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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.

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, 2008, 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 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., 1999, 2007, 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, 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

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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 et al., 2004). At age 6–7 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 h, 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