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Externalizing behavior and substance use related problems at 15 years in prenatally cocaine exposed adolescents

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A B S T R A C T

The effect of prenatal cocaine exposure (PCE) on externalizing behavior and substance use related problems at 15 years of age was examined. Participants consisted of 358 adolescents (183 PCE, 175 non-cocaine exposed (NCE)), primarily African–American and of low socioeconomic status, prospectively enrolled in a longitudinal study from birth. Regression analyses indicated that the amount of PCE was associated with higher externalizing behavioral problems ($\beta = .15$, $p = .02$). Adolescents with PCE were also 2.8 times (95% CI = 1.38–5.56) more likely to have substance use related problems than their NCE counterparts. No differences between PCE adolescents in non-kinship adoptive/foster care ($n = 44$) and PCE adolescents in maternal/relative care ($n = 139$) were found in externalizing behavior or in the likelihood of substance use related problems. Findings demonstrate teratologic effects of PCE persisting into adolescence. PCE is a reliable marker for the potential development of problem behaviors in adolescence, including substance use related problems.

Maternal substance use during pregnancy continues to be a serious public health problem, with approximately 200,000 infants exposed to illicit drugs in utero each year in the United States (SAMHSA, 2012). Prenatal drug exposure during critical windows of embryonic and fetal development may alter brain development due to teratogenic, epigenetic, or cytotoxic effects. Emerging evidence indicates that prenatal cocaine exposure (PCE) disrupts the monoaminergic neurotransmitter system (dopamine, norepinephrine, serotonin) in the prefrontal cortex, a brain region responsible for emotional and behavioral arousal and regulation, attention, and stress response (Mayes, 2002; Thompson, Levitt, & Stanwood, 2009). Prenatal disruptions in the developmental programming of an infant's behavioral regulatory system due to PCE may have lasting effects on behavioral regulation, manifested differently across development, including greater externalizing behavior problems in childhood and/or early substance use in adolescence (Minnes, Lang, & Singer, 2011). As the prefrontal cortex and its

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associated networks are still developing in adolescence, the extent of impairment associated with PCE warrants continued evaluation as children with PCE mature.

A review focused on the preschool years (Dixon, Kurtz, & Chin, 2008) provided conflicting evidence of PCE effects on behavior problems, probably reflecting methodological differences among studies in determination of exposure status, operationalization of outcome variables (direct observation vs. parent rating; broad- vs. narrow-band scores), sample composition, confounders controlled for, and inter-individual differences in vulnerability to cocaine effects. However, the effects of PCE on behavioral regulation at early school age and during preadolescence converge with few exceptions despite methodological variability (Ackerman, Riggins, & Black, 2010). In a study of 244 7 year-olds, PCE during the third trimester was related to both caregiver and teacher reported externalizing behavior problems (Richardson, Goldschmidt, Leech, & Willford, 2011). At the same age (7), Accornero and colleagues found no evidence linking PCE and behavior problems via parent report (Accornero, Anthony, Morrow, Xue, & Bandstra, 2006), but increased behavioral problems among PCE children were noted when behavior was rated by examiners blinded to exposure status (Accornero et al., 2011). Our previous studies also indicated PCE effects. At 6 years of age, associations between PCE and symptoms of oppositional defiant disorder and attention-deficit/hyperactivity disorder (ADHD) were reported using child self-report, although the same study found no differences for caregiver reported problems (Linares et al., 2006). At 9 years, PCE was related to greater odds of aggressive behavior ratings using caregiver report. In addition, girls with PCE were more likely to be rated by their caregivers as having clinically significant delinquent behavior than NCE girls, whereas no differences were found for boys (McLaughlin et al., 2011). Longitudinal studies also lend support for PCE effects on externalizing behavior problems (Bada et al., 2007, 2011) prior to adolescence. Our longitudinal analyses of caregiver reported, clinically elevated, behavioral problems at 4, 6, 9, and 10 years of age indicated PCE to be associated with higher rates of delinquent behaviors among girls (Minnes et al., 2010).

Findings regarding PCE effects on behavioral adjustment and early substance use during adolescence are just beginning to emerge. One recent longitudinal study reported that children with cocaine/poly-drug exposure were rated as having higher levels of caregiver-reported externalizing behaviors through age 15 years than those with no drug exposure (Bada et al., 2012). However, this study did not examine PCE specific effects.

Three studies assessed the effects of PCE on early substance use, producing mixed findings. Increased risk of early substance use (alcohol, tobacco & marijuana) initiation by age 16 (Frank et al., 2011) and cocaine use at age 14 (Delaney-Black et al., 2011) were reported for PCE adolescents, whereas another study (Warner, Behnke, Eyler, & Szabo, 2011) found no relationship between PCE and early adolescent (12.5 years) experimentation with cocaine. Our data also indicates adolescents with PCE use more alcohol, tobacco, and marijuana than their NCE counterparts by 15 years of age (Minnes et al., 2014).

Multiple factors can affect behavioral outcomes of adolescents with PCE including prenatal exposure to other drugs/alcohol (Singer, Arendt, Minnes, Farkas, & Salvator, 2000), elevated blood lead levels (Min et al., 2009), and environmental conditions related to maternal drug use. Women who use cocaine during pregnancy tend to use other substances, including alcohol, cigarettes, and marijuana, all of which have been linked to externalizing behavior problems (Goldschmidt, Day, & Richardson, 2000; Maughan, Taylor, Caspi, & Moffitt, 2004; Sood et al., 2001) and early adolescent substance use (Baer, Sampson, Barr, Connor, & Streissguth, 2003; Cornelius, Leech, Goldschmidt, & Day, 2000; Day, Goldschmidt, & Thomas, 2006; Goldschmidt, Cornelius, & Day, 2012; Monshouwer et al., 2011). Between 12.5% and 35% of high risk poly-drug exposed children had elevated blood lead levels ($\geq$10 μg/dL) during preschool assessment (Bandstra et al., 2002; Lumeng, Cabral, Gannon, Heeren, & Frank, 2007; Nelson, Lerner, Needlman, Salvator, & Singer, 2004), in contrast to the general population rate of 8.65% for African American children and 2.02% for Caucasian children (Meyer et al., 2003). Elevated lead levels may further predispose PCE children to delinquent behavior (Dietrich, Ris, Succop, Berger, & Bornschein, 2001; Needleman, Riess, Tobin, Biesecker, & Greenhouse, 1996) and tobacco use (Lane et al., 2008). Environmental factors associated with prenatal drug use, such as poor quality of the home environment, caregiver ongoing substance use and psychological distress, violence exposure (Bada et al., 2007, 2011; Frank et al., 2011), non-kinship adoptive/foster care placement (Linares et al., 2006), negative attachment to caregiver (Warner et al., 2011) and low levels of parental monitoring (Bohnert, Anthony, & Breslau, 2012; Laird, Criss, Pettit, Dodge, & Bates, 2008) may heighten the drug exposed child's vulnerability to maladaptive behavioral development and obscure the long-term effects of PCE. In contrast, positive environmental factors may be protective or compensate for earlier biologic risk factors (Bada et al., 2012; Singer, 2004, 2008).

The purpose of the present study is to extend our previous studies of the effects of PCE into adolescence controlling for confounding factors of prenatal drug exposures, lead, and environmental covariates. Earlier behavioral problems may resolve or may become more pronounced in response to greater developmental demands of adolescence (puberty, academic performance/success, changing relationships with parents and peers). However, there are few prospective studies on adolescents, and this study represents one of the first prospective studies examining PCE effects during adolescence. An advantage of the current cohort is that a significant proportion of PCE children were placed in foster/adoptive care with lower lead levels and better home environments (Singer et al., 2008), allowing us to more specifically assess effects of PCE. We examined PCE effects on externalizing behavior problems in general as well as specific substance use related problems. Adolescents with PCE were hypothesized to report more externalizing behaviors and substance use related problems compared to adolescents who were non-cocaine exposed (NCE). Since our previous findings and those of others (Sood et al., 2005) have implicated gender as an important individual difference factor, we also explored whether the PCE effect on behavioral outcomes was moderated by gender.