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Effects of prenatal cocaine exposure on early sexual behavior: Gender difference in externalizing behavior as a mediator

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ABSTRACT

Background: Prenatal cocaine exposure (PCE) is associated with increased risk for externalizing behavior problems; childhood externalizing behavior problems are linked with subsequent early sexual behavior. The present study examined the effects of PCE on early sexual initiation (sexual intercourse prior to age 15) and whether externalizing behavior in preadolescence mediated the relationship.
Methods: Three hundred fifty-four (180 PCE and 174 non-cocaine exposed; 192 girls, 142 boys), primarily African-American, low socioeconomic status, 15-year-old adolescents participated in a prospective longitudinal study. Adolescents' sexual behavior was assessed at 15 years using the Youth Risk Behavior Surveillance System. Externalizing behavior was assessed at 12 years using the Youth Self-Report.
Results: Logistic regression models indicated that adolescents with PCE ($n = 69$, 38%) were 2.2 times more likely (95% CI = 1.2–4.1, $p < .01$) to engage in early sexual intercourse than non-exposed peers ($n = 49$, 28%) controlling for covariates. This relationship was fully mediated by self-reported externalizing behavior in girls but not in boys, suggesting childhood externalizing behavior as a gender moderated mediator. Blood lead level during preschool years was also related to a greater likelihood of early sexual intercourse (OR = 2.6, 95% CI = 1.4–4.7, $p < .002$). Greater parental monitoring decreased the likelihood of early sexual intercourse, while violence exposure increased the risk.
Conclusions: PCE is related to early sexual intercourse, and externalizing behavior problems mediate PCE effects in female adolescents. Interventions targeting externalizing behavior may reduce early sexual initiation and thereby reduce HIV risk behaviors and early, unplanned pregnancy in girls with PCE.

1. Introduction

Early sexual initiation has been associated with an increased risk of unintended teen pregnancies (O'Donnell et al., 2001) and sexually transmitted infections including HIV (Kaestle et al., 2005). Data from the 2006–2010 National Survey of Family Growth indicated that 14% of females and 18% of males had sexual intercourse by their 15th birthday (Finer and Philbin, 2013). Substantial research has documented that childhood behavior problems (aggression, antisocial behavior, delinquency) predict subsequent early initiation of sexual intercourse (Ramrakha et al., 2007; Skinner et al., 2015). The current study examines the contribution of prenatal cocaine exposure (PCE) to early sexual initiation given accumulating evidence of teratogenic effects of PCE on externalizing behavior (Ackerman et al., 2010; Bada et al., 2011; Buckingham-Howes et al., 2013; Lambert and Bauer, 2012; Min et al., 2014a, 2014b; Minnes et al., 2010).

Maternal substance use during pregnancy continues to be a serious public health problem, with approximately 214,000 infants exposed to illicit drugs, including cocaine, in utero each year in the United States (Substance Abuse and Mental Health Services Administration, 2014). PCE disrupts the monoaminergic neurotransmitter system (dopamine, norepinephrine, serotonin) in the prefrontal cortex, affecting emotional and behavioral arousal and regulation, stress response, and executive function (Thompson et al., 2009), all of which are risk factors for engaging in early sexual behavior (Goldenberg et al., 2013; Khurana et al., 2012). The neurobehavioral teratology model (Vorhees, 1989) posits that the damage to the developing central nervous system incurred prenatally due to exposure to teratogens can extend through later periods of development, suggesting that PCE effects may be expressed

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differently across development, including externalizing behavior in childhood and/or early sexual behavior in adolescence. The model also posits that long-term developmental outcome is affected by the timing, duration, and dose of the teratogen in utero, with environmental context exacerbating or mitigating early teratogenic effects. Additionally, some teratogenic effects may not be evident until the cognitive or behavioral domains implicated are emergent.

To date, three studies from two prospective cohorts have investigated the effects of PCE on adolescent sexual behavior (Conradt et al., 2014; De Genna et al., 2014; Lambert et al., 2013). First trimester PCE was a significant predictor of early sexual intercourse, with most PCE effects occurring between the ages of 13 and 18 when rates of initiation of sexual intercourse were approximately 10% higher among adolescents with PCE (De Genna et al., 2014). They also found that the effect of PCE was fully mediated by marijuana and alcohol use prior to age 15, but not by caregiver-reported externalizing behavior at age 7. In another cohort, PCE was associated with early (≤age 14) onset of oral sex, but not with penetrative sex, which was partially mediated by caregiver-reported attention problems at age 13 (Lambert et al., 2013), while prenatal poly-drug exposure including cocaine was related to behavioral dysregulation at ages 13/14, which predicted sexual intercourse by age 16 only in boys (Conradt et al., 2014).

Establishing the causal effect of PCE on early sexual behavior is complicated due to multiple biological and environmental confounders, including high levels of prenatal exposure to other substances such as alcohol (Larkby et al., 2011), tobacco (Maughan et al., 2004), and marijuana (Goldschmidt et al., 2000), elevated lead (≥10 μg/dL) levels (Lane et al., 2008; Min et al., 2009; Singer et al., 2008), delayed pubertal development (Bennett et al., 2015), poor quality of the home environment (Lewis et al., 2011; Singer et al., 2008), caregiver postpartum substance use and psychological distress (Minnes et al., 2010) and adoptive/foster care placement (Singer et al., 2004). Further, family conflict (Fosco et al., 2012), violence exposure (Frank et al., 2011), poor attachment to caregiver (Warner et al., 2011), and inadequate parental monitoring (Min et al., 2014a, 2014b), all reflecting the interpersonal developmental contexts in which adolescents transact (Cicchetti and Rogosch, 2002), may heighten the drug exposed adolescent's vulnerability.

The present study examines the effects of PCE on early sexual initiation, defined as sexual intercourse prior to age 15, and whether externalizing behavior in preadolescence mediates the relationship. We previously reported significant PCE effects on adolescents' self-reported externalizing behavior at age 12 in both boys and girls (Min et al., 2014b). The data reported in the current paper were drawn from the same cohort. Building on previous studies linking PCE with externalizing behavior and externalizing behavior with early sexual behavior, we hypothesized that: (1) adolescents with PCE would be more likely to experience sexual intercourse before age 15 than non-cocaine exposed (NCE) adolescents, controlling for the effects of other risk factors and (2) externalizing behavior would mediate the relationship between PCE and sexual intercourse before age 15. Because a significant proportion of PCE adolescents in this sample were placed in non-kinship adoptive/foster care with lower lead levels and better quality home environments, we also explored the impact of such placement on early sexual behavior. Since normative expectation for sexual activity may differ by gender (e.g., norms may encourage sex for adolescent boys but not for adolescent girls; Martin, 1996) and there are mixed findings of PCE by gender interaction on behavioral adjustment (e.g., Carmody et al., 2011; Delaney-Black et al., 2000; Minnes et al., 2010), we explored gender as a potential moderator of PCE and externalizing behavior effects on early sexual initiation.

2. Methods

2.1. Sample

This study included 354 (180 PCE, 174 NCE) 15-year-old adolescents recruited at birth from an urban county hospital and their birth mothers or current caregivers. Pregnant women were recruited into the study if they had a urine toxicology screening ordered by the hospital due to: (1) lack of prenatal care; (2) a history of involvement with the Department of Human Services; (3) appearance of intoxication; or (4) self-reported substance use during pregnancy. A nurse recruiter approached all screened women ($N = 647$) immediately before or after infant birth. Of these 647 women, 54 were excluded, 155 refused to participate, and 23 did not come to the enrollment visit. Reasons for exclusion included maternal psychiatric history, low maternal intellectual functioning indicated in medical chart review, HIV-positive status, maternal chronic medical illness, and infants' Down syndrome, fetal alcohol syndrome, or congenital heart defect.

Maternal and infant urine samples and infant meconium were obtained shortly before or after infant birth and analyzed for cocaine and other drug metabolites, including benzoylecgonine, meta-hydroxybenzoylecgonine, cocaethylene, cannabinoids, opitates, phencyclidine, amphetamines, and benzodiazepines. A total of 415 newborns and their birth mothers were enrolled at birth, of which 218 infants were identified as cocaine-exposed based on positive screens of maternal and infant urine, infant meconium, or maternal self-report to hospital or research staff. Infants who were negative on all indicators of prenatal cocaine exposure were identified as NCE, but they may have been exposed to other substances (i.e., alcohol, tobacco, marijuana). Infants exposed to cocaine were further classified as being either heavier or lighter exposed. The heavier PCE group was defined a priori as >70th percentile for cocaine use, which corresponded to ≥216 ng/g benzoylecgonine in meconium screening or ≥17.5 units used ("rocks" of cocaine worth $20 each)/week by maternal self-report.

Since birth, 12 (9 PCE, 3 NCE) enrolled children died from sudden infant death syndrome (4 PCE, 2 NCE), cardiopulmonary arrest (1 PCE), pneumonia (1 PCE), accidental asphyxia (1 PCE), respiratory distress syndrome (1 PCE, 1 NCE), and unknown illness (1 PCE). The present study utilizes data from 354 adolescents who completed sexual behavior assessment at age 15, representing 88% retention of the 403 living participants in the original study. Of the 49 adolescents not included in these analyses (19 drop-out, 17 lost contact, 1 low intellectual functioning (IQ < 50), 12 missing data), the 29 PCE adolescents were not different from PCE adolescents who participated in the study. The 20 NCE adolescents not included in the analyses were more likely to be white, have birth mothers who were older, more likely to be married, and had lower psychological distress compared to the participating NCE adolescents. No difference was found by PCE status between the 354 participants and the 49 nonparticipants, although the nonparticipants were more likely to be white and male.

2.2. Procedure

Subjects and their mothers/caregivers were assessed shortly after birth and at follow-up visits conducted at ages 6, 12, and 18 months and 2, 4, 6, 9–12, and 15 years of age. This study was approved by the Institutional Review Board of the participating hospital. Written informed consent was obtained at each visit from the child's parent or legal guardian and written child assent was obtained beginning at age 9. A Certificate of Confidentiality was obtained from the U.S. Department of Health and Human Services to further protect the sensitive nature of the data acquired from caregivers and subjects during each phase of the study. Participants were given a monetary stipend for each assessment visit, along with lunch and assistance with transportation costs if needed.

2.3. Measures

2.3.1. Prenatal drug exposure. At the newborn visit, birth mothers were interviewed regarding their substance use during the month prior to becoming pregnant and during each trimester of their pregnancy. They were asked to recall the number of cigarettes per day and marijuana joints smoked per week, and the number of drinks of beer, wine, or hard liquor consumed per week, with each drink equivalent to 0.5 oz. of absolute alcohol. For cocaine, the number of "rocks" consumed and the amount of money spent per day were noted. For each drug, the frequency of use was recorded on a Likert-type scale ranging from 0 (not at all) to 7 (daily use). Frequency was multiplied by the amount used per day to compute an average use score for the month prior to pregnancy and for each trimester. These scores were then averaged to obtain a total score of prenatal exposure for each drug. At each follow-up visit, the substance use assessment was updated with the child's current caregiver to obtain a measure of their recent drug use in the past 30 days.

2.3.2. Early sexual behavior. At the 15-year follow-up visit, age at first time of sexual intercourse was assessed using one item from the Youth Risk Behavior Surveillance System (YRBSS; Centers for Disease Control and Prevention, 2009). Early sexual behavior was defined as any sexual intercourse before 15 years of age.

2.3.3. Externalizing behavior. At the age of 12 years, externalizing behavior (aggression and rule-breaking behavior) was assessed using the Youth Self-Report (YSR; Achenbach and Rescorla, 2001), a 105-item child self-rating of his or her own behavior designed to assess emotional, behavioral and social problems in the last 6 months. *T*-scores were standardized for gender and age, with higher scores indicating more problem behaviors ($\alpha = .87$).

2.3.4. Other adolescent and caregiver variables. Demographic, medical and birth characteristics were extracted from hospital records. These characteristics included maternal race, age, and marital status at the time of giving birth, years of education completed, number of prenatal care visits, parity, and infant's race, gender, and head circumference. Socioeconomic status was computed using the Hollingshead Two Factor Index of Social Position (Hollingshead, 1957), with a Hollingshead score of IV or V used as an indicator of low socioeconomic status. At the newborn visit, maternal vocabulary was assessed using the Peabody Picture Vocabulary Test-Revised (PPVT-R; Dunn and Dunn, 1981). This information was later updated using the PPVT-III (Dunn et al., 1997) at age 6 and later assessments. Maternal/caregiver self-reported psychiatric symptoms were assessed at each visit using the Brief Symptom Inventory (BSI; Derogatis, 1992). The BSI Global Severity Index (GSI; $\alpha = .95$), a summary scale of general psychological distress, was used in the present study. Also at each visit, the child's placement (with either biological mother/relative or adoptive/foster caregiver) was noted, with updated assessment of the current caregiver's vocabulary and psychiatric symptoms if there had been a change in caregiver. Adolescents' intelligence was assessed using the Wechsler Intelligence Scales for Children-Fourth Edition (WISC-IV; Wechsler, 2003) at age 11.

Lead exposure was assessed for a subset of children at ages 2 and 4 years. Venous blood samples could not be obtained from some children due to lack of parental consent, excessive stress related to the blood draw, child sickness or logistical difficulties. A greater percentage of African-American and married women and a lower percentage of foster parents consented to blood collection. Valid hematologic measures were obtained for 143 two-year and 274 four-year-old children. For the 122 children with valid blood measurements at both times, the values were averaged, resulting in a total of 298 valid blood lead assessments.

At age 12 years, the quality of the caregiving environment was assessed via interview using the Home Observation of the Environment-Early Adolescent (HOME; $\alpha = .83$; Caldwell and Bradley, 2003). Parental attachment and monitoring, family conflict, violence exposure, and pubertal development were also assessed using The Assessment of Liability and Exposure to Substance Use and Antisocial Behavior (ALEXSA; Ridenour et al., 2009), an illustration-based, audio, computer-assisted self-report of antisocial behavior, substance involvement and associated risk factors for children ages 9–12. The parental attachment subscale (Ridenour et al., 2006) is a 5-item questionnaire using a 4-point Likert scale ($\alpha = .79$), assessing the youth's perceived closeness with parents. The parental monitoring subscale (Capaldi and Patterson, 1989), a 5-item questionnaire using a 4-point Likert scale ($\alpha = .75$), assesses the youths' perceptions of whether their parent(s) usually is (are) aware of the youths' activities and whereabouts. The family conflict index (Straus et al., 1998) is a 10-item questionnaire assessing family conflict tactics such as yelling, threatening to hurt, throwing, or hitting; the variable was a total count of these incidents. The violence exposure subscale (Cooley et al., 1995) is an 8-item questionnaire using a 5-point Likert scale ($\alpha = .76$), measuring lifetime exposure to violence (e.g., beating, robbery, stabbing, shooting), either as a direct victim or witness, with higher scores indicating greater exposure. The pubertal development subscale (Petersen et al., 1988) uses a 4-point Likert scale. Items for girls include body hair development, growth spurt in height, skin changes, comparison to same-age and same-sex peers ("how old does the maturity of your physical development look compared to other girls/boys your age?"; responses are "Look younger than all girls your age (0)" to "Look older than all girls your age (3)"), and breast development (5 items; $\alpha = .82$); items for boys were the first four plus voice change and facial hair growth (6 items; $\alpha = .73$). Higher scores indicate greater maturity.

2.4. Statistical analyses

Data that were positively skewed were normalized using a log transformation (drug use, GSI, violence exposure, and lead) prior to analyses. Means and standard deviations (SD) were reported by the variables' original distribution, with transformations used in analyses. Sample characteristics were examined by PCE status using t-tests for continuous variables or Chi-square analyses for categorical variables. Zero-order Pearson correlations were estimated to examine relationships between study variables. Logistic regression was conducted to examine the effects of PCE on early sexual behavior and to test mediation via externalizing behavior. In order to avoid multicollinearity and saturation of the model, covariates correlated with the outcome at $p \leq .20$ were entered into the regression model stepwise (i.e., using a series of steps) and were retained if, on entry, they caused substantial (>10%) change in the PCE coefficient or were significantly related to the outcome at $p < .10$. PCE was entered first followed by socio-demographic covariates including race, other prenatal substance exposure, pubertal status, parenting, and violence exposure variables. Due to the reduced sample size, preschool lead level was entered last. Multicollinearity was examined using tolerance and variance inflation factor. The concentration of meconium metabolites of cocaine, levels of PCE (NCE, light PCE, heavy PCE), and combined effects of PCE and placement (PCE biologic/relative, PCE foster/adoptive care, and NCE) at age 12 were evaluated when a significant PCE effect was noted. Mediation was assessed using Baron and Kenney's approach (1986). Since our previous study established PCE effects on self-reported externalizing behavior in both boys and girls at age 12 (Min et al., 2014b), we fitted logistic regression models without and with externalizing behavior and examined the change in odds ratio and statistical significance of PCE. Child gender was tested for interaction with PCE as well as with externalizing behavior.

3. Results

3.1. Sample characteristics

Table 1 presents characteristics of birth mothers, caregivers at age 12, and adolescents. The birth mothers of adolescents with PCE were older, less educated, less likely to be married, had more children and less prenatal care than birth mothers of NCE adolescents. They had lower vocabulary scores, more psychological distress, and reported greater use of tobacco, alcohol and marijuana during pregnancy than non-cocaine-using mothers. The majority (>90%) of the cocaine-using mothers used the crack cocaine form. While more than half of the cocaine-using mothers used cocaine throughout pregnancy, the number of cocaine using mothers and the amount of use gradually decreased over the course of pregnancy. Fewer mothers used tobacco, alcohol, or marijuana as their pregnancy progressed, with less amount of use in both groups. Caregiver and home environment characteristics at age 12 years did not differ, except that caregivers of the adolescents with PCE had less education and smoked more cigarettes in the past 30 days than the current caregivers of NCE adolescents. Adolescents with PCE had a shorter gestational age, lower birth weight, length, and head circumference, and were less likely to be continuously cared for by their birth mothers. At age 12, 24% ($n = 43$) of adolescents with PCE were in non-kinship adoptive/foster care compared to 4.0% ($n = 7$) of their NCE counterparts, $\chi^2 = 29.03$, $p < .0001$. Adolescents with PCE reported a lower level of parental attachment, greater family conflict, and more externalizing behavior problems than their NCE counterparts.

3.2. Effect of PCE on early sexual intercourse

Sixty-nine PCE (38%) and 49 NCE (28%) adolescents reported sexual intercourse by age 14, with 37 PCE and 27 NCE adolescents reporting sexual intercourse by age 13. Table 2 summarizes the effect of PCE on early sexual intercourse after controlling for covariates. Adolescents with PCE were 2.24 (95% CI = 1.22–4.09, $p < .01$) times more likely to engage in early sexual intercourse than NCE adolescents controlling for covariates. When the PCE adolescents were further classified into heavier ($n = 96$) and lighter ($n = 84$) exposure groups, both PCE groups were associated with early sexual intercourse controlling for the covariates (OR = 2.11, 95% CI = 1.03–4.33, $p < .05$ for lighter PCE; OR = 2.36, 95% CI = 1.17–4.73, $p < .02$ for heavier PCE) with no difference between the two PCE groups. The concentrations of meta-hydroxybenzoylecgonine (OR = 1.11, 95% CI = 1.02–1.22, $p = .024$) and benzoylecgonine (OR = 1.08, 95% CI = 0.995–1.17, $p = .065$) were related to early sexual intercourse after controlling for the covariates. No PCE by gender interaction was found.

In terms of covariates, boys were three (95% CI = 1.79–5.24, $p < .001$) times more likely to be involved in early sexual intercourse than girls. Greater parental monitoring decreased the likelihood of early sexual intercourse, while violence exposure increased the risk. Further adjustment of preschool blood lead level did not change the effect of PCE, although higher lead level independently predicted an increased likelihood of early sexual intercourse (OR = 2.57, 95% CI = 1.42–4.66, $p < .002$). Due to the absence of changes in the effect of PCE on the outcome and reduced sample

Table 1
Maternal, caregiver, and adolescent characteristics.

	PCE (n = 180)		NCE (n = 174)		p
	M	*SD*	*M*	*SD*	
Biological mother					
Mother's age at birth	29.69	4.99	25.41	4.77	<.001
Education, years	11.56	1.68	11.95	1.38	.02
Married, *n* (%)	15	(8.33)	27	(15.52)	.04
Parity	3.59	1.90	2.69	1.84	<.001
Number of prenatal visits	5.20	4.60	8.82	4.82	<.001
PPVT-R Standard Score	73.68	14.45	78.09	14.62	.005
BSI Global Severity Index	0.81	0.74	0.51	0.54	<.001
Low SES, *n* (%)	175	(97.77)	170	(97.70)	.97
African-American, *n* (%)	147	(81.67)	142	(81.61)	.99
Substance use during pregnancy	*n* (%)	*M* (*SD*)	*n* (%)	*M* (*SD*)	*p*[a]
Tobacco, cigarettes per day[b]	154 (85.56)	13.12 (10.94)	67 (38.51)	9.61 (8.59)	<.001
Month prior	151 (83.89)	15.52 (12.05)	63 (36.21)	14.24 (11.24)	<.001
First trimester	149 (82.78)	14.88 (12.15)	54 (31.03)	12.30 (9.58)	<.001
Second trimester	141 (78.33)	13.24 (11.57)	45 (25.86)	11.60 (9.05)	<.001
Third trimester	134 (74.44)	12.33 (11.19)	46 (26.44)	10.72 (6.68)	<.001
Alcohol, drinks per week[b]	141 (78.33)	12.24 (19.14)	69 (39.66)	3.38 (6.85)	<.001
Month prior	121 (67.22)	18.75 (25.52)	58 (33.33)	7.34 (12.21)	<.001
First trimester	110 (61.11)	19.36 (28.05)	32 (18.39)	6.85 (6.62)	<.001
Second trimester	85 (47.22)	16.45 (26.24)	16 (9.20)	6.06 (8.33)	<.001
Third trimester	88 (48.99)	12.59 (22.81)	20 (11.49)	9.54 (21.89)	<.001
Marijuana, joints per week[b]	74 (41.11)	3.26 (4.85)	15 (8.62)	5.48 (9.43)	<.001
Month prior	59 (32.78)	4.91 (5.33)	15 (8.62)	15.13 (30.31)	<.001
First trimester	49 (27.22)	5.42 (6.31)	9 (5.17)	6.50 (6.91)	<.001
Second trimester	33 (18.33)	6.94 (7.88)	3 (1.72)	9.42 (10.58)	<.001
Third trimester	30 (16.67)	5.71 (7.91)	3 (1.72)	4.92 (3.61)	<.001
Cocaine, units per week[b]	180 (100)	23.06 (38.45)	–	–	–
Month prior	151 (83.89)	36.28 (62.04)	–	–	–
First trimester	146 (81.11)	39.96 (70.65)	–	–	–
Second trimester	124 (68.89)	37.33 (74.39)	–	–	–
Third trimester	132 (73.33)	16.92 (30.90)	–	–	–

	PCE (n = 180)		NCE (n = 174)		p
	M	*SD*	*M*	*SD*	
Caregiver at age 12 years					
Education, years	12.04	2.41	12.76	1.90	.003
PPVT-III Standard Score	79.74	14.96	80.11	15.57	.83
BSI Global Severity Index	0.35	0.44	0.36	0.49	.98
HOME environment	47.90	6.84	49.22	6.25	.06
Amount of substance use in the past 30 days[c]					
Tobacco, cigarettes per day	5.29	7.48	3.82	6.68	.02
Alcohol, drinks per week	1.47	3.80	1.78	5.61	.91
Marijuana, joints per week	0.93	7.29	0.11	1.10	.15
Adolescent					
Gestational age, weeks	37.78	2.78	38.43	2.90	.03
Hobel Neonatal Risk score	7.16	15.48	6.02	16.16	.50
Birth weight, g[d]	2700.8	643.6	3099.1	709.6	<.001
Birth length, cm[d]	47.24	3.87	49.14	3.80	<.001
Head circumference, cm[d]	32.26	2.11	33.45	2.43	<.001
Male, *n* (%)	79	(43.89)	83	(47.70)	.47
Blood lead level at 2 or/and 4 year[e]	7.00	4.12	8.04	4.71	.06
Elevated lead level (≥10 μg/dL)[e], *n* (%)	25	(17.73)	36	(26.67)	.07
Age at assessment, years	15.69	0.27	15.66	0.26	.29
WISC-IV Full Scale IQ at age 11	84.66	11.45	86.01	14.53	.33
Always in birth parents' care by age 12, *n* (%)	64	(35.56)	149	(85.63)	<.001
Parental attachment[f]	2.12	0.67	2.27	0.61	.03
Parental monitoring[f]	2.42	0.65	2.49	0.57	.32
Family conflict[f]	3.19	2.50	2.58	2.39	.03
Violence exposure[f]	0.61	0.76	0.56	0.79	.43
Pubertal development[f]	1.26	0.56	1.24	0.56	.79
YSR externalizing behavior[f]	50.82	9.90	47.59	9.69	.002

PPVT = Peabody Picture Vocabulary Test, PPVT-R (Revised) used at birth; PPVT-III (third edition) was used at 6 and later years; BSI = Brief Symptom Inventory; WISC-IV = Wechsler Intelligence Scales for Children-Fourth Edition; YSR = Youth Self Report.

[a] *p*-value based on *n* (%).
[b] Number of women who used the substance during pregnancy and their average use across pregnancy.
[c] No caregiver reported cocaine use in the past 30 days.
[d] Adjusted for gestational age.
[e] Sub-sample of 141 PCE and 135 NCE.
[f] Assessed at age 12.

Table 2
Effects of prenatal cocaine exposure on early sexual activity.

	OR	95% CI	*p*
Prenatal cocaine exposure	2.24	1.22–4.09	.009
Sex, male	3.06	1.79–5.24	<.001
Prenatal alcohol exposure[a]	0.83	0.64–1.07	.14
Total HOME score	0.96	0.93–1.00	.06
Parental monitoring	0.56	0.37–0.87	.01
Violence exposure	1.52	1.18–1.95	.001

[a] Average.

size, models without lead were used in subsequent mediation analyses.

3.3. Externalizing behavior at age 12 as a mediator

Since a significant gender by externalizing behavior interaction emerged ($b = -0.06$, SE = 0.03, $p < .05$), separate logistic regression models were run, without (Model 1) and with (Model 2) externalizing behavior as a mediator, by gender. Table 3 indicates that externalizing behavior fully mediated the effect of PCE on early sexual intercourse in girls, but not in boys. For boys, earlier externalizing behavior was not related to early sexual intercourse. Greater violence exposure was associated with early sexual intercourse in boys even in the model with externalizing behavior (OR = 1.55, 95% CI = 1.09–2.21, $p < .02$). Violence exposure was no longer related to early sexual intercourse in girls ($p = .18$) when externalizing behavior was accounted for.

3.4. Effects of adoptive/foster care placement

PCE adolescents in adoptive/foster care lived in better caregiving environments compared to those in biological/relative care, evidenced by higher HOME scores and caregivers with better vocabulary, educational attainment, and less alcohol and tobacco use (Table 4). They also had lower blood lead levels, but had more placement changes by age 12. Of those 43 adolescents with PCE in adoptive/foster care at age 12, 47% ($n = 20$) had only one placement change and 28% ($n = 12$) had two, indicating three quarters of them had been in relatively stable living arrangements. No significant difference was found in the likelihood of early sexual intercourse between the two PCE groups, although PCE adolescents in adoptive/foster care reported more externalizing problems than PCE adolescents in biological/relative care and NCE adolescents at 12 years.

4. Discussion

Adolescents with PCE were more likely to engage in sexual intercourse before age 15 compared to their non-exposed peers. This relationship was fully mediated by self-reported externalizing behavior at age 12 in girls but not in boys, suggesting childhood externalizing behavior as a gender moderated mediator. That is, although PCE effects on early sexual initiation was observed for both boys and girls, its underlying mechanism was gender-dependent, indicating childhood externalizing behavior as a pathway only for girls. Our study is in line with two previous studies indicating a greater risk of early sexual initiation among PCE adolescents (De Genna et al., 2014; Lambert et al., 2013), despite methodological differences in operationalization of early sexual initiation and analytical approaches. A stronger relationship between externalizing behavior and early sexual initiation for girls than for boys was observed in our high risk sample, although large population-based studies identified childhood externalizing behavior as a risk factor regardless of gender (McLeod and Knight, 2010; Skinner et al., 2015). Girls with externalizing problems may represent more serious impairment compared to boys given societal gender-based norms expecting stronger compliance from girls than boys (Maccoby, 1988).

We previously reported protective effects of non-kinship foster/adoptive care on cognitive (Singer et al., 2008, 2004) and language (Lewis et al., 2011) development during the preadolescent years, but not on behavioral outcomes including externalizing behavior (McLaughlin et al., 2011; Min et al., 2014a, 2014b; Minnes et al., 2010). However, PCE adolescents in foster/adoptive care (29%) had lower odds of early sexual intercourse than PCE adolescents in biologic/relative care (42%), although statistical significance was not achieved, probably due to limited power. Future research should investigate how enriched placement may differentially affect the expression of PCE effects across development stages and outcomes, given that children born with PCE are often placed outside of their birth mother's custody.

Independent of PCE and other biological risk factors, parental monitoring and violence exposure also additively contributed to increased odds of early sexual initiation, highlighting the importance of adolescents' interpersonal contexts. Gender was a significant predictor of early sexual initiation, with boys having a greater likelihood of early sexual intercourse than girls. Further, higher levels of blood lead during the preschool years, which have not typically been investigated simultaneously with PCE, additively increased odds of early sexual initiation, raising particular concern for those adolescents with co-occurring exposures. To our knowledge, no studies to date have examined the effects of lead on early sexual initiation in the context of PCE.

Limitations in our study should be considered. Although biological measures were used for detection of PCE, prenatal drug use assessment was obtained retrospectively and thus subject to recall error and social desirability bias. Similarly, we also relied on adolescents' self-reported sexual behavior. Our outcome variable, age at first sexual intercourse, was assessed with a single-item question, which may have compromised reliability and validity. Lack of data on adolescents' early substance use and paternal substance use and psychopathology are another limitations as they may impact adolescents' sexual behavior. Lastly, generalizability

Table 3
Effects of prenatal cocaine exposure on early sexual activity mediated via externalizing behavior by gender.

	Girls ($n = 192$)						Boys ($n = 142$)					
	Model 1			Model 2			Model 1			Model 2		
	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
Prenatal cocaine exposure	2.62	1.03–6.67	.04	2.09	0.79–5.53	.14	1.20	0.89–4.47	.09	1.99	0.89–4.56	.09
Prenatal alcohol exposure[a]	0.89	0.60–1.31	.55	0.89	0.59–1.34	.57	0.78	0.56–1.09	.15	0.78	0.56–1.10	.16
Total HOME score	0.95	0.90–1.02	.14	0.95	0.89–1.02	.14	0.97	0.92–1.02	.28	0.97	0.92–1.02	.28
Parental monitoring	0.57	0.29–1.08	.09	0.86	0.41–1.78	.68	0.57	0.31–1.04	.07	0.56	0.31–1.04	.07
Violence exposure	1.51	1.51–2.27	.04	1.34	0.88–2.06	.18	1.52	1.11–2.09	.009	1.55	1.09–2.21	.01
Externalizing behavior	–	–	–	1.07	1.02–1.13	.008	–	–	–	0.99	0.95–1.04	.80

[a] Average.

Table 4
Key characteristics and adolescent early sexual behavior by cocaine status and placement at age 12.

	PCE biological/relative	PCE non-kinship adoptive/foster	NCE	*p*
	n = 137	*n* = 43	*n* = 174	
	M (*SD*)	*M* (*SD*)	*M* (*SD*)	
PCE, units per week	21.40 (36.67)	28.35 (43.68)	–	.23
WISC-IV Full Scale IQ at age 11	85.04 (11.59)	83.49 (11.05)	86.01 (14.53)	.50
Number of placement changes by 12 year	1.35 (1.52)	2.70 (2.58)	0.60 (1.26)	<.001[1,2,3]
Range (5% tile–95% tile)	0–4	1–8	0–3	
Key covariates				
Birth maternal age	29.50 (5.07)	30.30 (4.71)	25.41 (4.77)	<.001[2,3]
Biological mother's GSI	0.79 (0.76)	0.86 (0.66)	0.51 (0.54)	<.001[2,3]
Prenatal alcohol exposure, average	10.60 (10.24)	14.63 (13.26)	3.88 (7.20)	<.001[2,3]
Prenatal cigarette exposure, average,	8.74 (5.29)	13.52 (24.29)	1.41 (4.70)	<.001[2,3]
Prenatal marijuana exposure, 3rd trimester	1.34 (3.22)	1.49 (4.44)	0.49 (3.17)	<.001[2,3]
HOME score	47.02 (6.70)	50.76 (6.57)	49.22 (6.25)	<.001[1,2]
Caregiver PPVT-III standard score	76.84 (13.60)	91.45 (14.67)	80.11 (15.57)	<.001[1,3]
Caregiver education	11.73 (2.10)	13.17 (3.07)	12.76 (1.90)	<.001[1,2]
Caregiver alcohol, dose per week	1.79 (4.21)	0.39 (1.32)	1.78 (5.61)	.049[1]
Caregiver tobacco, cigarettes per day	6.57 (7.92)	0.76 (2.33)	3.82 (6.68)	<.001[1,2,3]
Parental attachment	2.11 (0.66)	2.15 (0.73)	2.27 (0.61)	.09
Parental monitoring	2.45 (0.62)	2.32 (0.74)	2.49 (0.57)	.34
Family conflict	3.14 (2.47)	3.38 (2.65)	2.58 (2.39)	.08
Violence exposure	0.66 (0.77)	0.43 (0.66)	0.56 (0.79)	.17
Pubertal development	1.23 (0.55)	1.43 (0.60)	1.24 (0.56)	.32
Blood lead level at 2 and/or 4 years[a]	7.38 (4.18)	5.34 (3.45)	8.04 (4.71)	.01[1,3]
Elevated lead (≥10 μg/dL)[a], *n* (%)	24 (20.87)	1 (3.85)	36 (26.67)	.004[3]
YSR Externalizing behavior	49.60 (9.89)	54.67 (9.99)	47.59 (9.69)	.001[1,3]
Early sexual intercourse, adjusted % (se)[b]	41.9 (5.32)	29.4 (9.68)	22.7 (3.79)	.02[2]

[a] Sub-sample of 120 PCE biological/relative, 27 PCE adoptive/foster, and 142 NCE.
[b] Adjusted for the same covariates from Table 2.
[1] Significant ($p < .05$) difference between PCE biological mother/relative vs. PCE non-kinship adoptive/foster care.
[2] Significant ($p < .05$) difference between PCE biological mother/relative vs. NCE.
[3] Significant ($p < .05$) difference between PCE non-kinship adoptive foster care vs. NCE.

of the findings is limited to a high-risk population of low-income, urban, predominantly African-American adolescents whose mothers lacked prenatal care and/or exhibited signs of intoxication at delivery. Nevertheless, the present study has multiple strengths including the prospective design, assessing a large number of adolescents and their caregivers since birth with 88% retention at age 15. Multiple operationalization of PCE was utilized including cocaine metabolites, corroborating the effects of PCE. A large number of covariates and confounders were evaluated including blood lead levels, uncovering the interrelationships of PCE, lead, and early sexual initiation.

In conclusion, adolescents with PCE were more likely to engage in sexual intercourse before age 15 than NCE peers. Externalizing behavior may be a key pathway to early sexual initiation for adolescent girls with PCE. Interventions focusing on strengthening parental monitoring and decreasing violence and lead exposure may be promising in reducing early sexual initiation among high risk prenatally cocaine/poly-drug exposed adolescents. Interventions targeting externalizing behavior in girls may decrease early sexual behavior and promote sexual health.

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Contributors

Dr. Meeyoung Min conceptualized the paper, performed the statistical analyses, and wrote the initial and final draft. Dr. Sonia Minnes designed the study and interpreted the data. Dr. Adelaide Lang coordinated the study, performed the measurements, and proofread the manuscript. Ms. Susan Yoon assisted in the literature review, drafting, and proofing the manuscript. Dr. Lynn Singer participated in the study's conception and design, interpretation of data, and reviewed the manuscript. All authors read and approved the final manuscript.

Conflict of interest

No conflict of interest declared.

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