Published in final edited form as:
Neurotoxicol Teratol. 2015 ; 47: 146–153. doi:10.1016/j.ntt.2014.11.005.

Effects of Prenatal Cocaine Exposure on Pubertal Development

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Abstract

The purpose of the current study was to examine the relationship between prenatal cocaine exposure (PCE) and pubertal development. Children (n=192; 41% with PCE) completed the Pubertal Development Scale (Petersen, et al. 1988) and provided salivary dehydroepiandrosterone (DHEA) samples at 6 month intervals from 11 to 13 years. PCE was examined as a predictor of pubertal status, pubertal tempo, and DHEA levels in mixed models analyses controlling for age, sex, environmental risk, neonatal medical problems, other prenatal exposures, and BMI. PCE interacted with age such that PCE predicted slower pubertal tempo during early adolescence. PCE also interacted with age to predict slower increases in DHEA levels during early adolescence. These findings suggest that PCE may affect pubertal development and, if slower pubertal tempo continues, could lead to delayed pubertal status in mid-adolescence.

Keywords

prenatal cocaine exposure; pubertal status; pubertal tempo; dehydroepiandrosterone

1. Introduction

Prenatal cocaine exposure (PCE) has been associated with a variety of adverse developmental outcomes including attention and inhibitory control deficits, risky behavior, aggression, and cognitive deficits (Ackerman, et al. 2010; Bendersky, et al. 2006; Bennett, et al. 2007; Bennett, et al. 2008; Bennett, et al. 2013; Lambert and Bauer 2012). Research, however, has yet to examine the possible relationship between PCE and pubertal development despite findings that PCE is associated with a variety of other biophysiological

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An earlier report of preliminary data from this study was presented at the Society for Research in Child Development biennial meeting, Denver, April, 2009.

effects. These include decreased cerebral blood flow (Rao, et al. 2007), differences in frontal lobe white matter and gray matter (Grewen, et al. 2014; Warner, et al. 2006), and a blunted cortisol response to stress (Lester, et al. 2010). Specific to physical development, PCE has been associated with decreased intrauterine growth and with lower weight or slower growth during middle childhood (Bandstra, et al. 2001; Bateman and Chiriboga 2000; Bendersky and Lewis 1999; Eyler, et al. 1998; Lutiger, et al. 1991; Minnes, et al. 2006; Richardson, et al. 2007; Richardson, et al. 1999; Richardson, et al. 2013), although one study found PCE to be associated with greater body mass index (BMI) at 9 years (Shankaran, et al. 2010). Collectively, these findings suggest that PCE can affect physical development.

Pubertal development, including the timing of pubertal milestones, has been shown to be affected by teratogen exposure (Shrestha, et al. 2011; Wohlfahrt-Veje, et al. 2012a; Wohlfahrt-Veje, et al. 2012b). Among studies of prenatal substance exposure, tobacco has been most frequently examined. Boys, but not girls, prenatally exposed to tobacco reported reaching pubertal milestones earlier than their unexposed peers (Fried, et al. 2001). Similarly, a retrospective study of Danish men also found prenatal tobacco exposure to be associated with earlier pubertal onset (Ravnborg, et al. 2011). While prenatal exposures are generally more apt to affect males (Kestler, et al. 2012; Moe and Slinning 2001), girls whose mothers smoked heavily during pregnancy have been found to reach menarche at a younger age than unexposed girls in most studies (D'Aloisio, et al. 2013; Ernst, et al. 2012; Maisonet, et al. 2010; Morris, et al. 2010; Rubin, et al. 2009; Shrestha, et al. 2011; Windham, et al. 2004), although two studies found the opposite effect (Ferris, et al. 2010; Windham, et al. 2008). While the effects of tobacco exposure may be distinct from the effects of cocaine exposure, these studies indicate that prenatal substance exposure can affect the timing of pubertal development.

Research on pubertal development has traditionally focused on pubertal differences at specific age points (i.e., pubertal status). Studies of pubertal development, however, should examine both pubertal status and pubertal tempo. *Pubertal status* is defined as a child's pubertal development relative to same-sex and same–age peers at a given time point. In contrast, *pubertal tempo* is defined as the rate of change in pubertal development over a given period of time. Pubertal tempo is important because it has unique psychosocial correlates. For example, pubertal tempo was found to predict depressive symptoms better than pubertal status for boys since boys who developed more rapidly did not experience the reduction in depressive symptoms that their slower developing peers experienced (Mendle, et al. 2010). Similarly, rapid pubertal change has predicted increased depressive symptoms, internalizing problems, and externalizing problems (Ge, et al. 2003; Kretschmer, et al. 2013; Marceau, et al. 2011). These findings are consistent with the maturation compression hypothesis, which proposes that rapid pubertal tempo requires a relatively quick adaptation to new biological and social milestones, potentially increasing risk for adjustment problems (Mendle 2014). The precise mechanisms by which individual differences in pubertal tempo emerge is unclear, but may involve hormonal as well as psychosocial factors (Mendle 2014). While both pubertal status and pubertal tempo may contribute to adjustment, they are not consistently correlated with each other (Marceau, et al. 2011). As such, both pubertal status and tempo should be examined in relationship to PCE.

In addition to self-reports of pubertal status and tempo, hormonal changes can be used as a marker of pubertal development. Noticeable physical changes associated with puberty are preceded by hormonal changes such as increases in dehydroepiandrosterone (DHEA), an adrenal androgen and a precursor to testosterone and estrogen. DHEA levels rise dramatically during fetal development, when it may play a role in neuronal development (Compagnone and Mellon 1998), and then decline after the first year of life (Havelock, Auchus, & Rainey, 2004). At age 6 to 7 years, DHEA production again increases, corresponding to the beginning of adrenarche (Havelock, et al. 2004; Sulcova, et al. 1997), which is also characterized by axillary and pubic hair growth and the acceleration of bone growth and maturation (Papadimas 1997). DHEA is moderately correlated with pubertal status for both boys and girls (Shirtcliff, et al. 2007).

Apart from the possible teratogenic effects of prenatal substance exposure, psychosocial factors can also play a role in pubertal development. For example, the absence of a biological father or presence of a stepfather-figure in the home has been found to predict earlier pubertal development among girls (Ellis 2004; Ellis and Garber 2000; Tither and Ellis 2008). Likewise, maternal depression and family stress predict earlier pubertal development, especially for girls (Belsky, et al. 2007; Ellis and Garber 2000; Hulanicka 1999; Hulanicka, et al. 2001; Kim and Smith 1998; Saxbe and Repetti 2009).

The current study sought to examine individual differences in pubertal development as a function of PCE in a longitudinal study of children who were seen every 6 months between 11 and 13 years. We chose to focus on this age range because it captures the time of greatest variability in pubertal development for children in the United States (Parent, et al. 2003). In examining PCE as a predictor of pubertal development, we controlled for the effects of prenatal tobacco, alcohol, and marijuana exposure as well as neonatal medical problems, which also have been associated with differences in pubertal timing (Proos, et al. 2011). Given that increased BMI may be related to PCE (Shankaran, et al. 2010) and has been associated with earlier pubertal development (He and Karlberg 2001; Kaplowitz 2008), we also controlled for BMI. Likewise, given that pubertal development may be affected by psychosocial risk factors such as father absence, step-father presence, maternal depression, and family stress, these factors were examined in the current study, along with general environmental risk.

This study is the first to examine pubertal status and tempo in children with PCE. The study had three major aims. First, we examined whether children with PCE exhibit differences in pubertal development compared to their unexposed peers. In doing so, we examined differences in both pubertal status and pubertal tempo across ages 11 to 13. Second, we examined whether children with PCE exhibit differences in DHEA compared to their unexposed peers, both in mean levels and rate of change across ages 11 to 13. Third, we examined whether sex moderated any observed effects, based on prior research finding greater PCE effects for boys than girls (e.g., (Bennett, et al. 2008; Carmody, et al. 2011; Kestler, et al. 2012).

2. Methods

2.1. Participants

Participants were 192 children (52% male; 41% with PCE [46% of who were male]) and their mothers from a longitudinal study on the developmental effects of prenatal substance exposure. Pregnant women attending prenatal clinics in Philadelphia, Pennsylvania and Trenton, New Jersey were enrolled between February 1993 and December 1995. Children who were born before 32 weeks of gestation, required special care or oxygen therapy for more than 24 hours, exhibited congenital anomalies, or who were exposed to opiates or PCP in utero were excluded. Of the 258 children who participated in the first laboratory visit at 4 months, 192 children provided at least one assessment of pubertal status between the ages of 11.0 and 13.5. No significant differences were observed in perinatal variables (cocaine, alcohol, cigarette, or marijuana exposure; neonatal health problems), maternal age, or environmental risk at birth between participants in the current sample and those who did not participate. Mean child age at the six visits was as follows: 11.09 (SD=0.14), 11.61 (0.16), 12.08 (0.16), 12.58 (0.24), 13.09 (0.16), and 13.68 (0.22). Mothers were predominantly African-American (90%) and ranged in age from 13.7 to 42.1 (M = 25.9; SD = 6.0) years at the time of their child's birth. Three percent of caregivers reported using cocaine, marijuana, opiates, heroine, PCP, or “other street drugs” in the 6 months prior to study visits during the current time period.

2.2. Procedure

At 11.0, 11.5, 12.0, 12.5, 13.0, and 13.5 years, children's pubertal status and salivary DHEA levels were assessed. Examiners were blind to the children's drug exposure status. Incentives were provided to participants in the form of vouchers for use at local stores at each visit.

2.3. Measures

2.3.1. Predictors of Pubertal Development

2.3.1.1. Prenatal substance exposure: Prenatal substance exposure was assessed using a semi-structured interview administered to the mother within 2 weeks of their child's birth. The interview included questions assessing the frequency and amount of the mother's use of cocaine, alcohol, cigarettes, marijuana, and other substances throughout pregnancy. PCE was confirmed by analysis of the newborn's meconium for the presence of benzoylecgonine (cocaine metabolite) using radioimmunoassay followed by confirmatory gas chromatography/mass spectrometry. PCE was dichotomized (i.e., into unexposed and exposed groups; 0 vs. 1) in all analyses as prior reports from this sample have found the dichotomous measure to best predict outcomes.

2.3.1.2. Neonatal medical problems: Neonatal medical problems were abstracted by nurses from hospital records at birth using the Hobel Scale, a neonatal medical risk scale based on 35 possible complications (Hobel, et al. 1973). Complications included general factors (e.g., low birth weight, fetal anomalies, and feeding problems), respiratory problems (e.g., congenital pneumonia, apnea, and meconium aspiration syndrome), metabolic disorders (e.g., failure to gain weight and hypoglycemia), cardiac problems (e.g., murmur and cardiac

anomalies), and CNS problems (e.g., CNS depression and seizures). Items were summed such that higher scores indicated greater neonatal medical problems, and log transformed to correct for skew.

2.3.1.3. Environmental risk: A composite environmental risk score was computed from variables obtained by maternal interview at the 10 year laboratory visit. The score included maternal life stress based on the Social Environment Inventory (Orr, et al. 1992), maternal social support network size based on the Norbeck Social Support Questionnaire (Norbeck, et al. 1981), the number of regular caregivers (greater number being associated with higher risk), the irregularity of the child's schedule and the instability of the child's surroundings from the Family Chaos Scale (R. Seifer, personal communication, 1993), single parenthood (single parent = higher risk), maternal education (reverse scored), and public assistance status (whether the family received Temporary Assistance to Needy Families [TANF] funding). Each variable was standardized and summed. This cumulative risk score was then rescaled as a T-score (M = 50, range = 25 to 87). Such aggregate scores are more stable than individual measures, and there is increased power to detect effects of the environment because errors of measurement decrease as scores are summed and degrees of freedom are preserved. This and similar cumulative environmental risk measures have been found to explain more variance in child and adolescent outcomes than single factor scores (Atzaba-Poria, et al. 2004; Bendersky and Lewis 1994; Bendersky and Lewis 1998; Deater-Deckard, et al. 1998; Sameroff, et al. 1993).

2.3.1.4. Father absence and stepfather-figure presence: Father absence was assessed based on the primary caregiver's response as to the presence or absence of each child's biological father in the home. Absence of biological father was coded as “1” whereas presence of biological father in the home was coded as “0”. A dichotomous variable for father absence/presence was created for each lab visit from age 11.0 through 13.5 and then averaged across the six age points.

Similarly, “stepfather-figure” *presence* in the home was also assessed at each lab visit (0=absent, 1=present), and these variables were averaged to create an overall score for stepfather-figure presence over the age range 11.0 to 13.5 years. Assessment of stepfather figure presence was based on the primary caregiver's endorsement of a partner, other than the child's biological father, living in the home. Note that *absence* of biological father and *presence* of stepfather-figure were coded as “1” as these conditions are both associated with early puberty in girls.

2.3.1.5. Maternal depressive symptoms: Maternal depressive symptoms were assessed using the 21-item Beck Depression Inventory-II (Beck, et al. 1996), a well-validated measure of depressive symptomatology (Richter, et al. 1998). The BDI-II was administered to caregivers at the age 11.5 and 13.0 visits and scores were averaged over the two age points. This averaged score was then log-transformed to correct for skew.

2.3.2. Measures of Pubertal Development

2.3.2.1. Pubertal status and tempo: The Pubertal Development Scale (PDS)(Petersen, et al. 1988) was computer-administered at each visit. The examiner stepped out of the room while the child read and listened to the questions read aloud by the computer. Computer assisted self-interview of potentially sensitive questions, including questions regarding pubertal status, has been shown to have a high degree of validity (Lamb, et al. 2011). The PDS contains 5 items assessing pubertal status, including the presence of a growth spurt, pubic hair, and skin changes for both boys and girls. For boys, PDS items also assess facial hair growth and voice change; for girls, items also assess breast development and menarche. Each item ranges from 1 (development has not yet begun) to 4 (development seems completed). The PDS correlates significantly with pubertal status based on physical exam (Brooks-Gunn, et al. 1987; Petersen, et al. 1988; Shirtcliff, et al. 2009). Pubertal tempo was assessed by examining the rate of change in pubertal status across age 11 to 13 years.

2.3.2.2. DHEA: DHEA was measured by obtaining a saliva sample (1 ml minimum) shortly after arrival to the research office at each visit. Participants were asked to drool through a straw into a small tube. Samples were immediately frozen for storage until they were shipped in dry ice to a laboratory for the cortisol assay.

Salivary DHEA was determined using a commercially available high sensitivity EIA kit (No. 1-1202/1-1212, Salimetrics) according to the manufacturer's directions. The range of this assay is 10-1000 pg.ml. Standard curves were fit by a weighted regression analysis using commercial software (Revelation 3.2) for the ELISA plate reader (Dynex MRX). From these curves, unknown values were computed. The antibody in this kit shows minimal cross reactivity (less than 0.001%) with other steroids present in the saliva. As many samples as practical were run in the same assay and participants were not split across different assay plates if possible. Laboratory controls were run on every plate for determination of inter- and intra-assay coefficients of variability, which were less than 8% for DHEA. The median correlation between DHEA and pubertal status across the six time points indicated that higher DHEA levels were modestly associated with more advanced pubertal status ($r = 0.19$, $p = .03$).

2.4. Data analysis

Group differences in pubertal status, DHEA, and study covariates as a function of PCE, sex, and their interaction were initially examined using analyses of variance (ANOVA) following multiple imputation of missing data ($n = 20$ data sets; SPSS version 20.0, IBM Corp., 2011). The effect of PCE and its potential interaction with both sex and child age on pubertal status and DHEA, controlling for the other risk factors, was then examined using mixed models analyses (Singer and Willett 2003) with an unstructured covariance matrix for the random effects. Given that children had a 12 month window in which to complete each lab visit, ages actually ranged from 11 to 14 years during the six assessments and as such age was treated as a continuous variable in the mixed models analyses.

3. Results

3.1. Pubertal Status as a Function of PCE and Sex

Table 1 presents estimated means and standard errors for pubertal status as a function of PCE and sex. PCE did not predict pubertal status in a series of univariate ANOVAs with the exception of at 13.0 years, when children with PCE exhibited lower pubertal status than unexposed children ($F(1,187) = 6.53$, $p = .01$).

3.2. DHEA as a Function of PCE and Sex

Table 1 also presents estimated means and standard errors for DHEA levels as a function of PCE and sex, controlling for time since waking since DHEA levels decrease post-waking (Hucklebridge, et al. 2005). PCE exhibited a non-significant trend at 13.0 years as exposed children had lower DHEA levels than unexposed children ($F(1,187) = 2.79$, $p = .097$). PCE also interacted with sex at 12.5 years such that boys with PCE had lower DHEA levels whereas girls with PCE exhibited higher DHEA levels than their unexposed peers ($F(1,187) = 12.50$, $p = .001$).

3.3. Covariates as a Function of PCE and Sex

Table 2 presents estimated means and standard errors for covariates as a function of PCE and sex. PCE was associated with increased exposure to alcohol ($F(1,187) = 22.51$, $p < .001$), cigarettes ($F(1,187) = 56.68$, $p < .001$), and marijuana ($F(1,187) = 5.17$, $p = .025$) as well as greater environmental risk ($F(1,187) = 4.61$, $p = .033$) and biological father absence ($F(1,187) = 4.40$, $p = .037$). PCE also interacted with sex as girls, but not boys, in the sample were more likely to have experienced prenatal marijuana exposure ($F(1,187) = 4.09$, $p = .045$).

3.4. PCE as a Predictor of Pubertal Development, Controlling for Covariates

To examine whether PCE effects were present after controlling for covariates, two mixed models analyses were conducted with pubertal status and DHEA as the outcomes. Random effects were specified for the intercepts. PCE (exposed vs. unexposed), age (centered at 11.0 years using actual age at the time of the visit), environmental risk, neonatal medical problems, prenatal exposure to alcohol, cigarettes, and marijuana, sex, and BMI were entered as covariates. In addition, interactions between PCE and sex were included to test whether exposure effects on pubertal status and DHEA differed for boys and girls. Similarly, interactions between PCE and age (centered) were examined to test whether PCE effects varied with age. The slope of change in pubertal status across age was used to measure pubertal tempo.

3.4.1. Preliminary analyses—Maternal depressive symptoms, biological father absence, and stepfather figure presence in the home were included with the other covariates in two preliminary mixed models analyses predicting pubertal status and DHEA. Interaction terms between child sex and father absence, and between sex and stepfather figure presence also were included as covariates because father absence and stepfather figure presence have been found to predict pubertal status only for girls. In addition, the three-way interaction among PCE, sex, and age also was included. None of these six covariates were found to predict

pubertal status ($p > 0.30$) and were thus removed from the final pubertal status model to conserve statistical power. For DHEA, these covariates also did not approach significance ($p > 0.20$) with the exception of a non-significant trend for father absence ($p = 0.09$), which was thus retained in the final DHEA model. Maternal depressive symptoms, stepfather figure presence, and the interaction of each with sex was not significant and were dropped from the final DHEA model, as was the interaction of PCE by sex by age and the interaction of sex by age.

3.4.2. PCE and pubertal status—PCE was unrelated to pubertal status in the mixed models analysis (see Table 3). There was no specific time point between ages 11 and 14 at which exposed and unexposed children's pubertal status was significantly different when covariates were accounted for. The simple main effect of PCE at age 11 (as well as in models at age 12.0, 13.0, and 14.0) was not significant for boys or for girls, nor was there a significant PCE by sex interaction.

The simple main effect of age, as expected, was significant for both unexposed ($t(98.70) = 9.32$, $p < .001$) and exposed ($t(76.95) = 4.56$, $p < .001$) children, indicating that age was associated with more advanced pubertal status for participants in both groups. Greater BMI also was associated with more advanced pubertal status ($t(326.59) = 3.01$, $p = .003$). Environmental risk, neonatal medical problems, and other prenatal substance exposures did not predict pubertal status.

3.4.3. PCE and pubertal tempo—Pubertal tempo, as noted above, is the rate of change in pubertal status over time. As such, the presence of a PCE effect on pubertal tempo can be examined by testing for the presence of an interaction between PCE and age on pubertal status. The PCE by age interaction was significant, indicating that exposed children had slower rates of pubertal development ($t(154.52) = 1.98$, $p = 0.050$; see Table 3 and Figure 1). The pubertal status scores of exposed children were estimated to increase at a rate of only 0.19 per year compared to 0.28 per year for unexposed children after adjusting for covariates in the model.

3.4.4. PCE and DHEA levels—PCE predicted higher DHEA levels ($t(165) = 3.03$, $p = .015$). There was no specific time point, however, between ages 11 and 14 at which exposed and unexposed children's DHEA levels were significantly different when covariates were accounted for. Greater age ($t(463) = 14.84$, $p < .001$) and BMI also predicted higher DHEA levels ($t(463) = 3.94$, $p < .001$). Time since waking also was a significant covariate as participants tested closer to waking had higher DHEA levels ($t(463) = 2.49$, $p = .013$). In addition, children with an absent father had lower DHEA levels ($t(165) = 2.05$, $p = .042$). Environmental risk, neonatal medical problems, other prenatal substance exposures, sex, and the interaction of PCE and sex did not predict DHEA levels.

3.4.5. PCE and DHEA changes over time (DHEA tempo)—PCE interacted with age ($t(463) = 2.31$, $p = 0.021$; see Table 3). Specifically, exposed children's DHEA levels increased an average of only 4.90 per year, compared to 17.37 per year for unexposed children after adjusting for covariates in the model.

4. Discussion

To our knowledge, this is the first study to examine pubertal status and pubertal tempo in adolescents prenatally exposed to cocaine. PCE was associated with slower pubertal tempo in early adolescence when controlling for covariates. The slower pubertal tempo associated with PCE was observed for both boys and girls as sex did not moderate the relationship between PCE and pubertal tempo. Consistent with the pubertal tempo findings, PCE also predicted a slower increase in DHEA levels from 11 to 13 years.

Our findings indicate that children with PCE experience a slower rate of pubertal development as measured by self-report during early adolescence. If this slower rate of development persists during mid-adolescence, children with PCE may experience delayed physical maturation relative to their unexposed peers. In addition, the lack of findings for cigarette, alcohol, and marijuana exposure in the current study support prior research in suggesting that the effects of prenatal substances on pubertal development may vary by substance. Contrary to the current findings, prenatal tobacco exposure has generally been associated with earlier pubertal status in prior research (Håkonsen, et al. 2014). In contrast, the finding that prenatal alcohol exposure did not predict pubertal status is consistent with earlier studies that also have found no effect for alcohol exposure on the timing of pubertal milestones (Shrestha, et al. 2011; Windham, et al. 2004). Likewise, prenatal marijuana exposure has been found to have no association with pubertal status (Fried, et al. 2001).

Examining teratogens more broadly, there is precedence for associations between potential teratogens and delayed pubertal development (Wu, et al. 2012). In addition to two studies finding prenatal tobacco exposure to predict later menarche (Ferris, et al. 2010; Windham, et al. 2008), prenatal exposure to dioxin and to tea in humans and prenatal exposure to lead in rats have been associated with later pubertal development (Dearth, et al. 2002; Korrick, et al. 2011; Windham, et al. 2004). There is further precedence in the animal literature for prenatal substance exposures to delay pubertal maturation, as well as to reduce fertility and sex organ function (Dearth, et al. 2002; Holloway, et al. 2006; Vahakangas, et al. 1985; Wenger, et al. 1988). While the underlying mechanisms for these findings remain unknown, the noradrenergic system may be involved. PCE has been shown to affect the noradrenergic system (Elsworth, et al. 2007; Foltz, et al. 2004; Seidler and Slotkin 1992; Snow, et al. 2004), which in turn may influence pubertal development. Norepinephrine plays a role in regulating the hypothalamus (Christman and Gisolfi 1985; Oishi 1979; Tsigos and Chrousos 2002), which contains cells that produce gonadotropin releasing hormones that regulate pubertal development, particularly the onset of puberty (Plant 2002). Accordingly, it is plausible to hypothesize a pathway wherein PCE acts to dysregulate the noradrenergic system, leading to dysregulation of the hypothalamus and subsequently affecting pubertal development. Alternatively, cocaine use during pregnancy has been found to increase maternal cortisol levels in animal studies, raising the possibility that increased fetal exposure to cortisol could lead to dysregulated HPA function, which in turn may be associated with alterations in pubertal timing (Ellis, et al. 2011; Lester and Lagasse 2010; Owiny, et al. 1991). Attenuated HPA function has recently been associated with accelerated pubertal tempo in girls (Saxbe, et al. 2014).

DHEA levels also increased more slowly among children with PCE. However, children exposed to cocaine had higher overall levels of DHEA. In the current study, DHEA was found to be modestly correlated with pubertal status, consistent with some prior research showing significant but inconsistent relations between DHEA and pubertal status (Matchock, et al. 2007). Considering the hypothalamic-pituitary-adrenal system more broadly, cortisol levels have been found to increase in preparation for a perceived stressor such as coming to a research office visit, as was done in the current study (Kestler and Lewis 2009; Sullivan, et al. 2012). DHEA levels, however, have been found to decrease in response to such acute stress (Schwartz 2002), suggesting that increased stress reactivity by children with PCE at the time of DHEA collection does not explain their greater overall DHEA levels.

While there have been no prior reports on the effects of PCE on pubertal development or DHEA, animal studies have found PCE to be associated with differences in sexual behavior and gonadal hormones. Male rats prenatally exposed to cocaine show increased latency to initiate sexual behavior, as well as reduced scent marking and higher plasma luteinizing hormone (LH) levels, but no difference in testosterone levels which suggests a relative CNS insensitivity to androgens in these animals compared to controls (Raum, et al. 1990). In contrast, male rats with PCE were found to display shorter post-ejaculatory intromission intervals, suggesting enhanced sexual arousal, while exposed females showed reduced rearing, suggesting reduced sexual arousal (Vathy, et al. 1993). Norepinephrine and dopamine levels were higher in cocaine-exposed males in the preoptic area, a key brain area mediating steroid action on male sexual behavior (Vathy, et al. 1993). Similarly, perinatal cocaine exposure was found to reduce the volume of male rats' sexually dimorphic nucleus, which helps regulate sexual behavior (Maecker 1993). Collectively, these studies suggest that PCE affects perinatal androgenization, leading to changes in sexual behavior, gonadal hormones, and brain catecholamines that occur following pubertal development and highlight the potential importance of examining such measures in post-pubertal humans with PCE.

Several limitations of the current study deserve mention. First, our sample consists of predominantly African-American, urban children and as such our results may not generalize to other populations as, for example, African-American girls may experience earlier pubertal onset (Wu, et al. 2002). Second, our study assessed pubertal development from ages 11 to 13 as this is a time of great variability in pubertal status (Parent, et al. 2003), but it is unclear whether differences in pubertal status, tempo, or DHEA might be observed at earlier or later ages. Third, measures of prenatal alcohol, cigarette, and marijuana exposure were limited to self-report. PCE, which was confirmed by metabolite assay, was a dichotomous variable and as such did not allow for the examination of timing, continuity, or severity of exposure effects. Fourth, while the Pubertal Development Scale has been shown to be a valid measure of pubertal status (Brooks-Gunn, et al. 1987; Petersen, et al. 1988; Schmitz, et al. 2004), physician report (e.g., the Tanner Scale) may be a more sensitive, albeit difficult to obtain measure of pubertal development. Finally, repeated measurement of DHEA throughout the day (e.g., (Shirtcliff, et al. 2009) may provide a more valid measure of DHEA.

5. Conclusions

This study is the first to examine pubertal status and tempo in children with PCE. We found that children with PCE, while not showing significant differences in pubertal status during early adolescence, do show a slower pubertal tempo. Studies of pubertal tempo that examine psychosocial adjustment generally indicate that accelerated, not slower, tempo is a risk factor for greater adjustment problems (Ge, et al. 2003; Marceau, et al. 2011; Mendle, et al. 2010). Slower pubertal tempo, however, can be associated with health problems. For example, slow pubertal tempo may extend the window of vulnerability for breast carcinogenesis given prolonged exposure to endogenous hormones during a period of high mammary cell proliferation and differentiation (Ellis, et al. 2011). Furthermore, if this slower rate of pubertal development persists into mid-adolescence, children with PCE may lag behind their peers in pubertal status. Boys with late pubertal development have been found to exhibit increased rates of externalizing problems, substance use, and depressive symptoms (Graber, et al. 2004; Kaltiala-Heino, et al. 2003). These findings suggest that future research should examine the pubertal status of adolescents with PCE at older ages, as late pubertal development could mediate a potential relationship between PCE and adjustment problems in late adolescence and early adulthood.

Acknowledgments

This study was supported by Grant R01 DA007109 to Michael Lewis, David Bennett, and Dennis Carmody (MPI) from the National Institute on Drug Abuse. The authors greatly appreciate the statistical assistance of Charles Cleland.

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Ms. #: NTT-14-40 Highlights

- Prenatal cocaine exposure (PCE) was associated with slower pubertal tempo in early adolescence
- PCE also was associated with smaller increases in DHEA in early adolescence
- If these findings persist, children with PCE may be at-risk for delayed pubertal status at later ages

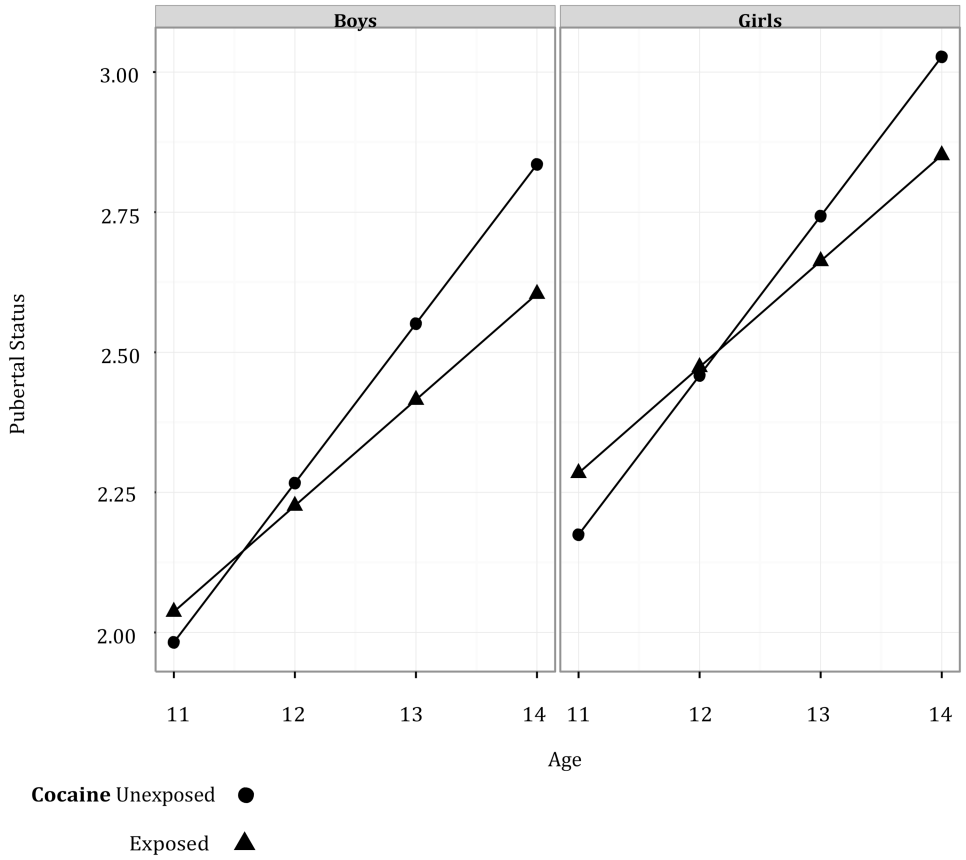

Figure 1. Change in Pubertal Status over Time by Age for Boys and Girls

Table 1

Estimated Means (and Standard Errors) of Pubertal Status and DHEA Levels by Cocaine Exposure and Sex

	Cocaine Exposed		Unexposed		Effects		
	Boys (n = 36)	Girls (n = 42)	Boys (n = 64)	Girls (n = 50)	Cocaine	Sex F (1,187)	Coc × Sex
Pubertal status							
11.0 years	2.02 (0.13)	2.33 (0.13)	2.05 (0.10)	2.32 (0.12)	0.18	7.93**	0.08
11.5 years	2.18 (0.13)	2.45 (0.13)	2.20 (0.11)	2.38 (0.12)	0.19	4.84*	0.57
12.0 years	2.21 (0.13)	2.63 (0.13)	2.38 (0.10)	2.50 (0.12)	0.22	2.49	0.39
12.5 years	2.30 (0.13)	2.70 (0.14)	2.52 (0.10)	2.68 (0.12)	2.19	3.38†	2.67
13.0 years	2.27 (0.13)	2.59 (0.15)	2.93 (0.10)	2.79 (0.12)	6.53*	0.52	1.48
13.5 years	2.77 (0.15)	2.97 (0.18)	2.77 (0.12)	2.94 (0.14)	1.94	1.75	0.90
DHEA levels							
11.0 years	64.73 (7.93)	106.30 (7.37)	74.98 (5.98)	94.70 (6.74)	0.08	18.58***	2.44
11.5 years	74.72 (10.12)	104.77 (9.37)	80.54 (7.51)	99.87 (8.59)	0.01	7.61**	0.38
12.0 years	70.63 (8.44)	94.37 (7.80)	84.99 (6.32)	84.91 (7.10)	0.12	2.53	2.59
12.5 years	76.91 (8.36)	120.44 (7.75)	99.36 (6.29)	89.91 (7.11)	0.27	5.46*	12.50**
13.0 years	99.22 (8.03)	109.57 (7.54)	114.05 (6.11)	118.88 (6.86)	2.79†	1.22	0.16
13.5 years	118.11 (8.91)	135.47 (8.22)	123.61 (6.66)	126.23 (7.55)	0.05	1.65	0.83

Note. Estimated means at a given age control for actual child age given minor age differences at each age point. In addition, estimated means for DHEA control for time since waking.

[a] Mean variables computed from dichotomous variables; all values between 0 and 1.

† $p < .10$.

* $p < .05$.

** $p < .01$.

*** $p < .001$.

Neurotoxicol Teratol. Author manuscript; available in PMC 2016 January 01.

Table 2

Estimated Means (and Standard Errors) of Covariates by Cocaine Exposure and Sex

	Cocaine Exposed		Unexposed		Effects		
	Boys (n = 36)	Girls (n = 42)	Boys (n = 64)	Girls (n = 50)	Cocaine	Sex	Coc × Sex
						F (1,187)	
Covariates							
Environmental risk	3.74 (0.22)	4.05 (0.21)	3.22 (0.17)	3.73 (0.19)	4.61*	4.21*	0.28
Maternal depressive symptoms	6.06 (1.07)	7.47 (1.00)	7.04 (0.82)	6.57 (0.91)	0.01	0.26	0.91
Biological father absence[a]	0.57 (0.07)	0.55 (0.07)	0.36 (0.06)	0.48 (0.06)	4.40*	0.49	1.07
Stepfather-figure presence[a]	0.24 (0.06)	0.24 (0.06)	0.26 (0.05)	0.18 (0.05)	0.18	0.48	0.46
Neonatal medical problems	0.90 (0.32)	1.52 (0.32)	0.70 (0.26)	0.43 (0.31)	0.05	8.98**	0.01
Prenatal substance exposure							
Alcohol (drinks/day)	0.95 (0.31)	1.71 (0.29)	0.03 (0.23)	0.02 (0.26)	22.51***	1.73	1.90
Cigarettes (per day)	7.20 (1.08)	9.68 (1.01)	1.53 (0.80)	0.98 (0.91)	56.68***	1.08	2.60
Cocaine (grams/day)	0.39 (0.09)	0.66 (0.08)	0.00 (--)	0.00 (--)	56.08***	3.74†	3.74†
Marijuana (joints/day)	0.09 (0.15)	0.57 (0.14)	0.04 (0.14)	0.00 (0.13)	5.17*	3.10†	4.09*
Body Mass Index (BMI)							
11.0 years	20.44 (0.97)	22.52 (0.90)	22.57 (0.73)	22.78 (0.82)	1.78	1.83	1.51
11.5 years	21.33 (0.91)	23.20 (0.82)	22.97 (0.70)	23.97 (0.76)	1.69	2.76	0.72
12.0 years	22.24 (0.89)	23.53 (0.83)	22.73 (0.69)	23.71 (0.76)	0.25	2.11	0.08
12.5 years	22.80 (0.86)	24.01 (0.77)	22.27 (0.64)	24.47 (0.71)	0.06	5.58*	0.48
13.0 years	23.26 (0.87)	24.97 (0.82)	22.83 (0.67)	24.84 (0.75)	0.12	6.06*	0.03
13.5 years	24.24 (0.94)	26.39 (0.87)	24.44 (0.71)	26.44 (0.78)	0.03	7.17**	0.02

Note. Estimated means for BMI at a given age control for actual child age given minor age differences at each age point.

[a]Mean values are computed from dichotomous variables; all values between 0 and 1.

†$p < .10$.

*$p < .05$.

**$p < .01$.

***$p < 001$.

Table 3

Coefficients (Standard Error; 95% Confidence Intervals) from Mixed Model Analyses Predicting Pubertal Status and DHEA

Predictors	Pubertal Status	DHEA Level
Intercept	1.92 (0.21; 1.51 to 2.32)***	62.06 (18.34; 29.02 to 101.33)***
Age	0.28 (0.03; 0.22 to 0.34)***	14.84 (3.38; 7.26 to 20.62)***
Environmental risk	0.01 (0.03; -0.06 to 0.07)	-1.30 (2.69; -6.87 to 3.77)
Neonatal medical problems	-0.06 (0.16; -0.39 to 0.26)	-4.40 (13.69; -30.52 to 23.59)
Prenatal substance exposure		
Alcohol	-0.01 (0.05; -0.11 to 0.09)	-5.69 (3.96; -13.68 to 1.99)
Cigarettes	-0.04 (0.03; -0.11 to 0.03)	-3.97 (2.77; -9.17 to 1.79)
Cocaine	0.11 (0.16; -0.21 to 0.43)	38.95 (13.87; 17.31 to 72.09)**
Marijuana	-0.09 (0.07; -0.22 to 0.04)	-3.46 (5.37; -13.83 to 7.42)
Child sex	-0.19 (0.11; -0.40 to 0.02)†	-8.95 (8.69; -23.64 to 10.71)
Body Mass Index	0.02 (0.01; 0.01 to 0.03)**	1.97 (0.50; 0.81 to 2.77)***
Prenatal cocaine exposure × sex	-0.06 (0.16; -0.38 to 0.27)	-19.83 (15.54; -67.39 to -6.03)
Prenatal cocaine exposure × age	-0.10 (0.05; -0.19 to -0.00)*	-12.26 (6.96; -32.89 to -5.37)*
Time since waking	--	-2.24 (0.90; -4.09 to -0.55)*
Biological father absent	--	-15.98 (8.15; -30.98 to 1.23)*

Note. Cocaine exposure was entered as a dichotomous variable (0 = no exposure; 1 = exposed). Age was centered at 11.0 years.

† $p < .10$.

* $p < .05$.

** $p < .01$.

*** $p < .001$. (2-tailed).