age (weeks)	[a]40	.92	37–43	[b]31	1.7	28–34	[c]29	2.3	25–33	[c]28	2	25–33	[b]32	2.7	28–36	172‡	4, 154
Hobel Neonatal Risk[1]	[e]1.4	3.4	0–15	[d]58	24	20–110	[b]90	26	30–129	[a]112	22	48–160	[c]77	34	8–136	109‡	4, 154
Length of Stay	[d]3	.4	2–4	[c]34	10	17–60	[b]53	24	18–103	[a]64	21	23–107	[b]52	32	9–134	44‡	4, 154
SES[2]	42.4	14	13–69	39.4	14.7	17–60	40.1	13.7	9–61	41.3	13.1	17–67	43.0	11.0	22–61	.328	4,154

	FT (*n*=37)		HPT (*n*=20)		MPT (*n*=48)		NPT (*n*=26)		SGA (*n*=24)		
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	χ^2
IVH I/II	0	0	0	0	2	4	10	38	1	4	χ^2 (16) = 70.1‡
IVH III/IV	0	0	0	0	0	0	[a]7	27	2	8	
BPD	0	0	0	0	12	25	[a]9	35	2	8	χ^2 (4) = 22.7‡
Necrotizing Enterocolitis	0	0	0	0	[a]6	12	2	1	3	12	χ^2 (4) = 7.5
Sepsis	0	0	0	0	5	10	[a]6	23	3	12	χ^2 (4) = 12.3#
Meningitis	0	0	0	0	0	0	3	11	1	4	χ^2 (4) = 11.3*
Shunted Hydro-cephalus	0	0	0	0	0	0	[a]3	11	0	0	χ^2 (4) = 15.1#

Note. FT=full term; HPT=healthy preterm; MPT=medical preterm; NPT=neurological preterm; SGA=small for gestational age preterm; Min-Max=minimum-maximum; *df*=degrees of freedom; SES=socioeconomic status; BPD=bronchopulmonary dysplasia; IVH=intraventricular hemorrhage. Post-hoc results indicate significant differences between preterm groups, a>b, b>c, c>d.

‡ *p*<.0001,

* *p*=.05,

\# *p*=.01,

[1] [Hobel, 1973];

[2] Hollingshead [Hollingshead, 1975].